Santiago de Cali, 10 de noviembre de 2021

Doctor
Víctor Hugo Sánchez Figueroa
Juez Segundo Civil del Circuito de Cali
E. S. D.

Referencia: Verbal
Radicación: 76001 31 03 002 **2018 00288** 00
Demandante: Édison Jauregui Belalcázar.
Demandados: Fundación Valle de Lili - Ingrid Katherine Álvarez Echeverry
Asunto: Contestación de la demanda.

Andrés Fernando Ortega Ordóñez, identificado con C.C. 1.085.277.335, abogado en ejercicio, con tarjeta profesional No. 218.687 del C.S. de la J., actuando en mi calidad de apoderado de la doctora Ingrid Katherine Álvarez Echeverry, identificada con cédula de ciudadanía No 1.085.245.468, según el reconocimiento de personería jurídica para actuar, encontrándome dentro del término legal, acudo respetuosamente ante su Despacho con el fin de **contestar la demanda** de la referencia, y en ese sentido elevo las siguientes:

I.- Pretensiones

Primera: Se declaren probadas las excepciones de mérito o argumentos de defensa propuestos en la presente contestación.

Segunda: En consecuencia, se nieguen las 2 pretensiones de la demanda formulada por el señor Edinson Jauregui Belalcázar, a través de apoderada judicial, en contra de mi representada.

Tercera: Se condene en costas a la parte demandante, y a favor de la parte demandada, acorde con lo prescrito en el artículo 365 de la Ley 1564 de 2012, y sean liquidadas, según lo consagrado en el artículo 366 *ibídem*.

II.- Oportunidad

De acuerdo al estado del proceso que fue consultado en la página *web* de la Rama Judicial, el despacho notificó el auto de 27 de septiembre de 2021, el 6 de agosto del presente año, por lo que los 20 días para contestar la demanda fenecen el 10 de noviembre de los corrientes, y comoquiera que se la radica en esta fecha, resulta oportuna.

III.- Sobre las pretensiones

Sin perjuicio de la sustentación de carácter fáctico, jurídico y probatorio que presentaré a lo largo del presente escrito, anticipadamente manifiesto mi oposición a las pretensiones formuladas por la parte accionante y, por el contrario, solicito se despachen de manera favorable las excepciones y mecanismos de defensa aquí propuestos.

Frente a la primera y segunda pretensión: Me opongo a su prosperidad por cuanto no existió, ni está demostrado en la demanda, que el fallecimiento del

señor Santiago Jauregui Bautista tuvo como causa eficiente la presunta defectuosa práctica de la atención médica brindada entre el 24 y 25 de agosto de 2017 y específicamente, el suministro del medicamento hidromorfona del 0.2 mg., y en esa razón, no le asiste, ni le asistirá derecho al reconocimiento de ningún perjuicio material que resulte de la declaratoria de su pretensión.

IV.- Frente a los hechos de la demanda

Con el propósito de referirse a los supuestos fácticos en que se basó la presente demanda, ha de seguirse el orden propuesto por la parte accionante:

De manera preliminar, y como un componente transversal al estudio de la contestación de esta demanda, ha de indicarse que, acorde con el sistema probatorio colombiano y, en especial, lo señalado en el artículo 167 de la Ley 1564 de 2014, *"incumbe a las partes probar el supuesto de hecho de las normas que consagran el efecto jurídico que ellas persiguen"*. O, dicho de otro modo, corresponde a la parte quien afirma el acaecimiento de un hecho, probarlo.

En ese mismo sentido, el doctrinante López Blanco, en su obra de derecho procesal general, señaló acerca de la citada premisa normativa[1]:

> *Si bien el efecto de dicha regla se atempera con lo indicado en el inciso segundo de la misma disposición y también al acogerse a la contraria o sea la de oficiosidad en el decreto y práctica de las pruebas, prevista en el art. 170 del CGP* ***es lo cierto que prevalece la primera pues nadie mejor que los interesados para conocer los medios de prueba que***

[1] LÓPEZ, Blanco Hernán Fabio. *Código General del Proceso. Pruebas.* Ed. Dupré. Bogotá. 2017. P.46.

deben emplear con el fin de demostrar los hechos en que fundamentan sus pretensiones o excepciones. (Negrillas fuera del texto original).

Por lo anterior, luego de referenciar la carga probatoria que debe soportar la parte que alega el acaecimiento de un determinado hecho, es dable afirmar que el principio procesal del *"Onus probandi, incumbit actori y Reus, in excipiendo, fit actor"*, constituye en un eje axial dentro de todo proceso judicial, de tal manera que si no se demuestra lo que se asevera, no prosperarán las respectivas pretensiones que se propongan.

Frente al hecho primero: No me consta. Es un supuesto fáctico que deberá acreditar la parte actora.

Frente al hecho segundo: No me consta. Es un supuesto fáctico que deberá acreditar la parte actora.

Frente al hecho tercero: No me consta la atención médica recibida por parte del señor Jauregui Bautista; sin embargo, **es cierto** que fue un paciente diagnosticado con insuficiencia renal crónica.

Frente al hecho cuarto: No me consta. Es un supuesto fáctico que deberá acreditar la parte actora.

Frente al hecho quinto: No me consta. Es un supuesto fáctico que deberá acreditar la parte actora.

Frente al hecho sexto: No me consta. No obstante, llama la atención que un familiar del señor Santiago Jauregui Bautista, hubiera determinado, sin ningún

conocimiento médico, la suspensión de los antibióticos que le habrían formulado al paciente. Con respecto a esta decisión unilateral adoptada por el familiar del señor Jauregui Bautista, no me opongo a su veracidad, por lo que solicito que sobre este hecho no se adelante ningún debate probatorio.

Frente al séptimo hecho: No me opongo al supuesto, según el cual el familiar del señor Jauregui Bautista, omitió informar acerca de la bacteria a fin que el paciente no continuara con el tratamiento de antibióticos.

Frente al octavo hecho: No me consta la atención médica recibida por parte del señor Jauregui Bautista. Es un supuesto fáctico que deberá acreditar la parte actora.

Frente al hecho noveno: Es la transcripción de la historia clínica del paciente Jauregui Bautista, por lo que tal cronología respecto a la atención deberá corroborarse con aquella.

Frente al hecho décimo: No es cierto. De acuerdo a la historia clínica, mi representada, la doctora Álvarez Echeverry, no fue la última médica tratante del señor Santiago Jauregui Bautista, si no, la doctora Mónica Patricia Vargas Ordóñez, identificada con cédula de ciudadanía N.º 66.827.295 y registro médico N.º 663.094.

Frente al hecho décimo primero: Es cierto parcialmente. La doctora Álvarez Echeverry formuló al señor Jauregui Bautista el medicamento hidromorfona en cantidad de 0.2 mg; sin embargo, **no es cierto** que aquel hubiera generado un evento adverso a la salud del paciente.

La finalidad del suministro de aquel fármaco fue disminuir el intenso dolor abdominal que presentó el señor Jauregui Bautista, dado que no fue posible controlarlo con acetaminofén, de conformidad con el reporte de 24 de agosto de 2017.

Frente al hecho décimo segundo: No es cierto. El diagnóstico efectuado por la doctora Álvarez Echeverry y la posterior formulación del medicamento hidromorfona al 0.2 mg. no fue lo que causó el fallecimiento del paciente, si no, contrario a lo afirmado por la parte demandante, fue su deteriorado cuadro clínico:

El señor Santiago Jauregui Bautista, al momento de su muerte (i) fue un paciente en estadio 5 con diálisis peritoneal, es decir, el más gravoso para la insuficiencia renal crónica, esto quiere decir que su Tasa de Filtración Glomerular [por sus siglas TFG] era menor a 15.

La TFG es el análisis de cuantifica la cantidad de mililitros de sangre que filtran los riñones por minuto [ml/min]. Entre menor sea la capacidad de filtración de sangre a través de los riñones o TFG, peor será la función renal.

Para una mejor comprensión, en la siguiente tabla se grafica los estadios de la insuficiencia renal crónica:

Estadio	**TFG ml/min**	**Descripción de la función renal**
1	90 o superior	Función renal normal
2	De 60 a 89	Ligera pérdida de la

		función renal
3A	De 45 a 59	Pérdida de ligera a moderada de la función renal
3B	De 30 a 44	Pérdida de moderada a grave de la función renal
4	De 15 a 29	Grave pérdida de la función renal
5	Menos de 15	Insuficiencia renal[2]

Dicho de otro modo, los riñones del señor Jauregui Bautista filtraban 15 mililitros de sangre por minuto, cuando lo normal es que sea de 90 mililitros o superior a ello.

Además, (ii) era un paciente de 88 años de edad, lo que en Colombia significa que, de acuerdo al Departamento Administrativo Nacional de Estadística [DANE], el paciente ya había superado la expectativa de vida proyectada[3], que para hombres es de 76.3 años[4].

Asimismo, (iii) el señor Jauregui Bautista, al ingresar el 24 de agosto de 2017, a la clínica Fundación Valle de Lili, tuvo un antecedente de hospitalización en ese mismo mes, por bacteremia por *clostridium tertium* y peritonitis asociada a la

[2] https://kdigo.org/ **KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease**
[3]https://www.dane.gov.co/index.php?option=com_content&view=article&id=853&Itemid=28&phpMyAdmin=3om27vamm65hhkhrtgc8rrn2g4
[4] Inclusive para el 2020.

infección del catéter de diálisis por la bacteria *Escherichia Coli BLEE positiva*. **De la última hospitalización tan solo habían trascurrido 11 días.**

Adicionalmente, (iv) el paciente al ingreso de su última hospitalización presentó un choque séptico, lo cual significa que todo su cuerpo sufría de una infección grave que le produjo entre otros síntomas, que su presión arterial fuera demasiado baja.

En suma, y únicamente para efectos de contextualizar al despacho, el señor Jauregui Bautista, el 24 de agosto de 2017, era un paciente de 88 años de edad, en el último estadio de una enfermedad terminal, como lo es la insuficiencia renal crónica, quien había sido dado de alta de su penúltima hospitalización hace apenas 11 días atrás, producto de una bacteremia o presencia de bacterias en la sangre, como consecuencia de la infección que se produjo a raíz del catéter peritoneal.

A pesar del severo cuadro clínico que precedía el ingreso del paciente a la clínica, se pretende endilgar responsabilidad a mi representada por su fallecimiento, por el suministro del fármaco hidromorfona de uso seguro y generalizado para pacientes renales crónicos, en única dosis y en una cantidad muy por debajo de la recomendada por la literatura médica, cuya finalidad **únicamente** tuvo calmar o disminuir el intenso dolor abdominal que no mejoró con acetaminofén.

Como se explicará más adelante, señor Juez, la parte actora no solo desconoce el protocolo médico establecido para pacientes renales, en el estado de salud que ingresó el señor Jauregui Bautista, el 24 de agosto de 2017, sino que omitió explicar, mucho menos, acreditar la relación causal entre los efectos del fármaco hidromorfona y su deceso.

Para la parte actora, el paciente de 88 años no falleció por haber padecido una enfermedad terminal, como lo es la insuficiencia renal crónica en el último estadio de gravedad, ni por haber ingresado a la clínica afectado por un choque séptico, sino, por la aplicación de un fármaco seguro, elaborado para aliviar fuertes dolores.

Tal criterio laxo, no solo desborda toda lógica argumentativa, sino que también desafía sin ningún material probatorio, el adecuado ejercicio de la *lex artis* por parte de mi prohijada.

V. Fundamentos de derecho de la defensa

5.1. Excepciones de mérito

En este acápite de la demanda, se centrará en la resolución del problema jurídico que plantea la demanda y su defensa, ¿el fallecimiento del señor Jauregui Bautista se produjo como consecuencia de la aplicación de hidromorfona?

A continuación, se expondrá al despacho que, contrario a lo expuesto por la parte demandante, el ejercicio profesional de la doctora Ingrid Álvarez Echeverry se ajustó a los protocolos establecidos para la atención de un choque séptico de un paciente aquejado por insuficiencia renal crónica en estadio 5 de la enfermedad.

5.1.1. Inexistencia de daño antijurídico

Para empezar, ha de indicarse que la doctrina autorizada ha definido el daño como[5]:

> *(…) toda afrenta a los intereses lícitos de una persona, trátese de derechos pecuniarios o de no pecuniarios, de derechos individuales o de colectivos, que se presenta como lesión definitiva de un derecho o como alteración de su goce pacífico y que, gracias a la posibilidad de accionar judicialmente, es objeto de reparación si los otros requisitos de la responsabilidad civil –imputación y fundamento del deber de reparar– se encuentran reunidos.*

A lo anterior, se añade lo que constituiría una obviedad, pero que en esta oportunidad tiene especial relevancia, y es que el daño debe ser antijurídico, es decir, *"el daño que el paciente no tiene la obligación jurídica de tolerar, particularmente por no ser inherente a su patología[6]".*

Este elemento de la estructuración de la responsabilidad civil extracontractual es el primero que debe analizarse, por lo que *"**si no hubo daño** o no se puede determinar o no se lo pudo evaluar, hasta allí habrá de llegarse; **todo esfuerzo adicional, relativo a la autoría y a la calificación moral de la conducta del autor resultará necio e inútil**, de ahí también el desatino de comenzar la indagación por la culpa de la demanda"[7].*

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[5] HENAO, Juan Carlos. Las formas de reparación en la responsabilidad del Estado. Revista de Derecho Privado N.º 28, enero – junio de 2015, p. 227 a 366.
[6] OVALLE, Polanía Ricardo León. "El dictamen pericial en procedimientos de responsabilidad civil médica". Ed. Leyer. 2021. P. 15.
[7] HINESTROZA, Fernando. *"Responsabilidad extracontractual: antijuricidad y culpa".* Citado en: HENAO, Juan Carlos. *"El daño. Análisis comparativo de la responsabilidad extracontractual del Estado en Derecho Colombiano y Francés."* Ed. Universidad Externado de Colombia. Bogotá. P.36.

Entonces, la ausencia del daño implica la inexistencia responsabilidad, de ahí la importancia en que el estudio del caso inicie por la verificación de aquel. El racionamiento que soporta esta premisa se concreta en que, si una persona no ha sufrido un daño, no resultaría viable estudiar el nexo de causalidad, menos aún, favorecerse de una condena, pues se enriquecería injustificadamente.

Señor Juez, en este acápite de la contestación, se argumentará y acreditará con el material probatorio anexo que, en el presente asunto, el demandante no ha sufrido un daño antijurídico debido al fallecimiento del señor Santiago Jauregui Bautista, comoquiera que su deceso se originó por la complicación inherente a su patología de insuficiencia renal crónica en estadio 5, aunado a un factor determinante riesgo como la avanzada edad del paciente.

La historia clínica del señor Jauregui Bautista da cuenta de lo siguiente:

1. Fue un paciente de 88 años de edad para el 2017, lo que significa que no solo era un adulto mayor [igual o más de 60 años[8]], sino una persona de la tercera edad, es decir, que había superado la esperanza de vida, en términos de la Corte Constitucional[9] ***(Prueba A).***

2. Ingresó el 24 de agosto de 2017 a la clínica Fundación Valle de Lili con diagnóstico de *shock* séptico, lo que se refiere a una afección grave que impide que el oxígeno y nutrientes llegue a las células, lo que causa la

[8] Corte Constitucional. Sentencia T – 015 de 2019.
[9] Corte Constitucional. Sentencia T - 013 de 2020. Por su parte, la calidad de "persona de la tercera edad" solo puede ostentarla quien no solo es un adulto mayor, sino que ha superado la esperanza de vida. No todos los adultos mayores son personas de la tercera edad; por el contrario, cualquier persona de la tercera edad será un adulto mayor.

muerte progresiva de aquellas y una falla sistemática de los órganos que produce el fallecimiento del paciente[10].

Tan solo con el propósito de dimensionar el grado de complejidad del diagnóstico del señor Jauregui Bautista, al margen, incluso de su patología de base [enfermedad renal terminal], ha de indicarse que, en un estudio estadístico de 2019, se estableció que la mortalidad de los pacientes que ingresan a salas de emergencias con *shock* séptico, es del 65.85%[11].

De la lectura de su historia clínica, la cual transcribió la parte actora en libelo inicial, desde el 2015, el paciente padeció al menos 3 infecciones [asociadas al catéter], 2 de las cuales se dieron en 2017, última que no pudo ser superada.

3. Adicionalmente, el señor Santiago Jauregui Bautista fue un paciente diagnosticado con insuficiencia renal crónica en etapa terminal y estadio 5, es decir, como se dijo con antelación, en la última fase de deterioro y funcionamiento de los riñones. Además, con diálisis peritoneal, lo que

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[10] http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S0186-48662017000300381. *versión impresa* ISSN 0186-4866- **Med. interna Méx. vol.33 no.3 Ciudad de México may./jun. 2017**
"El síndrome de respuesta inflamatoria sistémica (SIRS) se define por la presencia de al menos dos de las siguientes características: temperatura >38.3°C o <36°C, frecuencia cardiaca (FC) >90 latidos por minuto, taquipnea o PaCO2 <32 mmHg, leucocitos >12,000 o <4,000 o >10% bandas.2 La sepsis ocurre cuando el síndrome es concomitante con un foco infeccioso, ya sea probable o confirmado. La sepsis grave se define como sepsis más disfunción orgánica, hipoper-fusión o hipotensión (hiperlactatemia, oliguria, alteraciones en el estado mental). ***Finalmente, si no se trata la condición subyacente que genera la infección, se puede evolucionar al estado de choque séptico, el cual se define como hipotensión secundaria a sepsis con presión arterial sistólica (TAS) <90 mmHg o disminución de >40 mmHg en relación con la presión arterial basal a pesar de resucitación hídrica."***

[11] https://pubmed.ncbi.nlm.nih.gov/33877101/

implicó la implantación de un tubo blando **permanente** en su abdomen, denominado catéter.

A pesar que la diálisis peritoneal ofrece al paciente el beneficio de practicar el filtrado de sangre en casa, existe un alto riesgo de desarrollar infecciones, cuyo foco de generación de las bacterias es el propio catéter[12]. Esta clase de pacientes se exponen a un mayor riesgo de muerte, por la infección recurrente de aquel.

De hecho, la historia clínica del señor Jauregui Bautista indica que previo al último ingreso a la clínica Fundación Valle de Lili, él estuvo hospitalizado por una infección asociada al catéter. Incluso, después de su egreso, continuó con un cuadro clínico anormal con *"cifras tensionales bajas"*, asociadas a un fuerte dolor en su pierna izquierda, que irradiaba a su fosa ilíaca. Para el último ingreso al centro médico, el paciente presentó una tensión arterial demasiado baja de tan solo **60/30 mmHg**, lo que con medicación [norepinefrina] logró elevarse hasta 80/60 mmHg, cuando la presión arterial normal oscila entre 90/60 mmHg y 120/80 mmHg. Es decir, que incluso, con medicación, ni siquiera alcanzó el rango inferior de una presión arterial en condiciones estables. Esto únicamente para contextualizar la gravedad del estado de salud con el cual ingresó el paciente ***(Prueba B)***.

Adicionalmente, con relación a la incidencia de la causa eficiente del deceso del señor Jauregui Bautista, se aporta el dictamen pericial del doctor Leonardo Marín Restrepo, médico internista, intensivista y nefrólogo, actual Coordinador de

[12] https://www.nefrologiaaldia.org/es-articulo-peritonitis-e-infecciones-del-cateter-223

FMExpress – *Fresenius Medical Care*, compañía médica especializada en atención de pacientes hospitalizados o críticos en unidades de cuidado intensivo que requieren urgentes terapias extracorpóreas, tales como hemodiálisis y diálisis peritoneal.

En la experticia adjunta, el doctor Marín Restrepo concluyó, con base en el estudio de la historia clínica del señor Jauregui Bautista, que no es dable atribuirle al fármaco hidromorfona, el avanzado deterioro del cuadro clínico del paciente, dado que su suministro fue "*en una única dosis y en la quinta o décima parte de la cantidad que la literatura médica recomienda"* ***(Prueba C)***.

Asimismo, sostiene que factores de riesgo de mortandad, "*como la falla renal en estadio G5, que requería terapia de reemplazo renal, y los antecedentes de infecciones por gérmenes con patrón de resistencia antibiótica y gérmenes que solo afectan a pacientes con compromiso de su estado inmunológico de manera severa y sobre todo, su avanzada edad de 88 años, produjeron su deceso"*.

De lo anterior, razonablemente se infiere que el fallecimiento del señor Jauregui Bautista no se produjo como consecuencia del presunto error en el diagnóstico y tratamiento brindado por la doctora Álvarez Echeverry, como temerariamente lo afirmó la parte demandante, si no al deteriorado estado de salud que ingresó el paciente el 23 de agosto de 2021 a la clínica Fundación Valle de Lili, pues fue su comprometido cuadro clínico, y no otro factor, lo que determinó su deceso.

5.1.2. Exoneración de responsabilidad. Inexistencia de nexo causal. Procedimiento médico ajustado a la *lex artis*

Como es de conocimiento y se lo ha reiterado en este escrito, la ausencia de daño antijurídico imposibilita que se continúe con el estudio de los demás elementos de la responsabilidad civil extracontractual; sin embargo, **y en gracia de discusión**, partiendo de la falsa premisa de la demostración que, en efecto, la parte actora sufrió un daño antijurídico que no estuvo obligado a soportar, la doctrina plantea que para imputar un daño médico se exige la concurrencia de 2 elementos[13]:

(i) Que exista una relación de causalidad entre la actuación médica y el daño producido y;
(ii) Que esa actuación sea contraria a la *lex artis ad hoc*

Lo anterior implica que la parte demandante se enfrenta a 2 retos: el primero, demostrar que la actuación generó el daño antijurídico y, el segundo, que tal actuación no se ciñó a la *lex artis ad hoc*.

5.1.2.1. En este punto, se abordará la ausencia argumentativa y probatoria del primero de los elementos enunciados, y, en cambio, se explicará y acreditará el ejercicio profesional de mi prohijada se ajustó a los protocolos establecidos para atender a un paciente con insuficiencia renal crónico aquejado por *shock* séptico.

Ante todo, resulta oportuno expresar que la actuación de la doctora Álvarez Echeverry se circunscribió a una **obligación de medio**, no de resultado, esto es que su servicio médico consistió en poner a disposición del paciente todos los medios científicos y técnicos estudiados, con el propósito de intentar el restablecimiento de su salud, lo cual **no garantiza el resultado,** pero sí la

[13] GASCÓN, M. *"Valoración de la prueba y causalidad jurídica".* Ciencia Forense. Disponible en https://ifc.dpz.es/recursos/publicaciones/36/85/05gasconabellan.pdf. (2017).

demostración que se obró oportunamente, diligentemente y con apego a la *lex artis*[14].

Al respecto, ha de indicarse que la conducta diligente se traduce en la aplicación del principio de proporcionalidad, que no es algo distinto a comprender que la diligencia se limita a analizar que no exista una desproporción entre el coste de la adopción de una determinada medida médica y la probabilidad de producción de un daño[15].

Pues bien, la parte demandante alega que el fallecimiento del señor Santiago Jauregui Bautista se causó como una reacción adversa a la hidromorfona al 0.2 mg., mas no a que fue un paciente de 88 años, con insuficiencia renal crónica en el último estadio de la enfermedad, y aquejado por un deterioro generalizado de sus órganos como consecuencia del *shock* séptico.

A fin de contextualizar al despacho, se pone de presente que la sepsis y el shock séptico son problemas de salud importantes, que impacta a millones de personas en todo el mundo cada año y tiene una altísima incidencia de mortalidad, pues entre uno de cada tres y uno de cada seis de los afectados fallece, respetivamente[16].

[14] POLANÍA, Ovalle. Op Cit. P.20
[15] FACHAL, N. "Las reglas de la carga de la prueba en la responsabilidad civil médica: cuestiones polémicas. En Abel, X. y Picó J. (Ed.), Objeto y carga de la prueba civil. J.M. Bosch editor. Disponible en: https://www.globaleconomistjurist.com/BDI/doctrina/biblioteca/descargar.php?id=1337275. (2007).
[16] https://pubmed.ncbi.nlm.nih.gov/28101605/ Surviving_Sepsis_Campaign__International.21.pdf.

Otros estudios relacionados con el grado de mortalidad de pacientes que ingresan a atención hospitalaria con *shock* séptico, señalan que va desde el 26.7[17] al 41.9%[18], es decir que de cada 100 personas que llegan a la unidad de cuidados intensivos, de 26 a 41 fallecen.

Para comprender de mejor manera tales guarismos, debe mencionarse que enfermedades de un conocimiento más generalizado, como las cardíacas, tienen 20% de mortandad por infarto, la cual es altísima en términos de estadística médica[19].

En la historia clínica del paciente, se refiere que la primera medida de manejo que le fue suministrada, ante el intenso dolor padecido, fue el acetaminofén, y dado que no presentó ninguna mejoría, se escaló a un opioide seguro como lo es la hidromorfona, en una única dosis y en una cantidad mucho menor a la sugerida, con el único propósito de disminuir o contener el dolor que lo afectaba.

De otra parte, debe manifestarse que las reacciones a los medicamentos son inevitables de predecir, salvo la penicilina, que es posible advertir alguna consecuencia adversa con la aplicación del benzetacil. En otras palabras, el paciente puede ser alérgico, incluso, al acetaminofén, pero si nunca se lo han aplicado, no existen pruebas para anticipar una complicación derivada del mismo.

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[17] https://pubmed.ncbi.nlm.nih.gov/26414292/ Assessment of Global Incidence and Mortality of Hospital-treated Sepsis Current Estimates and Limitations
[18] https://pubmed.ncbi.nlm.nih.gov/32572531/ Incidence and mortality of hospital and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis.
[19] https://pubmed.ncbi.nlm.nih.gov/29246884/ **Mortality of Myocardial Infarction by Sex, Age, and Obstructive Coronary Artery Disease Status in the ACTION Registry–GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines)**

Con respecto a lo enunciado, resulta pertinente remitirse al dictamen presentado en esta oportunidad procesal, estudio en el cual el profesional idóneo precisó que es imposible prever eventos adversos al suministro del medicamento (Prueba C).

5.1.2.2. La correcta observancia de los protocolos clínicos y apego a la *lex artis ad hoc*

El acto médico o quirúrgico corresponde a un ejercicio legal de la profesión por una persona entrenada académicamente, el cual debe reunir unas especiales características relacionadas con el autor, la profesión, la complejidad del paciente y la influencia de factores endógenos del mismo. Bajo esta consideración, la Corte Suprema de Justicia ha indicado que los siguientes son los factores que deben evaluarse para considerar que la actividad médica se ha ajustado a la *lex artis ad hoc*[20]:

a) La *lex* es una regla de medición de una conducta a la luz de unos baremos que permiten su valoración.
b) La actuación médica debe adecuarse o corresponder a la generalidad de conductas profesionales en casos análogos.
c) El correcto uso de la técnica según la ciencia.
d) El estado de enfermedad del paciente
e) La valoración de cada caso concreto, pues son las peculiaridades de cada cuadro clínico las que influyen en un sentido o en otro, el resultado de la práctica médica.

[20] Corte Suprema de Justicia. Sala de Casación Civil. Sentencia de 30 de enero de 2001. M. P. José Fernando Ramírez Gómez. Expediente N.º 5507.

Para empezar, se pone de manifiesto que el protocolo de sedación de la clínica Fundación Valle de Lili indica que la hidromorfona tiene un metabolismo hepático, esto es, que se elimina a través del hígado y no por los riñones, por lo que es efectivo y no genera daño a un paciente con insuficiencia renal.

Además, señala que tal opioide debe suministrarse si la intensidad del dolor al ingreso es mayor a 4/10 en la escala EVN, **en dosis cada 15 minutos que no superen los 2 mg. *(Prueba C)*.**

En este punto, recuérdese que inicialmente, según lo anotado en la historia clínica (Prueba A), únicamente se decidió pasar a la administración de hidromorfona comoquiera que el dolor intenso que referenció el paciente no mejoró con acetaminofén.

De acuerdo a la experticia adjunta, el perito expuso que la hidromorfona "*es el medicamento de elección en los pacientes con enfermedad renal crónica, es tan efectivo como la morfina y 8,5 veces más poderoso por vía endovenosa para el control del dolor, con una baja unión a proteínas y una vida media de 39 horas"*.

Asimismo, expresó que los efectos adversos neurológicos, como agitación, mioclonías y tremor se presentan en dosis repetitivas, lo cual para el actual asunto no fue formulado, dado que se le aplicó en **una única dosis** en una cantidad muy inferior a la recomendada.

Sumado a lo anterior, debe señalarse que el paciente presentó nivel de 5,4 g/dl de hemoglobina en la sangre, es decir demasiado bajo, en comparación con un nivel normal que debe ser igual o superior a 10 g/dl, lo que representó que el señor

Santiago Jauregui Bautista sufría de un cuadro anémico debido a una eventual hemorragia interna desconocida, por lo que la doctora Álvarez Echeverry transfundió al paciente inmediatamente, a fin de evitar el avance de su deteriorado estado de salud. Este, sin duda, fue un factor endógeno que escapaba al control médico.

5.2. Innominada

Solicito respetuosamente, señor Juez, se dé aplicación a lo prescrito en el artículo 282 del Código General del Proceso, según el cual cuando el Juez halle probados los hechos que constituyen una excepción, deberá reconocerla oficiosamente en la sentencia.

VI. Pruebas

6.1.- Las solicitadas en la demanda por la parte actora

A. Dictamen pericial

La parte demandante solicitó se oficiara al Instituto Nacional de Medicina Legal y Ciencias Forenses para que con base en la historia clínica del paciente se determinara si se incurrió en error del diagnóstico y tratamiento brindado debido a la aplicación de hidromorfona.

Al respecto, debe señalarse que el artículo 227 de la Ley 1564 de 2012 determina que la parte que pretenda valerse de un dictamen pericial **deberá aportarlo** en la respectiva oportunidad para pedir pruebas[21]. Para la parte actora, la oportunidad

[21] **Artículo 227.** Dictamen aportado por una de las partes. **La parte que pretenda valerse de un dictamen pericial deberá aportarlo en la respectiva oportunidad para pedir pruebas**. Cuando

para solicitar el decreto y práctica de pruebas es, según los artículos 82[22] y 173[23] de la mencionada norma, **la instauración de la demanda**, por lo que precluido dicho término, toda solicitud probatoria deviene extemporánea. Y, en consideración a que las citadas disposiciones normativas procedimentales son de orden público y, en consecuencia, de obligatorio cumplimiento, de acuerdo a lo regulado en el artículo 13 del mismo código[24], ha de concluirse que no resulta dable decretarla, dado que, se reitera, la parte actora debió aportar el dictamen sobre el cual sustentaría sus pretensiones.

El incumplimiento del principio del *onus probandi*

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el término previsto sea insuficiente para aportar el dictamen, la parte interesada podrá anunciarlo en el escrito respectivo y deberá aportarlo dentro del término que el juez conceda, que en ningún caso podrá ser inferior a diez (10) días. En este evento el juez hará los requerimientos pertinentes a las partes y terceros que deban colaborar con la práctica de la prueba.
El dictamen deberá ser emitido por institución o profesional especializado.

[22] Ley 1564 de 2012. Artículo 82. Requisitos de la demanda. Salvo disposición en contrario, la demanda con que se promueva todo proceso deberá reunir los siguientes requisitos:
(…)
6. La petición de las pruebas que se pretenda hacer valer, con indicación de los documentos que el demandado tiene en su poder, para que este los aporte.

[23] Ley 1564 de 2012. Artículo 173. Oportunidades probatorias. Para que sean apreciadas por el juez las pruebas deberán solicitarse, practicarse e incorporarse al proceso dentro de los términos y oportunidades señalados para ello en este código.
En la providencia que resuelva sobre las solicitudes de pruebas formuladas por las partes, el juez deberá pronunciarse expresamente sobre la admisión de los documentos y demás pruebas que estas hayan aportado. El juez se abstendrá de ordenar la práctica de las pruebas que, directamente o por medio de derecho de petición, hubiera podido conseguir la parte que las solicite, salvo cuando la petición no hubiese sido atendida, lo que deberá acreditarse sumariamente.
Las pruebas practicadas por comisionado o de común acuerdo por las partes y los informes o documentos solicitados a otras entidades públicas o privadas, que lleguen antes de dictar sentencia, serán tenidas en cuenta para la decisión, previo el cumplimiento de los requisitos legales para su práctica y contradicción.

[24] Ley 1564 de 2012. Artículo 13. Observancia de normas procesales. Las normas procesales son de orden público y, por consiguiente, de obligatorio cumplimiento, y en ningún caso podrán ser derogadas, modificadas o sustituidas por los funcionarios o particulares, salvo autorización expresa de la ley.

Este principio procesal el *"Onus probandi, incumbit actori y Reus, in excipiendo, fit actor"*, se halla positivizado en el artículo 167 del Código General del Proceso[25], al preceptuar que *"Incumbe a las partes probar el supuesto de hecho de las normas que consagran el efecto jurídico que ellas persiguen"*, o, en otras palabras, corresponde a la parte que formula la demanda o a quien la contesta, acreditar los supuestos de hecho que alega o las excepciones que propone[26].

Así, quien pretenda el amparo de un derecho fundamental debe demostrar los hechos en que se funda su pretensión, a fin de que la determinación del Juez, obedezca a la certeza y convicción de que se ha quebrantado o amenazado el derecho[27].

Por su parte, la Corte Suprema de Justicia ha expresado que en el proceso judicial se exige, en mayor o menor grado, que cada uno de los litigantes aporte al Juez los suficientes elementos de convicción para el esclarecimiento de la verdad, propósito que por lo general concierne al demandante respecto de sus pretensiones, y al demandado frente de las excepciones.

Y, bajo esa óptica, el Alto Tribunal, ha precisado que al juzgador no le basta la sola enunciación de las partes para decidir la controversia, puesto que ello resultaría en permitir que el mero discurso persuasivo que se presenta, sea provechoso para la

[25] Norma a la cual resulta válidamente remitirse en virtud de lo señalado en el artículo 4 del Decreto 306 de 1992, "*Por el cual se reglamenta el Decreto 2591 de 1991*", el cual dispone:

> *"De los principios aplicables para interpretar el procedimiento previsto por el Decreto 2591 de 1991. Para la interpretación de las disposiciones sobre el trámite de la acción de tutela previstas por el Decreto 2591 de 1991 se aplicarán los principios generales del Código de Procedimiento Civil, en todo aquello que no sean contrarios a dicho decreto."*

[26] Corte Constitucional. Sentencia T – 733 de 2013.
[27] Corte Constitucional. Sentencia T – 131 de 2017.

sentencia; "*de ahí que, la ley impone a cada extremo del litigio la tarea de traer al juicio de manera oportuna y conforme a las ritualidades del caso, los elementos probatorios destinados a verificar que los hechos alegados efectivamente sucedieron, o que son del modo como se presentaron, todo con miras a que se surta la consecuencia jurídica de las normas sustanciales que se invocan*"[28].

La Corte Constitucional ha añadido que este principio impone a la parte que asuma un rol activo en el litigio y no únicamente se refugie en la diligencia del Juez[29]. Así pues, "*las partes en el proceso deben cumplir con el deber de diligencia en lo que pretenden probar. Ninguna debe obrar con inercia porque ello causa que las consecuencias adversas de la decisión sean deducidas en su contra. El proceso no premia la estrategia sino la solución del conflicto con la participación de las partes[30].*"

La propia Corte, en el análisis de la sentencia de constitucionalidad del artículo 167 de la Ley 1564 de 2012[31], ha distinguido las excepciones al principio de la carga de la prueba, es decir, los eventos en los cuales se releva a la parte de acreditar los supuestos fácticos que alega o las excepciones que propone. Estas son:

a) Hechos notorios: Amplia difusión del hecho, por lo que cualquiera se halla en la posibilidad de observarlo.

[28] Corte Suprema de Justicia, Sala de Casación Civil, Sentencia del 28 de mayo de 2010. Exp. 23001-31-10-002-1998-00467-01.M.P. Edgardo Villamil Portilla.
[29] Corte Constitucional. Sentencia C-086 de 2016.
[30] Corte Constitucional. Sentencia T-733 de 2013.
[31] Corte Constitucional. Sentencia C-086 de 2016.

b) Afirmaciones o negaciones indefinidas: Hechos que por su carácter indeterminado de tiempo, modo o lugar resultan lógica u ontológicamente imposible demostrarlos por quien los aduce.

c) Presunciones legales o de derecho: Solo se requiere probar el hecho conocido que hace creíble el hecho principal y desconocido, de cuya prueba está exento[32].

De lo anterior, se aduce que la afirmación según la cual se pretende endilgar responsabilidad a mi representada, consistente en que la formulación de 0.2 mg. de hidromorfona causó la muerte del señor Jauregui Bautista, no se ajusta a ninguno de los 3 eventos en los que la Corte Constitucional ha manifestado que no se requiere acreditar el supuesto fáctico que sirve de sustento de las pretensiones de la demanda o de las excepciones de la defensa.

A la parte actora le correspondía acreditar que la presunta mala práctica médica tuvo una incidencia suficiente y directa en el deceso del paciente, o dicho de otro modo, que fueron los 0.2 mg. de hidromorfona los que causaron su fallecimiento, y no el *shock* séptico con el cual ingresó a la unidad de cuidados intensivos de la clínica demandada, aunado a su avanzada edad y la enfermedad renal en su último estadio.

Evidentemente, la parte demandante tuvo a su alcance la posibilidad de presentar una experticia que, basado en conocimientos técnicos sobre la materia, dictamine

[32] Corte Constitucional. Sentencia C – 070 de 1993.

que el deceso del señor Jauregui Bautista tuvo como causa eficiente los 0.2 mg. de hidromorfona; no obstante, permitió que su oportunidad probatoria precluyera.

Por lo esgrimido, solicito, señor Juez, se niegue el decreto y práctica de la prueba pericial solicitada por la parte demandante, puesto que no se circunscribe a los postulados normativos citados líneas atrás.

6.2- Las que se aportan o solicitan:

A.- Documentales

Prueba A. Historia clínica específica del señor Santiago Jauregui en la clínica Fundación Valle de Lili. 7 folios.
Prueba B. Historia clínica general del señor Santiago Jauregui en la clínica Fundación Valle de Lili. 15 folios.
Prueba C. Protocolo de sedación de la Clínica Fundación Valle de Lili. 3 folios.

B. Testimoniales

- Sírvase señor Juez, decretar y practicar la declaración del doctor Gustavo Ospina, médico intensivista de turno del 25 de agosto de 2017, en la clínica Fundación Valle de Lili. El objeto de esa prueba se concreta en precisar la razón científica por la cual se resolvió administrar al señor Santiago Jauregui Bautista, 0.2 mg de hidromorfona.
-
- El testigo puede ser citado a través de la dirección electrónica que se indican en el acápite de notificaciones.

C. Interrogatorio de parte

Asimismo, con fundamento en lo prescrito en el artículo 198 de la Ley 1564 de 2012, solicito se decrete el interrogatorio de parte de la doctora Ingrid Álvarez Echeverry. El objeto de esta prueba consiste en indagársele acerca de la valoración y decisión de la formulación del medicamento hidromorfona en una cantidad de 0.2 mg.

D. Dictamen pericial

En atención a lo regulado en los artículos 226 y siguientes de la Ley 1564 de 2012, adjunto la experticia del doctor Leonardo Marín Restrepo, identificado con C.C. N.º 94366458 de Tuluá y registro médico N.º 760189-97, médico internista, intensivista y nefrólogo, quien basado en sus conocimientos profesionales, ha presentado su concepto frente al uso de la hidromorfona en el señor Santiago Jauregui Bautista, a partir del estudio de la historia clínica del paciente. 308 folios.

Frente a esta prueba anexa, solicito sea practicada de acuerdo a lo prescrito en los artículos 226 y 227 del Código General del Proceso y, en ese sentido, se cite al perito para que rinda su experticia en la respectiva audiencia de pruebas.

El perito puede ser citado a través de la dirección electrónica que se indican en el acápite de notificaciones o a la dirección que se registra en su dictamen.

VII.- Anexos

Las pruebas atrás enunciadas

VIII.- Notificaciones

Agradezco que las notificaciones judiciales sean enviadas a la dirección electrónica litis.aortega@gmail.com

Del señor Juez, atentamente,

Andrés Fernando Ortega Ordóñez
C.C. No. 1.085.277.335
T.P. No. 218.687 del C. S. de la J.

PRUEBA A

FUNDACIÓN VALLE DEL LILI
Excelencia en Salud al servicio de la comunidad

Avenida Simón Bolivar
Carrera 98 No. 18 - 49
Conmutador 032 3319090
Fax 032 3316728
Nit. 8903241775
www.valledellili.org
CALI - COLOMBIA

HISTORIA CLÍNICA UCI

DATOS GENERALES

Paciente: **SANTIAGO JAUREGUI BAUTISTA**			Doc.Identificación: **CC 6061103**
Fecha Nacimiento: **26.06.1929**	Edad: **88** Años	Sexo: **M**	Nº. Episodio: **4711194**
Aseguradora: **NUEVA EPS S.A. RC**			Nº. Historia Clínica: **779141**
Médico Tratante: **VELASCO BAYUELO, CARLOS ALBERT**	MEDICINA INTERNA		

El paciente viene recibiendo medicamentos antes del ingreso?

Realizó Conciliación de estos medicamentos?

Explique por qué no prescribe medicación previa?

Responsable:

Cédula:

RM:

Valido como Firma Electrónica

Factor de Aislamiento

Evolución UCI

Fecha: 24.08.2017 09:47:40 **Categoría de cuidado:** Cuidados Intensivos

Intensivista de turno: DR JORGE MARTINEZ

Problemas Últimas 24 Horas

EVOLUCION UCI DIA 24.08.2017
NOMBRE: SANTIAGO JAUREGUI BAUTISTA
CC: 6061103
EDAD : 88 años

DIAGNOSTICOS:
- Shock séptico
-- Bacteremia a descartar?
-- Neumonía asociado a los cuidados de la salud?
- Insuficiencia renal cronica estadio V

ANTECEDENTES PERSONALES:
-Patológicos: ERC estadio 5 en diálisis peritoneal.
-Farmacológicos: Acido fólico
-Alérgicos: Niega
-Quirúrgicos: Niega
-Transfusiones:

PARACLNICOS IMAGENOLOGICOS:
- Rx de torax 23.08.2017: Atelectasia plana en base pulmonar derecha, derrame pleural leve izquierdo
-EVDA 23.08.2017: Esofagitis erosiva

EXAMEN FISICO:
Paciente en cama, tranquilo, hemodinamicamente estable, orientado en tiempo, persona y lugar.

CARDIOVASCULAR: TA:102/57 TAM :67 MMHG FC :87 LPM. Ruidos cardiacos rítmicos, sin soplos. Norepinefrina 0.2mcg/kg/min
LACTATO: 1,83
EKG: Bloqueo de 1er grado, Ondas T negativas en DI-AVL

RESPIRATORIO: FR: 18 , SO2:96%. Murmullo vesicular normal, no ruidos sobreagregados. Gases Arteriales: pH: 7,38, PCO2:26, PO2:224,HCO3:15, BE:-9. Rx torax : Atelectasia plana en base pulmonar derecha, derrame pleural leve izquierdo

ABDOMEN: Blando, depresible, sin dolor a la palpación, sin masas ni megalias. Cateter de dialisis peritoneal sin signos inflamatorios evidentes.

EXTREMIDADES: móviles, sin edemas, llenado capilar < 2 segundos.
RENAL: Diuresis espontanea adecuada
SODIO:141 POTASIO:4,1 CLORO: 103 CREAT:9,7 BUN:39

HEMATOLOGICO: sin signos de sangrado activo.
HB:10,2 HTO:31,5 PTS:373000 PT:18 PTT:32

INFECCIOSO: T:36,4 °c. SIN PICOS FEBRILES
LEUCOS:12320 NEUTROS:88 LINFOS:5 PCR: 25
HEMOCULTIVO – UROCULTIVO: En proceso
ANTIBIOTICO FECHA: Vancomicina/meropenem (FI:24/08/2017)

NEUROLOGICO: No deficit motor ni sensitivo, reflejos ++/++++, respuesta plantar flexora bilateral, glasgow 15/15

ANALISIS / PLAN:
Paciente con antecedente de ERC estadio V en diálisis peritoneal. Con hospitalización reciente en la institución por Bacteremia por clostridium tertium y peritonitis asociada a catéter de diálisis por E. coli BLEE positiva. Se dio alta médica el 13.08.2017 con tratamiento ambulatorio durante 5 días con metronidazol. Ingresa por cuadro clínico de dos días de evolución consistente en dos episodios de hematemesis, un episodio de melena y un episodio de rectorragia. Asociado presenta tos con expectoración blanquecina y dolor de tipo urente en miembro inferior derecho con irradiación a fosa iliaca ipsilateral. Al ingreso taquicardico, hipotenso y consignos de hipoperfusión. Se inicia reanimación hídrica, soporte con vasopresor, reposicion de K e inician cubrimiento antibiótico con Vancomicina/meropenem. En el momento, paciente en regulares condiciones generales, hipoperfundido, con TAM limítrofes dependiente de goteo de norepinefrina. En paraclínicos de control con acidosis metabólica, leucocitosis mas neutrofilia, pcr elevadae hipocalcemia. Se administra bolo 300cc de SSN con mejoría de TAM. Continua con soporte de norepinferina 0,2mcg/kg/min. Se suspendereposición central de K. Se solicita cultivo y gramm de catéter de diálisis peritoneal. Pendiente realización de dialisis peritoneal. Debe continuar manejo integral en UCI por alto riesgo de descompensación hemodinámica. Se le explica a su hijo situacióncompleja situación clinica actual entiende y acepta.

Dr: Fabian Campos Medico Hospitalario De Uci
Carlos Velez Interno ICESI
Dr: Jorge Martinez Internista/intensivista.

Ayudas diag. últ 24 horas : Sin estudios pendientes

Responsable: MARTINEZ BUITRAGO, JORGE EDUARDO INTENSIVISTA - MEDICINA INTERNA

Cédula: 16637341

RM: 567288

Valido como Firma Electrónica

Fecha: 24.08.2017 18:09:26 **Categoría de cuidado:** Cuidados Intensivos

Intensivista de turno: DR JANER VARON

Problemas Últimas 24 Horas

NOMBRE: SANTIAGO JAUREGUI BAUTISTA
CC: 6061103
EDAD : 88 años

DIAGNOSTICOS:
- Shock séptico de origen a determinar
  Foco abdominal a descartar
- Insuficiencia renal cronica estadio V

ANTECEDENTES PERSONALES:
-Patológicos: ERC estadio 5 en diálisis peritoneal.
-Farmacológicos: Acido fólico
-Alérgicos: Niega
-Quirúrgicos: Niega
-Transfusiones:

ANALISIS / PLAN:
Paciente en la novena década de la vida conocido en nuestra institución con relación a enfermedad renal crónica E V en diálisis peritoneal, quien se encuentra hospitalizado en el contexto de shock séptico de origen no filiado, desde su ingreso con sospecha de foco pulmonar sin embargo al revisar radiografias previas no se evidencian cambios significativos,con persistencia de atelectasia basal izquierda y leve derrame pleural ,no se descarta origen abdominal dados sus multiples antecedentes. desde su ingreso hipotenso, hipoperfundido con acidosis metabolica quien inicialmente respondió de forma transitoria a liquidos endovenosos con depuración de lactato, sin embargo requirió posteriormente goteo de norepinefrina y vasopresina por cifras tensionales bajas.
Actualmente con cobertura antibiótica meropenem – vancomicina con cultivos en proceso incluyendo de liquido peritoneal dado su antecedente de hospitalización reciente por bacteremia por clostridium tertium y peritonitis asociada a catéter de diálisis por E.coli BLEE positiva, se continua manejo medico instaurado en unidad de cuidado intensivo dada su delicada condición clínica.
Se explica claramanete a su hijo quien entiende y acepta.

Dr: Fabian Campos Medico Hospitalario De Uci
Dr: Janer Varon Internista/intensivista

Ayudas diag. últ 24 horas : Sin estudios pendientes

Responsable: VARON ARENAS, JANER MEDICINA INTERNA - CUIDADO INTENSIVO ADULTOS

Cédula: 94491803

RM: 7635482002

Valido como Firma Electrónica

Fecha: 24.08.2017 19:52:31 **Categoría de cuidado:** Cuidados Intensivos

Intensivista de turno: DR GUSTAVO OSPINA

Problemas Últimas 24 Horas

EVOLUCION UCI NOCHE 24.08.2017
NOMBRE: SANTIAGO JAUREGUI BAUTISTA
CC: 6061103
EDAD : 88 años

DIAGNOSTICOS:
- Shock séptico
-- Bacteremia a descartar
--- absceso psoas??
- Insuficiencia renal cronica estadio V

ANTECEDENTES PERSONALES:
-Patológicos: ERC estadio 5 en diálisis peritoneal.
-Farmacológicos: Acido fólico
-Alérgicos: Niega
-Quirúrgicos: Niega
-Transfusiones:

PARACLNICOS IMAGENOLOGICOS:
- Rx de torax 23.08.2017: Atelectasia plana en base pulmonar derecha, derrame pleural leve izquierdo
-EVDA 23.08.2017: Esofagitis erosiva

EXAMEN FISICO
t 34.2 fc 85 x min ta 110/48 tam 69
sat 100% fio2 .5 fr 24
norepienfrina 80cc/h (0.35micg(kg/min) vasopresina 0.03UI/min
diuresis 250cc balance 1512 cc balane general 1512 cc
glucos 146mg/dl
Paciente en cama, tranquilo, hemodinamicamente estable, orientado en tiempo, persona y lugar.
Ruidos cardiacos rítmicos, sin soplos.
Murmullo vesicular normal, no ruidos
sobreagregados. Blando, depresible, sin dolor a la palpación, sin masas ni megalias. Cateter de dialisis peritoneal sin signos inflamatorios evidentes. extremidades móviles, sin edemas, llenado capilar < 2 segundos. No deficit motor ni sensitivo, reflejos ++/++++, respuesta plantar flexora bilateral, glasgow 15/15

gases pH 7.31 pco2 29 po2 92 hco3 14 sat 96 be -10
gases venosos pco2 35 sat 57
na 139 k 3.8 ac lactico 1.8

ANALISIS / PLAN:
Paciente con antecedentes anotados , hospitalziación en esta misma sala reciente por PBE y bacteremia por clostidium tertrium.
Ahora con cuadro de dolor en miembto inferior derecho y fosa iliaca derecha , en ocasiones asociado a alodinia, además deposciiones melenicas, curiosamente no ha habido caída de Hb, la EVDa fue normal y esta pendiente realización de colonosocopia.
Llamativamente en choque con diferencial de presion de pulso amplio que hace pensar en choque distributivo, el ac lactico se ha depurado , sin embargo hay un delta de co2 amplio y saturación venosa baja , consdiero oportuno inicio de dobutamina para mejorar flujo.
No cursa con neumonía como se habpia cosndierado ,s e revisan placas previas se videncia el mismo derrame basal izquierdo y atelectasias basales ya conocidas, me preocupa que el dolor hacia miembro inferior sea manifestaión de algo mas , discutire con intensivista de turno la cosnideración de realizar una imagen abdomino-pelvica para descartar absceso a nivel de psoas, ya que no tenemos fuenre de infección lñocalizada, el liquido peritoneal es negativo para PBE, Por el momento continuamos soporte y pauta antibiotica establecida .
Paciente con algo de diuresis residual se solicita urocultivo.

Ingrid Alvarez Fellow UCI

Ayudas diag. últ 24 horas : Anormales **Desc. anorm :** VER HC

Responsable: ALVAREZ ECHEVERRY, INGRID KATHERINE MEDICINA INTERNA

Cédula: 1085245468

RM: 52 1740 2009

Valido como Firma Electrónica

Fecha: 25.08.2017 00:34:38 **Categoría de cuidado:** Cuidados Intensivos

Intensivista de turno: DR GUSTAVO OSPINA

Problemas Últimas 24 Horas

nota de evento.
Paciente que posterior a cateterización vesical presenta dolor abdominal intenso que no mejora con accetaminofen.
Se decide paso de hidromorfona 0.2mg .
Posterior a paso de medicamento presenta estupor, hipoperfusión , y palidez generalziada , ante disminución de respuesta neurológicase decide revertir con naloxona 1 ampolla , sin embargo paciente persiste sin respuesta , y se decide iot en el cambio de posicion presenta asistolia y se inicia RCCP con masaje cardiaco , se pasa bolo de

liquidos ev y se inicia adrenalina , ciclos 30x 2 (masaje respiracion) y c/ 3 minutos adrenalina se pasa 6 dosis. Durante paro dos bradicardias extremas con pulso se pone dos dosis de atropina .
Dada la historia d ehipocalcemia , se pasan 20 mg de gluconato de calcio, y bicarbonato 100meq.
Paciente sale de ritmo de paro a sinusal , posteriormente presenta ritmo con extrasistoles frecuentes y taquicardia ,s e pasa dos ampollas de calcio- con lo que se estabiliza membrana .
eco control con corazon aaturdido severa depersion miocardica se indica dobutamina a 15 micg/kg/min.
Se toman paraclinicos de control Hb 5.4 se indica trasfusion .
Pendiente paraclinicos
se explica a hijo riesgod e fallecer y derequerir terapia de reempalzo renal .

Ingrid Alvarez Fellow UCI

Ayudas diag. últ 24 horas : Sin estudios pendientes

Responsable: ALVAREZ ECHEVERRY, INGRID KATHERINE MEDICINA INTERNA

Cédula: 1085245468

RM: 52 1740 2009

Valido como Firma Electrónica

Fecha: 25.08.2017 01:10:55 **Categoría de cuidado:** Cuidados Intensivos

Intensivista de turno: DR GUSTAVO OSPINA

Problemas Últimas 24 Horas

reporte de paraclinicos
acidosis metabolica severa con hiperlactatemia .
hiperkalemia severa
mientras se monta maquina de dialisis se indica bolo de bicarbonato de 50 miequ seguida de infusion de bicarbonato a 70cc/h
se realzairá paso de cateter mahurkar recto 19 .
se indica dialisis filtro FX 80 mezcla 1 a 140 ml/min sin UF.
Familiar de paciente (edinson Jauregui) me solicita grabación de información. se acepta.

Ingrid Alvarez Fellow UCI

Ayudas diag. últ 24 horas : Sin estudios pendientes

Responsable: ALVAREZ ECHEVERRY, INGRID KATHERINE MEDICINA INTERNA

Cédula: 1085245468

RM: 52 1740 2009

Valido como Firma Electrónica

Fecha: 25.08.2017 02:59:07 **Categoría de cuidado:** Cuidados Intensivos

Intensivista de turno: DR GUSTAVO OSPINA

Problemas Últimas 24 Horas

nota adicional
Paso de cateter mahurkar.
previa asepia antisepsia
colocaciond e campos quirurgicos.
se visualiza con guia eocgrafica vena femoral izqueirda , se punciona avnaza guia se visualiza con eco que esta en vaso , se dilata y avanza cateter , al recuperar guia se quiebra y tengo que retirarla con cateter , por lo que se debe abrir nuevo cateter mahurkar.
se realiza via ecografica puncion derecha , varios intentossin retorno , se logra canazlizar vena se hepariniza y se fija
se iniciar TRR.

Ingrid Alvarez Fellow UCI

Ayudas diag. últ 24 horas : Sin estudios pendientes

Responsable: ALVAREZ ECHEVERRY, INGRID KATHERINE MEDICINA INTERNA

Cédula: 1085245468

RM: 52 1740 2009

Valido como Firma Electrónica

Fecha: 25.08.2017 10:14:23 **Categoría de cuidado:** Cuidados Intensivos

Intensivista de turno: DRA. MÓNICA PATRICIA VARGAS

Problemas Últimas 24 Horas

EVOLUCION UCI DIA - 25.08.2017
NOMBRE: SANTIAGO JAUREGUI BAUTISTA, EDAD : 88 AÑOS, CC: 6061103

DIAGNOSTICOS:

- Shock séptico de causa no clara
- Disfunción multiorgánica
- Insuficiencia renal cronica estadio V

ANTECEDENTES PERSONALES:
-Patológicos: ERC estadio 5 en diálisis peritoneal.
-Farmacológicos: Acido fólico
-Alérgicos: Niega
-Quirúrgicos: Niega
-Transfusiones:

PARACLNICOS IMAGENOLOGICOS:
- Rx de torax 23.08.2017: Atelectasia plana en base pulmonar derecha, derrame pleural leve izquierdo
-EVDA 23.08.2017: Esofagitis erosiva

EXAMEN FISICO:
Paciente en malas condiciones generales, polisoportado con norepipnefrina, vasopresina y dobutamina. En ventilación mecánica invasiva y con hemofiltración continua. Sin sedoanalgesia. glasgow 3. pupilas anisocóricas.

CARDIOVASCULAR: FC: 106 /lpm TA: 103/45 mmHg TAM: 61 mmHg PVC 11
Ruidos cardiacos rítmicos, sin soplos. Norepinefrina 300 cc/hr, Vasopresina 12 cc/hr, Dobutamina 9 cc/hr

RESPIRATORIO: FR: 21 /rpm SatO2: 97% FIO2: 0.60 PEEP 8 IMV 24
Murmullo vesicular normal, no ruidos sobreagregados.
- Gases art/ven Ph: 7.16 pCO2 26/38 pO2 84 HCO3 9.3 SatO2 94/54% BE
-19
GASTROINTESTINAL: Abdomen blando, ddolor no evauable por estado neurológico. Cateter de dialisis peritoneal sin signos inflamatoriosevidentes.

HEMATOLÓGICO: Sin evidencia de sangrado
- Hb: 11 Hto: 33% Pqt: 136.000

INFECCIOSO: Temperatura 34.5°C
- Leucocitos: 9780 Neutrs:77 % Linfs:9 % // PCR: 9.5
HEMOCULTIVO – UROCULTIVO: En proceso
ANTIBIOTICO FECHA: Vancomicina/meropenem (FI:24/08/2017)

RENAL: Diuresis 250 cc, balance 6374 cc, balance acumulado 6374 cc
- Na: 140 Cl: 99 K: 3.7 BUN: 11 Cr: 2.0

METABÓLICO: Glucometrías 146-163-258 mg/dl

EXTREMIDADES: Simétricas, hipoperfundidas, pipel motetada, frialdad distal, llenado capiplar mayor a 5 segundos.

ANALISIS Y PLAN:
Paciente con antecedente de ERC estadio V en diálisis peritoneal. Con hospitalización reciente en la institución por Bacteremia por clostridium tertium y peritonitis asociada a catéter de diálisis por E. coli BLEE positiva. Se dio alta médica el 13.08.2017 con tratamiento ambulatorio durante 5 días con metronidazol. Ingresa por cuadro clínico de dos días de evolución consistente en dos episodios de hematemesis, un episodio de melena y un episodio de rectorragia. Asociado presenta tos con expectoración blanquecina y dolor de tipo urente en miembro inferior derecho con irradiación a fosa iliaca ipsilateral. Al ingreso taquicardico, hipotenso y consignos de hipoperfusión. Se inicia reanimación hídrica, soporte con vasopresor, reposicion de K e inician cubrimiento antibiótico empirico con Vancomicina/meropenem. Se realiza cateterismo vesical para toma de muestra de urocultivo, después de este procedimientopresenta dolor severo por lo que se administró hidromorfona 0.2mg, posterior a lo cual presenta deterioro del estado de consciencia y signos de hipoperfusión por lo que se decide revertir con naloxona 1 ampolla, sin embargo paciente persiste sin respuesta, y se decide iot. Durante el cambio de posicion presenta asistolia y se inicia RCCP con masaje cardiaco, tras reanimación avanzada sale a ritmo sinusal. Posteriormente presenta ritmo con extrasistoles frecuentes y taquicardia, se pasan dos ampollas de calcio con lo que se estabiliza. Eco control con corazon aturdido severa depersion miocardica. Posteriormente acidosis metabolica severa con hiperlactatemia e hiperkalemia severa, se emprende manejo dialítico. El día de hoy paciente en malas condiciones generales, inestable, dependiente de soporte vasopresor e inotropico a altas dosis, asi como ventilatorio, en hemofiltro extendido, severamentehipoperfundido. Se considera paciente frágil y con pronóstico clinico reservado, y alto riesgo de fallecer, situacion que se explicaa su hijo.

Dra. Mónica Patricia Vargas O. Anestesióloga - Intensivista
Dra. Maria Paulina Martinez R. Médico general, asistencial UCI

Ayudas diag. últ 24 horas : Anormales **Desc. anorm :** VER HC

Responsable: VARGAS ORDONEZ, MONICA PATRICIA INTENSIVISTA

Cédula: 66827295

RM: 663094

Valido como Firma Electrónica

Egreso UCI

Fecha: 25.08.2017 11:33:08

Nota de Egreso:

RESUMEN HOSPITALIZACIÓN UCI 25.08.2017
NOMBRE: SANTIAGO JAUREGUI BAUTISTA
EDAD: 88 AÑOS
CC: 6061103
N° EPISODIO: 4711194
ASEGURADORA: NUEVA EPS S.A.
INGRESO FCVL/UCI:24.08.17
INTENSIVISTA: DRA MONICA VARGAS

DIAGNÓSTICOS:
- SHOCK SÉPTICO
--BACTEREMIA A DESCARTAR
--ABSCESO PSOAS??
- INSUFICIENCIA RENAL CRONICA ESTADIO V

ANTECEDENTES:
-Patológicos: ERC estadio 5 en diálisis peritoneal.
-Farmacológicos: Acido fólico
-Alérgicos: Niega
-Quirúrgicos: Niega

ESTUDIOS Y PROCEDIMIENTOS:
23.08.17 Rx de torax: Atelectasia plana en base pulmonar derecha, derrame pleural leve izquierdo
23.08.217 EVDA: Esofagitis erosiva

CULTIVOS/ ANTIBIOTICOS:
24.08.17 Hisopados: En proceso
24.08.17 Liquido peritoneal: en proceso
23.08.17 Hemocultivos: Negativos
02.08.17 Hisopados: Negativos
01.08.17 Hemocultivos: Positivo Clostridium tertium

RESUMEN DE LA HOSPITALIZACION EN UCI:
Paciente de 88 años, con antecedente de ERC estadio 5 en manejo con nefrologia institucional con dialisis peritoneal. Estuvo hospitalizado hace aproximadamente 10 dias por infeccion asociada a cateter donde se aislo clostridium tertium también en hemocultivos, manejado con meropenem y metronidazol, el familiar refirio que durante la hospitalizacion el paciente presento disminucion de las cifras tensionales llegando 60/30 mmHg, manejadas con norepinefrina con lo que se logro elevar a 80/60 mmHg y se dio salida para terminar tratamiento ambulatorio con metronidazol oral. Sin embargo posterior al egreso el paciente persistia con cifras tensionales bajas, asociadas a dolor tipo urente en miembro inferior izqueirdo que se irradiaba a fosa iliaca ipsilateral. Adicionalmente el 23.08.17 incio con deposiciones melenicas, episodios de emesis con pintas de sangre, astenia, adinamia, hiporexia y somnolencia, por lo cual el familiar llamo en repetidas ocasiones a EMI, quienes dieron manejo con liquidos endovenosos, hasta hace un dia que decidieron trasladar a la institucion por empeoramiento del estado general, persistencia de hipotension y aumento delos episodios emeticos, Se considero posible sepsis de origen peritoneal, adicionalmente presento cuadro de hemorragia GI por melenas y vomito con algo de sangre pero al revisar histórico de HGB esta ha permanecido estable, se realizo endoscopia que lo unicoque evidencio fue una esofagitis erosiva sin sangrado por lo cual se suspendio infusion de omeprazol, se dejo cada 12 horas. Al reinterrogar paciente es claro un cuadro respiratorio bajo con necesidad de oxigeno con FIO elevado y fiebre adicional ademas, dolorabdominal y familiar refirio cambio en patron de liquido de diálisis peritoneal, al ingreso se encontro con hipotensión sostenida que no respondio a reto de liquidos y necesidad de vasoactivos. Con leucocitosis neutrofilia y Rx de torax que solo evidencio banda atelectasica derecha y opacidad basal izquierda que sugirio derrame con una imagen retrocardiaca que sugirio consolidación. Por estado de choque y reciente hospitalización se manejo como una neumonia asociada a cuidados de salud y no se descarta una peritonitios asociada a DP. Por lo que se solicitaron policultivos (hemocultivos, urocultivos, cultivos de liquido peritoneal) y se continuo antibiótico de amplio espectro. Se traslado a UCI por choque séptico y necesidad de vasoactivo además de alto requerimientode oxigeno. se indico cbrimiento antibiótico con Vancomicina/ meropenem. hipoperfundido, con TAM limítrofes dependiente de goteo de norepinefrina. Llamativamente en choque con diferencial de presion de pulso amplio que hace pensar en choque distributivo, se considero oportuno inicio de dobutamina para mejorar flujo. No cursa con neumonía como se habia consdierado se revisan placas previas en donde se videncio el mismo derrame basal izquierdo y atelectasias basales ya conocidas, el liquido peritoneal fue negativo para PBE, Paciente que posterior a cateterización vesical para realizacion de uroanalisis, presento dolor abdominal intensoque no mejoro con accetaminofen. Se decidio paso de hidromorfona 0.2mg. Posterior a paso de medicamento presento estupor, hipoperfusión , y palidez generalizada, ante disminución de respuesta neurológica se decidio revertir con naloxona 1 ampolla, sin embargo paciente persistia sin respuesta, por lo cual se decidio intubacion orotraqueal, en el cambio de posicion presento asistoliay se inicia RCCP con masaje cardiaco, se paso bolo de liquidos ev y se inicio adrenalina ,ciclos 30x 2 (masaje respiracion)y c/3 minutos adrenalina se pasaron 6 dosis.Durante paro dos bradicardias extremas con pulso se pone dos dosis de atropina. Dada la historia de hipocalcemia, se pasaron 20 mg de gluconato de calcio, y bicarbonato 100meq. Paciente sale de ritmo de paro a sinusal, posteriormente presento ritmo con extrasistoles frecuentes y taquicardia, se pasaron dos ampollas de calcio con lo que se estabilizomembrana , eco control con corazon aturdido, severa depersion miocardica se indico dobutamina a 15 micg/kg/min.
Se tomaron paraclinicos de control Hb 5.4 se indico trasfusion .
se explico a hijo riesgo de fallecer y derequerir terapia de reemplazo renal. en reporte de paraclinicos con acidosis metabolica severa con hiperlactatemia, hiperkalemia severa, mientras se monta maquina de dialisis se indico bolo de bicarbonato de 50 miequ seguida de infusion de bicarbonato a 70cc/h se realzairá paso de cateter mahurkar recto 19 . se indica dialisis filtro FX 80 mezcla 1 a 140 ml/min sin UF....

Responsable: RESTREPO MAYA, JULIANA MARCELA MEDICINA GENERAL

Cédula: 31437158

RM: 63302012

Valido como Firma Electrónica

Indicaciones de Enfermería

PRUEBA B

FUNDACIÓN VALLE DEL LILI
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HISTORIA CLÍNICA GENERAL

DATOS GENERALES

Paciente: **SANTIAGO JAUREGUI BAUTISTA**			Doc.Identificación: **CC 6061103**
Fecha Nacimiento: **26.06.1929**	Edad: **88** Años	Sexo: **M**	Nº. Episodio: **4711194**
Aseguradora: **NUEVA EPS S.A. RC**			Nº. Historia Clínica: **779141**
Médico Tratante: **VELASCO BAYUELO, CARLOS ALBERT**	MEDICINA INTERNA		

ATENCIÓN CLÍNICA

Tipo de Atención: **Atención Hospitalaria** Tipo de Evento: **Enfermedad general**

Anamnesis

Fecha: 23.08.2017 20:52:41

Motivo de consulta:

Sangrado de vias digestivas altas

Enfermedad Actual:

Paciente masculino de 88 años de edad con antecedente de ERC estadio 5 en manejo con nefrologia intrainstitucional con dialisis peritoneal. Estuvo hospitalizado hace 20 dias por infeccion asociada a cateter donde se aisla clostridium, manejada con meropenem y metronidazol, el familiar refiere que durante la hospitalizacion el paciente presenta disminucion de las cifras tensionales llegando 60/30 mmHg, manejadas con norepinefrina con lo que se logra elevar a 80/60 mmHg y se da salida para terminar tratamiento ambulatorio con metronidazol oral. Sin embargo posterior al egreso el paciente persiste con cifras tensionales bajas, asociadas a dolor tipo urente en miembro inferior izqueirdo que se irradiaba a fosa iliaca ipsilateral. Adicionalmente el dia de ayer inciia condeposiciones melenicas, episodios de emesis con pintas de sangre, astenia, adinamia, hiporexia y somnolencia, por lo cual el familiar llama en repetidas ocasiones a EMI, quienes dan manejo con liquidos endovenosos, hasta el dia de hoy que deciden trasladar a la institucion por empeoramiento del estado general, persistencia de hipotension y aumento de los episodios emeticos.

Antecedentes personales:
-Patologicos: ERC estadio 5 en dialisis peritoneal.
-Farmacologicos: Acido folico
_ Alergicos: Niega
- Quirurgicos: Niega
-Transfusiones: Niega

Antecedentes familiares: Niega

Antecedentes

Alérgicos :	NIEGA
Familiares :	NIEGA
Farmacológicos :	ERITROPROYECTINA INTERDIARIA, ACIDO FOLICO
Gineco-Obstétricos :	NIEGA
Hábitos :	NIEGA
Patólogicos :	HTA IRC DM, ERC
Quirúrgicos :	HERNIORRAFIA, NIEGA
Transfusionales :	NIEGA
Traumáticos :	NIEGA
Vacunación/Pediátricos :	NIEGA

Revisión por sistemas

Negativo para todos los sistemas

Signos Vitales

TA: 70 / 60 TAM: 63,33 TºC: 37,7 FC: 140 FR: 25

Peso(Kg): 68 Talla(Cms): 15

S.Sin O2: 92

Examen Físico

Aspecto General	paciente en regulares condiciones generales, sin dificultad respiratoria pero cianosis distal.
Cabeza	Normal
Cara	Normal
Ojos	Normal
Cuello	Sin ingurgitacion yugular
ORL	Palidez mucocutanea, mucosas deshidtadas
Tórax	Ruidos cardiacos ritmicos, regulares sin soplos. Murmullo vesicular presente en todos los campos pulmonares, sin ruidos sobreagregados.
Abdomen	Abdomen blando, depresible, sin signos de irritacion peritoneal. Cateter de dialisis peritoneal sin signos inflamatorios evidentes. No se palpan masas ni megalias.
SNC	Paciente somnoliento, desorientado, sin signos de focalizacion. Glasgow 12
Genitourinario	Normal
Extremidades	Extremidades sin edemas, cianosis distal, pulsos perifericos disminuidos, llenado capilar > 2 segundos.
Pulsos Periférico	Pulsos distales disminuidos
Piel y Tejidos	Cianosis distal

Paciente viene recibiendo medicamentos antes del ingreso? No

Realizó Conciliación de estos medicamentos? Seleccione una

Explique por qué no prescribe medicación previa?

Responsable:MORELL PAZ, TATIANA MEDICINA URGENCIAS

Cédula: 0067011915 RM:762339/2006

Diagnósticos

E872	ACIDOSIS	
R798	OTROS HALLAZGOS ANORMALES ESPECIFICADOSE N LA QUIMICA SANGUINEA	
I469	PARO CARDIACO, NO ESPECIFICADO	
R571	CHOQUE HIPOVOLEMICO	
K922	HEMORRAGIA GASTROINTESTINAL, NO ESPECIFI CADA	
N180	INSUFICIENCIA RENAL TERMINAL	
K590	CONSTIPACION	
A419	SEPTICEMIA, NO ESPECIFICADA	PULMONAR VS PERITONEAL
R578	OTRAS FORMAS DE CHOQUE	CHOQUE MIXTO

Análisis y Conducta

Paciente masculino en la 9 decada de la vida, con antecedentes anotados, que ingresa por cuadro clinico de hipotension asociado a deposiciones melenicas y episodios emeticos con sangre. Al ingreso en shock hipovolemico, hemodinamicamente inestable, hipotenso y taquicardico, con signos de hipoperfusion por lo cual se traslada a sala de reanimacion donde se pasan dos bolos de 500cc de Hartman, se inicia goteo de omeprazol, norepinefrina (0,05 mcg/kg/min). Gases arteriaeles evidencia hipokalemia moderada (2.8), lactato de 5.3. Se inicia reposicion de potasio por via central. Se transfuden 2 UGR, se firma consentimiento informado. Se solicitan paraclinicos, hemograma, funcion renal, hemoclasificacion, quimica sanguinea y gases arteriales.

MORELL PAZ, TATIANA MEDICINA URGENCIAS

Cédula: 0067011915 RM:762339/2006

Valido como Firma Electrónica

Factor de Aislamiento

Ordenes Clínicas

Ordenes Generales

Fecha	Código	Nombre	U. Organizativa	Responsable
23.08.2017	873444-3	PORTATILES PARA ESTUDIOS RADIOGRAFICOS	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	451600	ESOFAGOGASTRODUODENOSCOPIA [EGD] CON BIO PSIA CERRADA SOD	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	902212	HEMOCLASIFICACION GRUPO ABO Y FACTOR RH	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903895	CREATININA EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903856	NITROGENO UREICO	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	902210	HEMOGRAMA IV (HEMOGLOBINA HEMATOCRITO RE CUENTO DE ERITROCITOS INDICES ERITROCITA RIOS LEUCOGRAMA RECUENTO DE PLAQUETAS	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	902049	TIEMPO DE TROMBOPLASTINA PARCIAL [TTP]	UE Urgencias adulto	TATIANA MORELL PAZ

Fecha	Código	Nombre	U. Organizativa	Responsable
23.08.2017	389002	COLOCACION CATETER ARTERIAL PERIFERICO (LINEA ARTERIAL)	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903111	ACIDO LACTICO [L-LACTATO] AUTOMATIZADO	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903810	CALCIO SEMIAUTOMATIZADO	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903813	CLORO	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903839	GASES ARTERIALES (EN REPOSO O EN EJERCIC IO)	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903854	MAGNESIO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903859	POTASIO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903864	SODIO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903859-31	LOCAL POTASIO	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903841-31	LOCAL GLUCOSA EN SUERO LCR U OTROS FLUID OS DIFERENTE A ORINA	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903813-3	LOCAL CLORO	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903604-3	LOCAL CALCIO IONICO	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903111-3	LOCAL ACIDO LACTICO (L-LACTATO) PORMETOD O ENZIMATICO	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	902213-3	LOCAL HEMOGLOBINA	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	902211-3	LOCAL HEMATOCRITO	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	389101	IMPLANTACION DE CATETER VENOSO SUBCLAVIO O FEMORAL	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	881302-33	ULTRASONOGRAFIA FAST PARA GUIA DE ACCESO VASCULAR	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	871121	RADIOGRAFIA DE TORAX (P.A. O A.P. Y LATE RAL DECUBITO LATERAL OBLICUAS O LATERAL)	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	890702	CONSULTA DE URGENCIAS POR OTRAS ESPECIAL IDADES MEDICAS	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	901221	HEMOCULTIVO AEROBIO AUTOMATIZADO CADA MU ESTRA	UE Urgencias adulto	CAMILO ANDRES MEDINA
23.08.2017	901221-3	SEGUNDO HEMOCULTIVO AEROBIO POR METODO A UTOMATICO	UE Urgencias adulto	CAMILO ANDRES MEDINA
23.08.2017	911004	ANTICUERPOS IRREGULARES DETECCION (COOMB S INDIRECTO, RASTREO ANTICUERPOS IRREGUL ARES, PRUEBA DE ANTIGLOBULINA INDIRECT	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	911022	PRUEBA CRUZADA MAYOR ERITROCITARIA EN TU BO	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	911022	PRUEBA CRUZADA MAYOR ERITROCITARIA EN TU BO	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	902045	TIEMPO DE PROTROMBINA [TP]	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	903864-3	LOCAL SODIO	UE Urgencias adulto	TATIANA MORELL PAZ
23.08.2017	881302-33	ULTRASONOGRAFIA FAST PARA GUIA DE ACCESO VASCULAR	UE Urgencias adulto	TATIANA MORELL PAZ
24.08.2017	549802	DIALISIS PERITONEAL AUTOMATIZADA	UE Urgencias adulto	JOHANNA SCHWEINEBERG LOPEZ
24.08.2017	901217-3	CULTIVO RASTREO EN FOSA NASAL	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
24.08.2017	901217-31	CULTIVO RASTREO EN HISOPADO RECTAL	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
24.08.2017	896600	MEDICION DE GASES EN SANGRE VENOSA MIXTA SOD	UE Urgencias adulto	JAIRO ALEJANDRO BEJARANO ZULETA
24.08.2017	890402	INTERCONSULTA POR OTRAS ESPECIALIDADES M EDICAS	UE Urgencias adulto	JAIRO ALEJANDRO BEJARANO ZULETA
24.08.2017	903851	LIQUIDO PERITONEAL (EXAMEN FISICO Y CITO QUIMICO CON DETECCION DE ERITROCITOS REC UENTO Y MORFOLOGIA DE LEUCOCITOS GLUCO	UE Urgencias adulto	JAIRO ALEJANDRO BEJARANO ZULETA
24.08.2017	896600	MEDICION DE GASES EN SANGRE VENOSA MIXTA SOD	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	903111	ACIDO LACTICO [L-LACTATO] AUTOMATIZADO	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	903111	ACIDO LACTICO [L-LACTATO] AUTOMATIZADO	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	903839	GASES ARTERIALES (EN REPOSO O EN EJERCIC IO)	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	903859	POTASIO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO

Fecha	Código	Nombre	U. Organizativa	Responsable
24.08.2017	903864	SODIO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	903839	GASES ARTERIALES (EN REPOSO O EN EJERCIC IO)	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	903856	NITROGENO UREICO	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	906914	PROTEINA C REACTIVA MANUAL O SEMIAUTOMAT IZADO	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	903813	CLORO	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	903835	FOSFORO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	903854	MAGNESIO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	903859	POTASIO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	903839	GASES ARTERIALES (EN REPOSO O EN EJERCIC IO)	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
24.08.2017	903111	ACIDO LACTICO [L-LACTATO] AUTOMATIZADO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
24.08.2017	896600	MEDICION DE GASES EN SANGRE VENOSA MIXTA SOD	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
24.08.2017	903864	SODIO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	903604	CALCIO IONICO	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	902210	HEMOGRAMA IV (HEMOGLOBINA HEMATOCRITO RE CUENTO DE ERITROCITOS INDICES ERITROCITA RIOS LEUCOGRAMA RECUENTO DE PLAQUETAS	UE Urgencias adulto	FABIAN ALBERTO CAMPOS ARANGO
24.08.2017	549801-001	DIALISIS PERITONEAL MANUAL POR ENFERMERI A	UE Urgencias adulto	MARIA DEL PILAR DUQUE GUEVARA
24.08.2017	890116-001	TOMA DE CULTIVO POR ENFERMERIA	UE Urgencias adulto	MARIA DEL PILAR DUQUE GUEVARA
24.08.2017	901107	COLORACION GRAM Y LECTURA PARA CUALQUIER MUESTRA	UE Urgencias adulto	JAIRO ALEJANDRO BEJARANO ZULETA
24.08.2017	901217	CULTIVO PARA MICROORGANISMOS EN CUALQUIE R MUESTRA DIFERENTE A MEDULA OSEA ORINA Y HECES	UE Urgencias adulto	JAIRO ALEJANDRO BEJARANO ZULETA
25.08.2017	896600	MEDICION DE GASES EN SANGRE VENOSA MIXTA SOD	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	903111	ACIDO LACTICO [L-LACTATO] AUTOMATIZADO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	903839	GASES ARTERIALES (EN REPOSO O EN EJERCIC IO)	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	903856	NITROGENO UREICO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	906914	PROTEINA C REACTIVA MANUAL O SEMIAUTOMAT IZADO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	903813	CLORO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	903859	POTASIO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	903864	SODIO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	902210	HEMOGRAMA IV (HEMOGLOBINA HEMATOCRITO RE CUENTO DE ERITROCITOS INDICES ERITROCITA RIOS LEUCOGRAMA RECUENTO DE PLAQUETAS	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	911004	ANTICUERPOS IRREGULARES DETECCION (COOMB S INDIRECTO, RASTREO ANTICUERPOS IRREGUL ARES, PRUEBA DE ANTIGLOBULINA INDIRECT	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	911022	PRUEBA CRUZADA MAYOR ERITROCITARIA EN TU BO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	911022	PRUEBA CRUZADA MAYOR ERITROCITARIA EN TU BO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	911022	PRUEBA CRUZADA MAYOR ERITROCITARIA EN TU BO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	911022	PRUEBA CRUZADA MAYOR ERITROCITARIA EN TU BO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	906232	HTLV-I Y II ANTICUERPOS TOTALES SEMIAUTO MATIZADO O AUTOMATIZADO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	911090	BOLSAS RECOLECCION CON FILTRO BANCO DE S ANGRE	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	911106	PROCESAMIENTO DE LA UNIDAD DE GLOBULOS R OJOS ESTANDAR	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	912002	TRANSFUSION DE LA UNIDAD DE GLOBULOS ROJ OS O ERITROCITOS	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	903856	NITROGENO UREICO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	906914	PROTEINA C REACTIVA MANUAL O SEMIAUTOMAT IZADO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY

Fecha	Código	Nombre	U. Organizativa	Responsable
25.08.2017	903810	CALCIO SEMIAUTOMATIZADO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	903813	CLORO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	902210	HEMOGRAMA IV (HEMOGLOBINA HEMATOCRITO RE CUENTO DE ERITROCITOS INDICES ERITROCITA RIOS LEUCOGRAMA RECUENTO DE PLAQUETAS	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	903864	SODIO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	903859	POTASIO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	903854	MAGNESIO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	903835	FOSFORO EN SUERO U OTROS FLUIDOS	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	389103-001	SEGUIMIENTO DE CATETERES VENOSOS CENTRAL ES	UE Urgencias adulto	NELSY LUCUMI CARVAJAL
25.08.2017	389103-003	CURACION DE CATETER VENOSO CENTRAL	UE Urgencias adulto	NELSY LUCUMI CARVAJAL
25.08.2017	399804 -3	HEMOFILTRACION (DIALISIS)	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	906232	HTLV-I Y II ANTICUERPOS TOTALES SEMIAUTO MATIZADO O AUTOMATIZADO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	911090	BOLSAS RECOLECCION CON FILTRO BANCO DE S ANGRE	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	911106	PROCESAMIENTO DE LA UNIDAD DE GLOBULOS R OJOS ESTANDAR	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	912002	TRANSFUSION DE LA UNIDAD DE GLOBULOS ROJ OS O ERITROCITOS	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	906232	HTLV-I Y II ANTICUERPOS TOTALES SEMIAUTO MATIZADO O AUTOMATIZADO	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	911090	BOLSAS RECOLECCION CON FILTRO BANCO DE S ANGRE	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	911106	PROCESAMIENTO DE LA UNIDAD DE GLOBULOS R OJOS ESTANDAR	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	912002	TRANSFUSION DE LA UNIDAD DE GLOBULOS ROJ OS O ERITROCITOS	UE Urgencias adulto	INGRID KATHERINE ALVAREZ ECHEVERRY
25.08.2017	890612	ASISTENCIA INTRAHOSPITALARIA POR TERAPIA RESPIRATORIA	UE Urgencias adulto	ALEXANDER ASCUNTAR ARZAYUS
25.08.2017	890612	ASISTENCIA INTRAHOSPITALARIA POR TERAPIA RESPIRATORIA	UE Urgencias adulto	ALEXANDER ASCUNTAR ARZAYUS
25.08.2017	890612	ASISTENCIA INTRAHOSPITALARIA POR TERAPIA RESPIRATORIA	UE Urgencias adulto	ALEXANDER ASCUNTAR ARZAYUS

Prescripciones

Fecha	Hora	Medicamento	Dosis	Unidad	Vía	Ciclo	Responsable
23.08.2017	21:10:41	CLORURO DE POTASIO 0,2mEq/mL x 100mL EN SSN	100	ML	INTRAVE	CADA 8 HORAS	MORELL PAZ, TATIANA
23.08.2017	20:28:13	NOREPINEFRINA 4MG/4ML AMP 4ML	4	MG	PARENT	CADA 8 HORAS	MORELL PAZ, TATIANA
23.08.2017	20:28:13	OMEPRAZOL 40 MG VI	80	MG	PARENT	CADA 12 HORAS	MORELL PAZ, TATIANA
23.08.2017	20:28:13	OMEPRAZOL 40 MG VI	80	MG	PARENT	DOSIS UNICA	MORELL PAZ, TATIANA
24.08.2017	14:18:46	ALBUMINA HUMANA 10G/50ML FCO 50ML	20	G	PARENT	DOSIS UNICA	CAMPOS ARANGO, FABIAN
24.08.2017	18:18:51	VANCOMICINA 500MG VIAL	1.000	MG	INTRAVE	CADA 2 DIAS	ALVAREZ ECHEVERRY, INGRID
24.08.2017	18:18:51	HIDROCORTISONA 100MG/2ML VIAL	50	MG	INTRAVE	CADA 6 HORAS	ALVAREZ ECHEVERRY, INGRID
24.08.2017	18:18:51	VASOPRESINA 20 UI /1ML SOL INY	20	UI	INTRAVE	CADA 8 HORAS	ALVAREZ ECHEVERRY, INGRID
24.08.2017	18:18:51	MEROPENEM 1000MG AMP	1.000	MG	INTRAVE	CADA 8 HORAS	ALVAREZ ECHEVERRY, INGRID
23.08.2017	23:31:20	MEROPENEM 1000MG AMP	1.000	MG	INTRAVE	CADA 8 HORAS	MEDINA, CAMILO ANDRES
23.08.2017	23:31:20	OMEPRAZOL 40 MG VI	40	MG	PARENT	CADA 12 HORAS	MEDINA, CAMILO ANDRES
24.08.2017	05:54:02	CLORURO DE POTASIO 0,2mEq/mL x 100mL EN SSN	100	ML	INTRAVE	CADA 4 HORAS	GUEVARA CHAUX, JESSICA
24.08.2017	08:39:47	HIDROCORTISONA 100MG/2ML VIAL	50	MG	INTRAVE	CADA 6 HORAS	BEJARANO ZULETA, JAIRO
24.08.2017	18:18:51	NOREPINEFRINA 4MG/4ML AMP 4ML	4	MG	INTRAVE	CADA 6 HORAS	ALVAREZ ECHEVERRY, INGRID
24.08.2017	08:40:15	NOREPINEFRINA 4MG/4ML AMP 4ML	4	MG	INTRAVE	CADA 6 HORAS	BEJARANO ZULETA, JAIRO
24.08.2017	02:36:28	NOREPINEFRINA 4MG/4ML AMP 4ML	4	MG	PARENT	CADA 4 HORAS	GUEVARA CHAUX, JESSICA
24.08.2017	19:19:11	DOBUTAMINA HCL 250 MG/ 20ML	250	MG	PARENT	CADA 12 HORAS	ALVAREZ ECHEVERRY, INGRID
24.08.2017	19:49:05	ACETAMINOFEN 500 MG TAB	1.000	MG	ORAL	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID

Fecha	Hora	Medicamento	Dosis	Unidad	Vía	Ciclo	Responsable
24.08.2017	19:19:11	ALBUMINA (HUMANA) 20%-BOLX 50ML	20	G	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
24.08.2017	19:35:35	POLIETILENGLICOL 59G SOB	4	SOB	ORAL	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
23.08.2017	23:31:20	VANCOMICINA 500MG VIAL	1.000	MG	INTRAVE	DOSIS UNICA	MEDINA, CAMILO ANDRES
24.08.2017	02:07:14	NOREPINEFRINA 4MG/4ML AMP 4ML	4	MG	PARENT	DOSIS UNICA	GUEVARA CHAUX, JESSICA
24.08.2017	02:53:59	HIDROCORTISONA 100MG/2ML VIAL	100	MG	INTRAVE	DOSIS UNICA	MEDINA, CAMILO ANDRES
24.08.2017	02:53:59	NOREPINEFRINA 4MG/4ML AMP 4ML	4	MG	INTRAVE	DOSIS UNICA	MEDINA, CAMILO ANDRES
24.08.2017	02:54:04	MIDAZOLAM 1 MG /ML AMP 5 ML	1	MG	PARENT	DOSIS UNICA	MEDINA, CAMILO ANDRES
24.08.2017	08:39:19	VANCOMICINA 500MG VIAL	1.000	MG	INTRAVE	CADA 2 DIAS	BEJARANO ZULETA, JAIRO
24.08.2017	14:20:20	VASOPRESINA 20 UI /1ML SOL INY	20	UI	INTRAVE	DOSIS UNICA	CAMPOS ARANGO, FABIAN
24.08.2017	13:53:39	VASOPRESINA 20 UI/ML JG 1ML	20	UI	INTRAVE	DOSIS UNICA	CAMPOS ARANGO, FABIAN
25.08.2017	11:38:02	ALBUMINA HUMANA 10G/50ML FCO 50ML	20	G	PARENT	DOSIS UNICA	VARGAS ORDONEZ, MONICA
25.08.2017	11:38:02	MEROPENEM 1000MG AMP	1.000	MG	INTRAVE	CADA 8 HORAS	VARGAS ORDONEZ, MONICA
25.08.2017	11:38:02	DOBUTAMINA HCL 250 MG/ 20ML	250	MG	PARENT	CADA 6 HORAS	VARGAS ORDONEZ, MONICA
25.08.2017	11:38:02	HIDROCORTISONA 100MG/2ML VIAL	50	MG	INTRAVE	CADA 6 HORAS	VARGAS ORDONEZ, MONICA
25.08.2017	11:38:02	NOREPINEFRINA 4MG/4ML AMP 4ML	16	MG	INTRAVE	CADA 2 HORAS	VARGAS ORDONEZ, MONICA
25.08.2017	11:38:02	VASOPRESINA 20 UI /1ML SOL INY	20	UI	INTRAVE	CADA 8 HORAS	VARGAS ORDONEZ, MONICA
25.08.2017	11:38:02	OMEPRAZOL 40 MG VI	40	MG	PARENT	CADA 12 HORAS	VARGAS ORDONEZ, MONICA
24.08.2017	18:18:51	OMEPRAZOL 40 MG VI	40	MG	PARENT	CADA 12 HORAS	ALVAREZ ECHEVERRY, INGRID
24.08.2017	19:35:35	DOBUTAMINA HCL 250 MG/ 20ML	250	MG	PARENT	CADA 8 HORAS	ALVAREZ ECHEVERRY, INGRID
25.08.2017	01:22:54	NOREPINEFRINA 4MG/4ML AMP 4ML	8	MG	INTRAVE	CADA 4 HORAS	ALVAREZ ECHEVERRY, INGRID
24.08.2017	19:49:38	NOREPINEFRINA 4MG/4ML AMP 4ML	8	MG	INTRAVE	CADA 4 HORAS	ALVAREZ ECHEVERRY, INGRID
25.08.2017	00:48:59	SODIO BICARBONATO 1 MEQ/ML AMP 10ML	70	ML	INTRAVE	CADA 24 HORAS	ALVAREZ ECHEVERRY, INGRID
25.08.2017	00:48:59	CALCIO GLUCONATO 1G/10ML AMP 10ML	20	ML	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
25.08.2017	00:48:59	ATROPINA SULFATO 1MG/ML AMP 1ML	1	MG	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
24.08.2017	22:27:27	NALOXONA 0,4MG/ML AMP 1ML	0,4	MG	PARENT	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
25.08.2017	00:48:59	ADRENALINA HCL 1 MG/ML AMP 1ML	11	MG	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
25.08.2017	00:48:59	SODIO BICARBONATO 1 MEQ/ML AMP 10ML	16	ML	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
24.08.2017	19:35:35	ALBUMINA (HUMANA) 20%-BOLX 50ML	10	G	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
25.08.2017	04:09:39	ADRENALINA HCL 1 MG/ML AMP 1ML	6	MG	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
25.08.2017	01:20:16	CALCIO GLUCONATO 1G/10ML AMP 10ML	20	ML	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
25.08.2017	01:20:16	ATROPINA SULFATO 1MG/ML AMP 1ML	1	MG	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
25.08.2017	01:20:16	SODIO BICARBONATO 1 MEQ/ML AMP 10ML	170	ML	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
25.08.2017	03:25:52	SODIO BICARBONATO 1 MEQ/ML AMP 10ML	20	ML	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
25.08.2017	03:19:15	CALCIO GLUCONATO 1G/10ML AMP 10ML	10	ML	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
25.08.2017	03:26:49	HIDROMORFONA JERINGA PRELLENA 0.2MG/ML X 5ML	1	MG	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID
25.08.2017	03:19:15	HIDROMORFONA 2MG/ML AMP 1ML	0,2	MG	INTRAVE	DOSIS UNICA	ALVAREZ ECHEVERRY, INGRID

Evoluciones Médicas

Fecha: 24.08.2017 00:05:23 **Tipo de Evolución:** Valoración en Sala de observac

Subjetivo:
Evolucion urgencias
Santiago Jauregui Bautista
88 años

Diagnosticos:
- Shock Vasodilatado
-- Sepsis de origen pulmonar
- Hemorragia de vias digestivas altas??
-- esofagitis erosiva por endoscopia
- Insuficiencia renal cronica estadio V

Subjetivo: paciente sedado por realizacion de endoscopia.

Objetivo:
paciente en regulares condiciones generales, mucosasa palidas y secas. Signos vitales: TA 101/51 FC 98 FR 20 SO2 100 FiO2 85%
NOrepinefrina 0.4mcg/kg/min. ORL: mucosas secas y palidas. Torax: Ruidos cardiacos ritmicos sin soplos, mv bilateral disminuido en base izquierda. Abdomen: blando,

depresible, con cateter de dialisis peritoneal sin signos inflamatorios. Genitourinario: tacto rectal sin sangrado activo. Extremidades: palidas, con pulsos perifericos presentes pero disminuidos en intesidad, sin edemas, llenado capilar 4seg. SNC: Paciente bajo sedacion, responde al dolor. No focalizacion evidente.

Paraclinicos:
- 23/08/2017: Leucos 13770 N 86% L 7.40% Hb 10.40 HTO 10.40 HTO 33.20 PLT 371MIL. PT 18.2 INR 1.63 PTT 32 BUN 34.7 CR 9.70

Análisis:
Paciente quien al ingreso se encuentra en shock, por historia clinica (sangrado de vias digestivas altas) se oriento inicialmente como hipovolemica SIN EMBARGO la endoscopia lo unico que evidencia es esofagitis erosiva sin sangrado lo cual no explica el estado de shock del paciente, por lo cual se suspende infusion de omeprazol, se deja cada 12 horas.
Reporte paraclinicos con hb de 10.2, soporte vasopresor en aumento con norepinefrina (0.453 mcg/kg/min), se adiciona hidrocortisona.Se orienta hacia un shock vasodilatado. A la reevaluacion clinica hipoventilacion en base izquierda, FAST con patron de consoliacion pulmonar izqueirda y derrame pleural. Foco pulmonar (neumonia en base izquierda). Actualmente se encuentra con cifras tensionales estables, con reanimacion hidrica. Se solicitaran pruebas adicionales (hemocultivos) y se iniciara cubrimiento antibiotico (meropenem- vancomicina).

Plan:
-continua en reanimacion
-no via oral
-bolos de SSN guiados por metas
-Se solicitan hemocultivos #1 y 2
-Norepinefrina (0.453 mcg/kg/min) IV. Meropenem Vancomicina
-monitoria continua de signos vitales.

Problemas actuales:

Problemas resueltos:

Ayudas diagnó. ult. 24 horas :Normales

Responsable:MEDINA, CAMILO ANDRES MEDICINA INTERNA

Cédula: 0006550699 RM:7621842013

Valido como Firma Electrónica

Evoluciones Médicas

Fecha: 24.08.2017 02:57:44 **Tipo de Evolución:** Valoración en Sala de observac

Subjetivo:
paciente que durante la evolucion y dada ausencia de pronostico clinico se pasa a tubo en T

Objetivo:
-

Análisis:
-

Plan:
-

Problemas actuales:

Problemas resueltos:

Ayudas diagnó. ult. 24 horas :Sin estudios pendientes

Responsable:MEDINA, CAMILO ANDRES MEDICINA INTERNA

Cédula: 0006550699 RM:7621842013

Valido como Firma Electrónica

Evoluciones Médicas

Fecha: 24.08.2017 04:35:17 **Tipo de Evolución:** Valoración en Sala de observac

Subjetivo:
la nota anterior no corresponde a este paciente

Objetivo:
-

Análisis:

-

Plan:

-

Problemas actuales:

Problemas resueltos:

Ayudas diagnó. ult. 24 horas :Sin estudios pendientes

Responsable:MEDINA, CAMILO ANDRES MEDICINA INTERNA

Cédula: 0006550699 RM:7621842013

Valido como Firma Electrónica

Evoluciones Médicas

Fecha: 24.08.2017 08:42:08 **Tipo de Evolución:** Interconsulta x especialista

Subjetivo:
Nefrología
Santiago Jauregui Bautista
88 años

Resumen atención:
Hijo refiere posterior a egreso tos con movilización de secreciones blanquecinas algo de disnea no otros respiratorios. Adicionalmente desde ayer incia con deposiciones melenicas, episodios de emesis con pintas de sangre, astenia, adinamia, hiporexia ysomnolencia, ayer un episodio de rectorragia, por lo cual el familiar llama a EMI, quienes dan manejo con liquidos endovenosos, hasta el
dia de hoy que deciden trasladar a la institucion por empeoramiento del estado general, persistencia de hipotension y aumento de losepisodios emeticos.

Antecedentes personales:
Patologicos: ERC estadio 5 en dialisis peritoneal automatizada, dolor neuropatico a estudio
Farmacologicos: Acido folico
Alergicos: Niega
Quirurgicos: Niega
Transfusiones: Niega
Antecedentes familiares: Niega

Subjetivo: Paciente responde preguntas niega dolor en el momento.

Objetivo: Delgado, palido con respiración superficial episodios de tos humeda, con mascara de no reinhalación, con los siguientes signos vitales:

HORA TEMP FC FR PAS PAD PAM SAT 01:00:3236,0096,0022,00120,0055,0076,67100,00 03:00:2335,8080,0019,00106,0049,0068,0096,00 05:00:3236,6088,0019,00102,0050,0067,3396,00 07:00:0736,4087,0020,0088,0040,0056,0096,00

C/C: mucosasa pálidas y secas, recibe norepinefrina. Torax: Ruidos cardiacos ritmicos sin soplos, mv bilateral disminuido en base
izquierda con roncus. Abdomen: blando, depresible, con cateter de dialisis peritoneal sin signos inflamatorios, sin dolor en el momento, ni signos de irritación peritoneal, no secreción por catéter. Extremidades: palidas, con pulsos periféricos presentes pero disminuidos en intensidad, cianosis distal, sin edemas, llenado capilar 4seg. SNC: Paciente respond preguntas simples. No focalización evidente.

Paraclinicos:
23.08.2017: k: 3.57, Leucos 13770 N 86% L 7.40% Hb 10.40 HTO 10.40 HTO 33.20, PLT 371MIL. PT 18.2 INR 1.63 PTT 32 BUN 34.7 CR 9.70, gases PH: 7.38 PCo2 30 PO2200 sat 99 CHCo3 17 BE -7, Na: 145, Cl: 99.5, mg: 1.4, acido lactico: 3.59, calcio: 6.6

Diagnósticos:
1. Shock Vasodilatado
a. Sepsis de origen pulmonar?
2. NAC?
3. Insuficiencia renal cronica estadio V en diálisis peritoneal
4. HVDB

Análisis y plan:
Paciente de 88 años de edad con antecedente de ERC en dialisis peritoneal, ahora hospitalizado en UCI en el contexto de choque vasodilatado hiperlactatemico de posible foco pulmonar por clinica y examen físico, sin embargo por antecedente se solicita citoquimico de liquido peritoneal. Ya con manejo ATB, LEV y norepinefrina. PAcinete muy fragil se indica inicio de diálisis peritoneal automatizada ayer no la realizó, hijo va a traer la máquina. Se explica conducta a seguir.

Objetivo:
*

Análisis:
*

Plan:
*

Problemas actuales:

Problemas resueltos:

Ayudas diagnó. ult. 24 horas :Anormales **Desc. anorm.** :VER HC

Responsable:SCHWEINEBERG LOPEZ, JOHANNA NEFROLOGIA

Cédula: 0030325432 RM:1513096

Valido como Firma Electrónica

Evoluciones Médicas

Fecha: 24.08.2017 14:12:09 **Tipo de Evolución:** Evolución

Subjetivo:
Paciente de 88 años de edad con antecedente de ERC en dialisis peritoneal, ahora hospitalizado en UCI en el contexto de choque vasodilatado hiperlactatemico de posible foco pulmonar vs peritoneal por clinica y examen físico, sin embargo por antecedente se solicita citoquimico de liquido peritoneal. Ya con manejo ATB, LEV y norepinefrina. PAcinete muy fragil, persiste hipotenso por lo que se diligencia formato CTC y Mipres para vasopresina.
codigo mipres para vasopresina 20170824176002368793

Objetivo:
.

Análisis:

.

Plan:

.

Problemas actuales:

Problemas resueltos:

Ayudas diagnó. ult. 24 horas :Sin estudios pendientes

Responsable:CAMPOS ARANGO, FABIAN ALBERTO MEDICINA GENERAL

Cédula: 0016865959 RM:76196908

Valido como Firma Electrónica

NO POS Medicamentos

Número de Solicitud: 20170824176002368793		Fecha: 24-ago-17	Hora: 14:09:53
Tipo identi. médico: CC	N° identi. médico: 6061103	Nombre médico: FABIAN ALBERTO CAMPOS ARANGO	
Especialidad: MEDICINA GENERAL			Reg. Profesional: **76196908**
Justificación: PACIENTE CON ERC EV , AHORA CON CHOQUE SEPTICO REFRACTARIO A LEV Y NOREPINEFRINA A DOSIS ALTAS			

¿Paciente con enfermedad huérfana? No	¿Requiere soporte nutricional? No	¿El medicamento se enuentra cubierto por el PBS con cargo UPC? No	
¿El medicamento se encuentra en fase experimental? No	Medicamento utilizado del PBS	NOREPINEFRINA	
¿Ya utilizo medica. existentes en el PBS con cargo a la UPC? Si	Resultados clínicos no satisfactorios	Descripción: PERSISTENCIA DE CHOQUE SEPTICO	
¿Ya descartó los medic. existentes en el PBS con cargo UPC?No		Descripción:	
¿La indicación o uso previsto del medica. esta reg. por la autoridad competente? No		¿El medicamento aparece en la lista UNIR? No	
¿Existe evidencia cientifica sobre seguridad, eficacia y efectividad clínica? Si		¿Tipo de prestación?	

Cod. Medicamento	Nombre Medicamento	Concentración	Forma Farma.
2000001873	VASOPRESINA 20 UI/ML JG 1ML		SOLUCION

Vía Administración	N° Dosis	Unidad Dosis	Frecuencia Admin.
INTRAVENOSA	20	UI	DOSIS UNICA

Indicaciones Especiales	Duración Tratamiento	Cantidad Total	Unidad Total
Administrar en goteo		00001	JG

Indicaciones o recomendaciones para el paciente
PACIENTE CON CHOQUE SEPTICO PERSISTENTE

NO POS Medicamentos

Número de Solicitud: 20170824176002368793	Fecha: 24-ago-17	Hora: 14:22:06

Tipo identi. médico: CC	N° identi. médico: 6061103	Nombre médico: FABIAN ALBERTO CAMPOS ARANGO

Especialidad: MEDICINA GENERAL	Reg. Profesional: **76196908**

Justificación: PACIENTE CON ERC EV , AHORA CON CHOQUE SEPTICO REFRACTARIO A LEV Y NOREPINEFRINA A DOSIS ALTAS

¿Paciente con enfermedad huérfana? No	¿Requiere soporte nutricional? No	¿El medicamento se enuentra cubierto por el PBS con cargo UPC? No

¿El medicamento se encuentra en fase experimental? No	Medicamento utilizado del PBS	NOREPINEFRINA	
¿Ya utilizo medica. existentes en el PBS con cargo a la UPC? Si	Resultados clínicos no satisfactorios	Descripción:	PERSISTENCIA DE CHOQUE SEPTICO A PESAR DE VASOPRESORES
¿Ya descartó los medic. existentes en el PBS con cargo UPC?No		Descripción:	

¿La indicación o uso previsto del medica. esta reg. por la autoridad competente? No	¿El medicamento aparece en la lista UNIR? No
¿Existe evidencia cientifica sobre seguridad, eficacia y efectividad clínica? Si	¿Tipo de prestación?

Cod. Medicamento	Nombre Medicamento	Concentración	Forma Farma.
2000002240	VASOPRESINA 20 UI /1ML SOL INY		SOLUCION

Vía Administración	N° Dosis	Unidad Dosis	Frecuencia Admin.
INTRAVENOSA	20	UI	DOSIS UNICA

Indicaciones Especiales	Duración Tratamiento	Cantidad Total	Unidad Total
Sin indicación especial		00001	AMP

Indicaciones o recomendaciones para el paciente
PACIENTE CON CHOQUE SEPTICO REFRACTARIO A LEV Y NOREPINEFRINA

NO POS Medicamentos

Número de Solicitud: 20170824150002376233	Fecha: 24-ago-17	Hora: 18:26:42

Tipo identi. médico: CC	N° identi. médico: 6061103	Nombre médico: INGRID KATHERINE ALVAREZ ECHEVERRY

Especialidad: MEDICINA INTERNA	Reg. Profesional: **52 1740 2009**

Justificación: PACIENTE CON ERC EV , AHORA CON CHOQUE SEPTICO REFRACTARIO A LEV Y NOREPINEFRINA A DOSIS ALTAS

¿Paciente con enfermedad huérfana? No	¿Requiere soporte nutricional? No	¿El medicamento se enuentra cubierto por el PBS con cargo UPC? No

¿El medicamento se encuentra en fase experimental? No	Medicamento utilizado del PBS	NOREPINEFRINA	
¿Ya utilizo medica. existentes en el PBS con cargo a la UPC? Si	Resultados clínicos no satisfactorios	Descripción:	PERSISTENCIA DE CHOQUE SEPTICO A PESAR DE VASOPRESORES
¿Ya descartó los medic. existentes en el PBS con cargo UPC?No		Descripción:	

¿La indicación o uso previsto del medica. esta reg. por la autoridad competente? No	¿El medicamento aparece en la lista UNIR? No
¿Existe evidencia cientifica sobre seguridad, eficacia y efectividad clínica? Si	¿Tipo de prestación?

Cod. Medicamento	Nombre Medicamento	Concentración	Forma Farma.
2000002240	VASOPRESINA 20 UI /1ML SOL INY		SOLUCION

Vía Administración	N° Dosis	Unidad Dosis	Frecuencia Admin.
INTRAVENOSA	20	UI	CADA 8 HORAS

Indicaciones Especiales	Duración Tratamiento	Cantidad Total	Unidad Total
Sin indicación especial		00009	AMP

Indicaciones o recomendaciones para el paciente
PACIENTE CON CHOQUE SEPTICO REFRACTARIO A LEV Y NOREPINEFRINA

NO POS Medicamentos

Número de Solicitud: 20170824120002376892	Fecha: 24-ago-17	Hora: 19:40:10

Tipo identi. médico: CC	N° identi. médico: 6061103	Nombre médico: INGRID KATHERINE ALVAREZ ECHEVERRY

Especialidad: MEDICINA INTERNA	Reg. Profesional: **52 1740 2009**

Justificación: PACIENTE CON ERC EV , AHORA CON CHOQUE SEPTICO REFRACTARIO A LEV Y NOREPINEFRINA A DOSIS ALTAS

¿Paciente con enfermedad huérfana? No	¿Requiere soporte nutricional? No	¿El medicamento se enuentra cubierto por el PBS con cargo UPC? No		
¿El medicamento se encuentra en fase experimental? No	Medicamento utilizado del PBS	NO APLICA		
¿Ya utilizo medica. existentes en el PBS con cargo a la UPC? No		Descripción:		
¿Ya descartó los medic. existentes en el PBS con cargo UPC?Si	No existe alternativa	Descripción:		
¿La indicación o uso previsto del medica. esta reg. por la autoridad competente? Si		¿El medicamento aparece en la lista UNIR? No		
¿Existe evidencia cientifica sobre seguridad, eficacia y efectividad clínica? Si		¿Tipo de prestación?		

Cod. Medicamento	Nombre Medicamento	Concentración	Forma Farma.
2000000430	POLIETILENGLICOL 59G SOB	SOB X 60GR	POLVO

Vía Administración	N° Dosis	Unidad Dosis	Frecuencia Admin.
ORAL	4	SOB	DOSIS UNICA

Indicaciones Especiales	Duración Tratamiento	Cantidad Total	Unidad Total
Sin indicación especial		00004	SOB

Indicaciones o recomendaciones para el paciente
NA

Evolución UCI

Fecha: 24.08.2017 09:47:40

Evolución:
EVOLUCION UCI DIA 24.08.2017
NOMBRE: SANTIAGO JAUREGUI BAUTISTA
CC: 6061103
EDAD : 88 años

DIAGNOSTICOS:
- Shock séptico
-- Bacteremia a descartar?
-- Neumonía asociado a los cuidados de la salud?
- Insuficiencia renal cronica estadio V

ANTECEDENTES PERSONALES:
-Patológicos: ERC estadio 5 en diálisis peritoneal.
-Farmacológicos: Acido fólico
-Alérgicos: Niega
-Quirúrgicos: Niega
-Transfusiones:

PARACLNICOS IMAGENOLOGICOS:
- Rx de torax 23.08.2017: Atelectasia plana en base pulmonar derecha, derrame pleural leve izquierdo
-EVDA 23.08.2017: Esofagitis erosiva

EXAMEN FISICO:
Paciente en cama, tranquilo, hemodinamicamente estable, orientado en tiempo, persona y lugar.

CARDIOVASCULAR: TA:102/57 TAM :67 MMHG FC :87 LPM. Ruidos cardiacos rítmicos, sin soplos. Norepinefrina 0.2mcg/kg/min
LACTATO: 1,83
EKG: Bloqueo de 1er grado, Ondas T negativas en DI-AVL

RESPIRATORIO: FR: 18 , SO2:96%. Murmullo vesicular normal, no ruidos sobreagregados. Gases Arteriales: pH: 7,38, PCO2:26, PO2:224,HCO3:15, BE:-9. Rx torax : Atelectasia plana en base pulmonar derecha, derrame pleural leve izquierdo

ABDOMEN: Blando, depresible, sin dolor a la palpación, sin masas ni megalias. Cateter de dialisis peritoneal sin signos inflamatorios evidentes.

EXTREMIDADES: móviles, sin edemas, llenado capilar < 2 segundos.
RENAL: Diuresis espontanea adecuada
SODIO:141 POTASIO:4,1 CLORO: 103 CREAT:9,7 BUN:39

HEMATOLOGICO: sin signos de sangrado activo.
HB:10,2 HTO:31,5 PTS:373000 PT:18 PTT:32

INFECCIOSO: T:36,4 c. SIN PICOS FEBRILES
LEUCOS:12320 NEUTROS:88 LINFOS:5 PCR: 25
HEMOCULTIVO – UROCULTIVO: En proceso
ANTIBIOTICO FECHA: Vancomicina/meropenem (FI:24/08/2017)

NEUROLOGICO: No deficit motor ni sensitivo, reflejos ++/++++, respuesta plantar flexora bilateral, glasgow 15/15

ANALISIS / PLAN:

Paciente con antecedente de ERC estadio V en diálisis peritoneal. Con hospitalización reciente en la institución por Bacteremia por clostridium tertium y peritonitis asociada a catéter de diálisis por E. coli BLEE positiva. Se dio alta médica el 13.08.2017 con tratamiento ambulatorio durante 5 días con metronidazol. Ingresa por cuadro clínico de dos días de evolución consistente en dos episodios de hematemesis, un episodio de melena y un episodio de rectorragia. Asociado presenta tos con expectoración blanquecina y dolor de tipo urente en miembro inferior derecho con irradiación a fosa iliaca ipsilateral. Al ingreso taquicardico, hipotenso y consignos de hipoperfusión. Se inicia reanimación hídrica, soporte con vasopresor, reposicion de K e inician cubrimiento antibiótico con Vancomicina/meropenem. En el momento, paciente en regulares condiciones generales, hipoperfundido, con TAM limítrofes dependiente de goteo de norepinefrina. En paraclínicos de control con acidosis metabólica, leucocitosis mas neutrofilia, pcr elevadae hipocalcemia. Se administra bolo 300cc de SSN con mejoría de TAM. Continua con soporte de norepinferina 0,2mcg/kg/min. Se suspendereposición central de K. Se solicita cultivo y gramm de catéter de diálisis peritoneal. Pendiente realización de dialisis peritoneal. Debe continuar manejo integral en UCI por alto riesgo de descompensación hemodinámica. Se le explica a su hijo situacióncompleja situación clinica actual entiende y acepta.

Dr: Fabian Campos Medico Hospitalario De Uci
Carlos Velez Interno ICESI
Dr: Jorge Martinez Internista/intensivista.

Responsable: MARTINEZ BUITRAGO, JORGE EDUARDO INTENSIVISTA

Cédula: 0016637341 RM:567288

Evolución UCI

Fecha: 24.08.2017 18:09:26

Evolución:
NOMBRE: SANTIAGO JAUREGUI BAUTISTA
CC: 6061103
EDAD : 88 años

DIAGNOSTICOS:
- Shock séptico de origen a determinar
  Foco abdominal a descartar
- Insuficiencia renal cronica estadio V

ANTECEDENTES PERSONALES:
-Patológicos: ERC estadio 5 en diálisis peritoneal.
-Farmacológicos: Acido fólico
-Alérgicos: Niega
-Quirúrgicos: Niega
-Transfusiones:

ANALISIS / PLAN:
Paciente en la novena década de la vida conocido en nuestra institución con relación a enfermedad renal crónica E V en diálisis peritoneal, quien se encuentra hospitalizado en el contexto de shock séptico de origen no filiado, desde su ingreso con sospecha de foco pulmonar sin embargo al revisar radiografias previas no se evidencian cambios significativos,con persistencia de atelectasia basal izquierda y leve derrame pleural ,no se descarta origen abdominal dados sus multiples antecedentes. desde su ingreso hipotenso, hipoperfundido con acidosis metabolica quien inicialmente respondió de forma transitoria a liquidos endovenosos con depuración de lactato, sin embargo requirió posteriormente goteo de norepinefrina y vasopresina por cifras tensionales bajas.
Actualmente con cobertura antibiótica meropenem – vancomicina con cultivos en proceso incluyendo de liquido peritoneal dado su antecedente de hospitalización reciente por bacteremia por clostridium tertium y peritonitis asociada a catéter de diálisis por E.coli BLEE positiva, se continua manejo medico instaurado en unidad de cuidado intensivo dada su delicada condición clínica.
Se explica claramanete a su hijo quien entiende y acepta.

Dr: Fabian Campos Medico Hospitalario De Uci
Dr: Janer Varon Internista/intensivista

Responsable: VARON ARENAS, JANER MEDICINA INTERNA

Cédula: 0094491803 RM:7635482002

Evolución UCI

Fecha: 24.08.2017 19:52:31

Evolución:
EVOLUCION UCI NOCHE 24.08.2017
NOMBRE: SANTIAGO JAUREGUI BAUTISTA
CC: 6061103
EDAD : 88 años

DIAGNOSTICOS:
- Shock séptico
-- Bacteremia a descartar
--- absceso psoas??
- Insuficiencia renal cronica estadio V

ANTECEDENTES PERSONALES:

-Patológicos: ERC estadio 5 en diálisis peritoneal.
-Farmacológicos: Acido fólico
-Alérgicos: Niega
-Quirúrgicos: Niega
-Transfusiones:

PARACLNICOS IMAGENOLOGICOS:
- Rx de torax 23.08.2017: Atelectasia plana en base pulmonar derecha, derrame pleural leve izquierdo
-EVDA 23.08.2017: Esofagitis erosiva

EXAMEN FISICO
t 34.2 fc 85 x min ta 110/48 tam 69
sat 100% fio2 .5 fr 24
norepienfrina 80cc/h (0.35micg(kg/min) vasopresina 0.03UI/min
diuresis 250cc balance 1512 cc balane general 1512 cc
glucos 146mg/dl
Paciente en cama, tranquilo, hemodinamicamente estable, orientado en tiempo, persona y lugar.
Ruidos cardiacos rítmicos, sin soplos.
Murmullo vesicular normal, no ruidos
sobreagregados. Blando, depresible, sin dolor a la palpación, sin masas ni megalias. Cateter de dialisis peritoneal sin signos inflamatorios evidentes. extremidades móviles, sin edemas, llenado capilar < 2 segundos. No deficit motor ni sensitivo, reflejos ++/++++, respuesta plantar flexora bilateral, glasgow 15/15

gases pH 7.31 pco2 29 po2 92 hco3 14 sat 96 be -10
gases venosos pco2 35 sat 57
na 139 k 3.8 ac lactico 1.8

ANALISIS / PLAN:
Paciente con antecedentes anotados , hospitalziación en esta misma sala reciente por PBE y bacteremia por clostidium tertrium.
Ahora con cuadro de dolor en miembto inferior derecho y fosa iliaca derecha , en ocasiones asociado a alodinia, además deposciiones melenicas, curiosamente no ha habido caída de Hb, la EVDa fue normal y esta pendiente realización de colonosocopia.
Llamativamente en choque con diferencial de presion de pulso amplio que hace pensar en choque distributivo, el ac lactico se ha depurado , sin embargo hay un delta de co2 amplio y saturación venosa baja , consdiero oportuno inicio de dobutamina para mejorar flujo.
No cursa con neumonía como se habpia cosndierado ,s e revisan placas previas se videncia el mismo derrame basal izquierdo y atelectasias basales ya conocidas, me preocupa que el dolor hacia miembro inferior sea manifestaión de algo mas , discutire con intensivista de turno la cosnideración de realizar una imagen abdomino-pelvica para descartar absceso a nivel de psoas, ya que no tenemos fuenre de infección lñocalizada, el liquido peritoneal es negativo para PBE, Por el momento continuamos soporte y pauta antibiotica establecida .
Paciente con algo de diuresis residual se solicita urocultivo.

Ingrid Alvarez Fellow UCI

Responsable: ALVAREZ ECHEVERRY, INGRID KATHERINE MEDICINA INTERNA

Cédula: 1085245468 RM:52 1740 2009

Evolución UCI

Fecha: 25.08.2017 00:34:38

Evolución:
nota de evento.
Paciente que posterior a cateterización vesical presenta dolor abdominal intenso que no mejora con accetaminofen.
Se decide paso de hidromorfona 0.2mg .
Posterior a paso de medicamento presenta estupor, hipoperfusión , y palidez generalziada , ante disminución de respuesta neurológicase decide revertir con naloxona 1 ampolla , sin embargo paciente persiste sin respuesta , y se decide iot en el cambio de posicion presenta asistolia y se inicia RCCP con masaje cardiaco , se pasa bolo de liquidos ev y se inicia adrenalina , ciclos 30x 2 (masaje respiracion) y c/ 3 minutos adrenalina se pasa 6 dosis. Durante paro dos bradicardias extremas con pulso se pone dos dosis de atropina .
Dada la historia d ehipocalcemia , se pasan 20 mg de gluconato de calcio, y bicarbonato 100meq.
Paciente sale de ritmo de paro a sinusal , posteriormente presenta ritmo con extrasistoles frecuentes y taquicardia ,s e pasa dos ampollas de calcio- con lo que se estabiliza membrana .
eco control con corazon aaturdido severa depersion miocardica se indica dobutamina a 15 micg/kg/min.
Se toman paraclinicos de control Hb 5.4 se indica trasfusion .
Pendiente paraclinicos
se explica a hijo riesgod e fallecer y derequerir terapia de reempalzo renal .

Ingrid Alvarez Fellow UCI

Responsable: ALVAREZ ECHEVERRY, INGRID KATHERINE MEDICINA INTERNA

Cédula: 1085245468 RM:52 1740 2009

Evolución UCI

Fecha: 25.08.2017 01:10:55

Evolución:
reporte de paraclinicos
acidosis metabolica severa con hiperlactatemia .
hiperkalemia severa
mientras se monta maquina de dialisis se indica bolo de bicarbonato de 50 miequ seguida de infusion de bicarbonato a 70cc/h
se realzairá paso de cateter mahurkar recto 19 .
se indica dialisis filtro FX 80 mezcla 1 a 140 ml/min sin UF.
Familiar de paciente (edinson Jauregui) me solicita grabación de información. se acepta.

Ingrid Alvarez Fellow UCI

Responsable: ALVAREZ ECHEVERRY, INGRID KATHERINE MEDICINA INTERNA

Cédula: 1085245468 RM:52 1740 2009

Evolución UCI

Fecha: 25.08.2017 02:59:07

Evolución:
nota adicional
Paso de cateter mahurkar.
previa asepia antisepsia
colocaciond e campos quirurgicos.
se visualiza con guia eocgrafica vena femoral izqueirda , se punciona avnaza guia se visualiza con eco que esta en vaso , se dilata y avanza cateter , al recuperar guia se quiebra y tengo que retirarla con cateter , por lo que se debe abrir nuevo cateter mahurkar.
se realiza via ecografica puncion derecha , varios intentossin retorno , se logra canazlizar vena se hepariniza y se fija
se iniciar TRR.

Ingrid Alvarez Fellow UCI

Responsable: ALVAREZ ECHEVERRY, INGRID KATHERINE MEDICINA INTERNA

Cédula: 1085245468 RM:52 1740 2009

Evolución UCI

Fecha: 25.08.2017 10:14:23

Evolución:
EVOLUCION UCI DIA - 25.08.2017
NOMBRE: SANTIAGO JAUREGUI BAUTISTA, EDAD : 88 AÑOS, CC: 6061103

DIAGNOSTICOS:
- Shock séptico de causa no clara
- Disfunción multiorgánica
- Insuficiencia renal cronica estadio V

ANTECEDENTES PERSONALES:
-Patológicos: ERC estadio 5 en diálisis peritoneal.
-Farmacológicos: Acido fólico
-Alérgicos: Niega
-Quirúrgicos: Niega
-Transfusiones:

PARACLNICOS IMAGENOLOGICOS:
- Rx de torax 23.08.2017: Atelectasia plana en base pulmonar derecha, derrame pleural leve izquierdo
-EVDA 23.08.2017: Esofagitis erosiva

EXAMEN FISICO:
Paciente en malas condiciones generales, polisoportado con norepipnefrina, vasopresina y dobutamina. En ventilación mecánica invasiva y con hemofiltración continua. Sin sedoanalgesia. glasgow 3. pupilas anisocóricas.

CARDIOVASCULAR: FC: 106 /lpm TA: 103/45 mmHg TAM: 61 mmHg PVC 11
Ruidos cardiacos rítmicos, sin soplos. Norepinefrina 300 cc/hr, Vasopresina 12 cc/hr, Dobutamina 9 cc/hr

RESPIRATORIO: FR: 21 /rpm SatO2: 97% FIO2: 0.60 PEEP 8 IMV 24
Murmullo vesicular normal, no ruidos sobreagregados.
- Gases art/ven Ph: 7.16 pCO2 26/38 pO2 84 HCO3 9.3 SatO2 94/54% BE
-19
GASTROINTESTINAL: Abdomen blando, ddolor no evauable por estado neurológico. Cateter de dialisis peritoneal sin signos inflamatoriosevidentes.

HEMATOLÓGICO: Sin evidencia de sangrado
- Hb: 11 Hto: 33% Pqt: 136.000

INFECCIOSO: Temperatura 34.5C
- Leucocitos: 9780 Neutrs:77 % Linfs:9 % // PCR: 9.5
HEMOCULTIVO – UROCULTIVO: En proceso
ANTIBIOTICO FECHA: Vancomicina/meropenem (FI:24/08/2017)

RENAL: Diuresis 250 cc, balance 6374 cc, balance acumulado 6374 cc
- Na: 140 Cl: 99 K: 3.7 BUN: 11 Cr: 2.0

METABÓLICO: Glucometrías 146-163-258 mg/dl

EXTREMIDADES: Simétricas, hipoperfundidas, pipel motetada, frialdad distal, llenado capiplar mayor a 5 segundos.

ANALISIS Y PLAN:
Paciente con antecedente de ERC estadio V en diálisis peritoneal. Con hospitalización reciente en la institución por Bacteremia por clostridium tertium y peritonitis asociada a catéter de diálisis por E. coli BLEE positiva. Se dio alta médica el 13.08.2017 con tratamiento ambulatorio durante 5 días con metronidazol. Ingresa por cuadro clínico de dos días de evolución consistente en dos episodios de hematemesis, un episodio de melena y un episodio de rectorragia. Asociado presenta tos con expectoración blanquecina y dolor de tipo urente en miembro inferior derecho con irradiación a fosa iliaca ipsilateral. Al ingreso taquicardico, hipotenso y consignos de hipoperfusión. Se inicia reanimación hídrica, soporte con vasopresor, reposicion de K e inician cubrimiento antibiótico empirico con Vancomicina/meropenem. Se realiza cateterismo vesical para toma de muestra de urocultivo, después de este procedimientopresenta dolor severo por lo que se administró hidromorfona 0.2mg, posterior a lo cual presenta deterioro del estado de consciencia y signos de hipoperfusión por lo que se decide revertir con naloxona 1 ampolla, sin embargo paciente persiste sin respuesta, y se decide iot. Durante el cambio de posicion presenta asistolia y se inicia RCCP con masaje cardiaco, tras reanimación avanzada sale a ritmo sinusal. Posteriormente presenta ritmo con extrasistoles frecuentes y taquicardia, se pasan dos ampollas de calcio con lo que se estabiliza. Eco control con corazon aturdido severa depersion miocardica. Posteriormente acidosis metabolica severa con hiperlactatemia e hiperkalemia severa, se emprende manejo dialítico. El día de hoy paciente en malas condiciones generales, inestable, dependiente de soporte vasopresor e inotropico a altas dosis, asi como ventilatorio, en hemofiltro extendido, severamentehipoperfundido. Se considera paciente frágil y con pronóstico clinico reservado, y alto riesgo de fallecer, situacion que se explicaa su hijo.

Dra. Mónica Patricia Vargas O. Anestesióloga - Intensivista
Dra. Maria Paulina Martinez R. Médico general, asistencial UCI

Responsable: VARGAS ORDONEZ, MONICA PATRICIA INTENSIVISTA

Cédula: 0066827295 RM:663094

Alta Médica

Fecha:25.08.2017 20:53:50

Tipo Alta:Muerte Condición al Egreso:Muerto Fecha Muerte:25.08.2017 15:41:00

Causa:
CHOQUE, NO ESPECIFICADO

Complicaciones:
.

Recomendaciones:
.

Diagnóstico Alta: R578 OTRAS FORMAS DE CHOQUE

Responsable MARTINEZ GALLEGO, DIANA FERNANDA MEDICINA GENERAL

Cédula: 1130623317 RM:76690-2013

Valido como Firma Electrónica

PRUEBA C

PROTOCOLO DE SEDACIÓN FUNDACIÓN VALLE DEL LILI

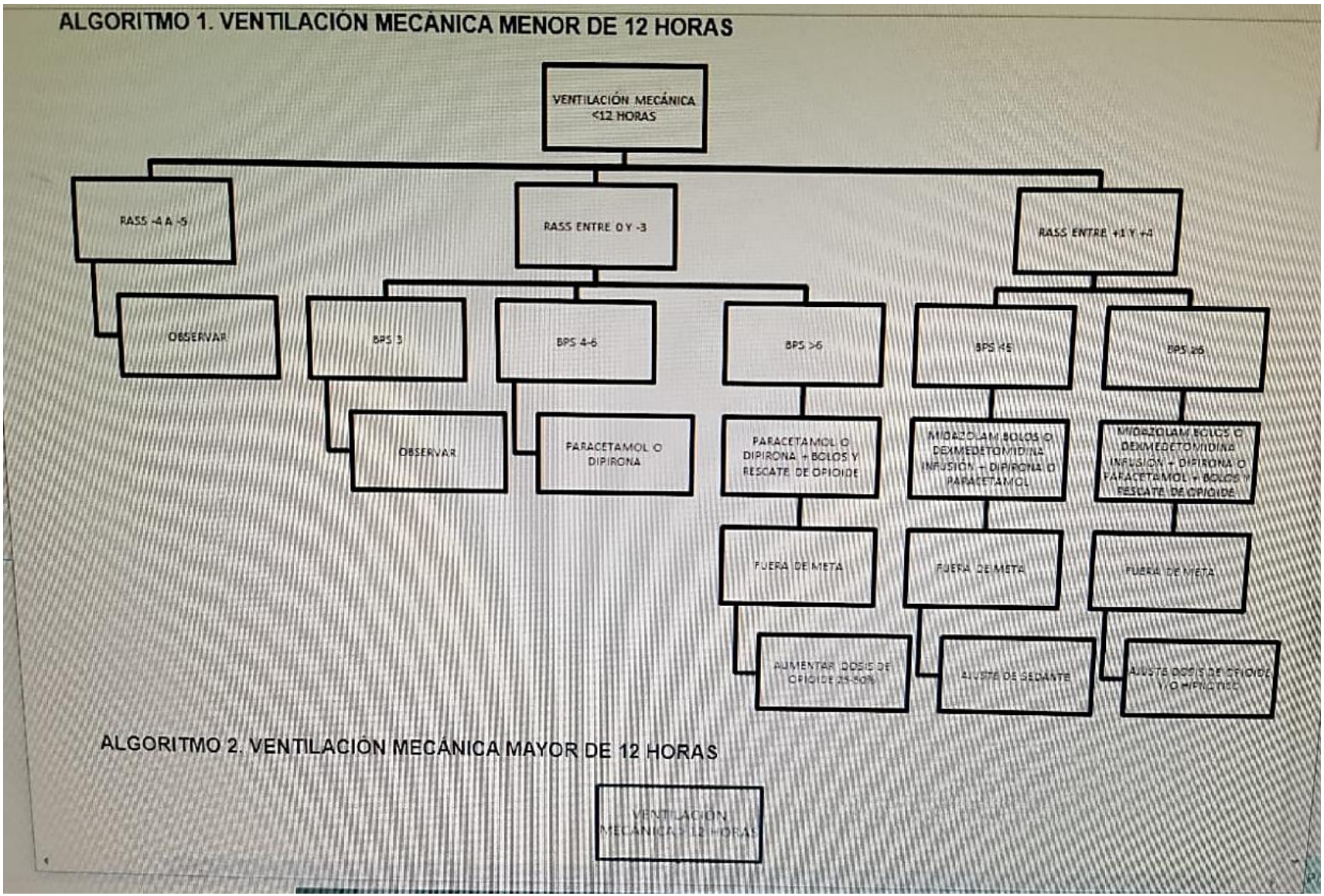
Tabla de agentes de sedación.

Sedantes y analgésicos en UCI	Dosis	Propiedades farmacocinéticas	Efectos adversos
Midazolam	Bolos 1-5 mg; infusión 1-5mg/h	Vida media 3-11 h. Metabolismo por oxidación hepática, excreción renal. Acumulación de metabolitos activos con infusión prolongada.	Asociación con delirium. Tolerancia
Propofol	Infusión 1-5 mg/k/h	Vida media 30-60 minutos en caso de infusión. Metabolismo por glucoronización e hidroxilación hepática.	Hipotensión, bradicardia, hipertrigliceridemia, pancreatitis, síndrome de infusión de propofol.
Dexmedetomidina	Infusión 0.2 - 1.5 mcg/k/h	Vida media 2 h. No se acumula con infusiones prolongadas. Metabolismo hepático, sin metabolitos activos.	Hipotensión, bradicardia, boca seca, náuseas
Fentanyl	Bolos 50-100 mcg. Infusión 50-100 mcg/h	Vida media 1.5-6 h. Acumulación con infusiones prolongadas. Metabolismo por oxidación hepática. Sin metabolitos activos.	Nauseas, depresión respiratoria, íleo, rigidez muscular con dosis de carga
Hidromorfona	Bolo 0.4 a 1.0 mg	Vida media 1.5-3.5 h. 7 a 11 veces más potente que la morfina. Metabolismo hepático por glucoronización, con metabolitos activos.	Náusea, íleo, depresión respiratoria
Morfina	Bolos 2-5 mg	Vida media 3-7 h. Inicio de acción más lento con menor acumulación comparado con Fentanyl. Metabolizado por glucoronización hepática, se deriva en morfina -6-glucorónido que es activo, y morfina 3 glucorónido que produce neuroexcitación.	Náusea, íleo, depresión respiratoria, liberación de histamina con hipotensión, prurito

9. PROCEDIMIENTO

Cada día durante la revista clínica, el grupo médico define los objetivos o metas de sedación (titulación de sedantes analgésicos, límite máximo de dosis, meta de RASS, entre otros), dejando consignados estos datos puntales en la pestaña de indicaciones de enfermería, en la hoja "Registro UCI"

ALGORITMO 1. VENTILACIÓN MECÁNICA MENOR DE 12 HORAS



ALGORITMO 2. VENTILACIÓN MECÁNICA MAYOR DE 12 HORAS

- Asma (según severidad de presentación)
- Enfermedad acido-péptica (historia de sangrado gastrointestinal)
- Insuficiencia renal (aguda o crónica)
- Mayores de 70 años
- Uso concomitante de Acido Acetil-salicílico
- Enfermedad ateroesclerótica / hipertensión no controlada

c. Uso de opioides:

Administrar preferiblemente 30-40 mins previo a finalización del procedimiento

- Morfina 0,05 a 0,1 mg/kg
- Hidromorfona 0,01 – 0,02 mg/kg
- Oxicodona 0,05 – 0,07 mg/kg

En la UCPA se debe garantizar el acceso a opioide fuerte de rescate para titulación rápida por el/la jefe de enfermería siguiente esquema si la intensidad del dolor al ingreso es mayor a 4/10 en la escala de EVN o hay signos indirect dolor no controlado según el flujograma y usando el opioide indicado por anestesiólogo a cargo del procedimiento o a de la vigilancia de los pacientes en UCPA

- Morfina 1-2 mg EV cada 15 minutos, hasta máximo 10 mg
- Hidromorfona 0 1-0 2 mg EV cada 15 minutos, hasta un máximo de 2 mg
- Oxicodona 1-2 mg EV cada 15 mins, hasta un máximo de 10 mg
- Fentanyl 10-20 mcg EV cada 10 mins, hasta un máximo de 100 mcg.

En el uso de opioides habrá que tener en cuenta la probabilidad de presentar nausea y vómito, por lo que se debe adi antiemético al tratamiento (referirse al protocolo de profilaxis de náusea y vómito postoperatorio)

Además de evaluar **dolor**, deberá hacerse una continua valoración del estado de conciencia, frecuencia respirat saturación de oxígeno por pulsoximetría, para evitar episodios de sedación extrema y depresión respiratoria. E posibilidad de rotación de opioide en caso de efectos secundarios que no mejoran con tratamiento convencional.

d. Coadyuvantes

- De forma individual y a criterio de anestesiólogo a cargo, evaluar la utilización de otros coadyuvantes analgésicc dexametasona, ketamina, lidocaína, sulfato de magnesio con indicación de continuar o no durante estancia en U

PRUEBA D

Dr. Leonardo Marín Restrepo.

- Médico internista, intensivista y nefrólogo.
- Cédula de ciudadanía N.º 94366458 de Tuluá
- Registro médico N.º 760189-97

Coordinador Nacional FMExpress

Dictamen médico solicitado el 11 de octubre de 2021 por el abogado Andrés Fernando Ortega Ordóñez, identificado con cédula de ciudadanía N.º 1.085.277.335 y tarjeta profesional N.º 218.685 del Consejo Superior de la Judicatura, apoderado judicial de la dra. Ingrid Álvarez Echeverry.

Santiago de Cali, 4 de noviembre de 2021.

El suscrito, Leonardo Marín Restrepo, identificado con C.C. N.º 94366458 de Tuluá y Registro médico N.º 760189-97, declaro bajo juramento que:

1. No he sido designado en procesos anteriores o en curso por la misma parte o por el mismo apoderado de la parte.

2. No me encuentro incurso en las causales contenidas en el artículo 50 del Código General del Proceso.

3. Declaro que la evaluación establecida en el documento de la referencia es independiente y corresponde a la real convicción profesional.

La aplicación de la hidromorfona en pacientes renales

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La aplicación de la hidromorfona como causa eficiente del deceso del señor Santiago Jauregui Bautista

Dictamen pericial por la muerte del señor Santiago Jauregui Bautista, vinculada a la atención médica brindada por la dra. Ingrid Álvarez Echeverry, el 25 de agosto de 2017, en la clínica Fundación Valle de Lili, en Santiago de Cali.

Dr. Leonardo Marín Restrepo

- **Formación**

Médico general de la Universidad Tecnológica de Pereira

Médico internista de la Universidad Nacional de Colombia

Médico intensivista de la Universidad del Valle

Médico nefrólogo de la Universidad de Universidad Javeriana

25 años de ejercicio de la profesión.

Cédula de ciudadanía N.º 94366458 de Tuluá

Registro médico N.º 760189-97

- **Experiencia laboral**

Baxter. Nefrólogo director URenal la flora. 2001-2007

Fundación Leonor Goelkel. Nefrólogo 2008-2010

Fresenius Medical Care. Nefrólogo FMExpress. 2010-actualidad.

Clínica de los Remedios, Nefrologo 2005-actualidad.

Clínica de los remedios. Cuidado Intensivo 2007-2017 (Coordinador 2013-2017)

Clínica Amiga. Coordinador cuidado intensivo 2018-2020.

Actualmente Coordinador Nacional del Programa de Nefrología Crítica y Hospitalaria (FMExpress) de Fresenius Medical Care

Domiciliado en Santiago de Cali, carrera 117 # 9 – 195, casa 9.

Contacto: leomarin@hotmail.com.

Celular: 315 590 0990

I. Introducción

La finalidad del presente dictamen pericial se concreta en determinar si la hidromorfona constituyó la causa eficiente del fallecimiento del señor Santiago Jauregui Bautista, el 25 de agosto de 2017, en la clínica Fundación Valle de Lili.

II. Formulación del problema de investigación

¿El uso de hidromorfona estuvo asociado con el desenlace del paciente?

¿Existió mala práctica clínica al indicar hidromorfona a este paciente con dolor?

2.1. Antecedentes del paciente

- Nombre: Santiago Jauregui Bautista
- Edad: 88 años

Paciente con historia de enfermedad renal crónica estadio G5, en diálisis peritoneal, quien había estado hospitalizado desde el 1 de agosto de 2017 hasta el 13 de agosto de 2017 por cuadro de bacteriemia por *clostridium tertium* y peritonitis asociada al catéter de diálisis por *Escherichia coli* inductora de betalactamasas positiva.

Reingresó el 23 de agosto de 2021, por cuadro de 2 días de hematemesis y melenas, con un episodio de rectorragia, tos con expectoración blanquecina y dolor en fosa iliaca derecha irradiado a miembro inferior ipsilateral. Al reingreso, se presentó frecuencia cardiaca elevada, presión arterial baja, signos de mala perfusión periférica, con requerimiento de soporte vasoactivo. Se solicitaron cultivos y se indicó inicio de pauta antibiótica de amplio espectro y reanimación guiada.

Durante su estancia en la Unidad de Cuidados Intensivos – UCI, se percibió mejoría inicial del cuadro; sin embargo, se apreció un lactato no completamente depurado, con delta de CO2 elevado y persistencia de requerimiento de soporte vasoactivo. Con posterioridad, nuevamente con dolor en fosa iliaca derecha e irradiación a miembro inferior de difícil control. No mejoró con acetaminofén, por lo que requiere cateterización vesical para evaluar orina residual y por dolor (posible globo vesical). Se indicó analgesia con hidromorfona 0,2 mg., dosis única. Luego, el paciente presenta deterioro de su estado general.

Paciente somnoliento, con hipoperfusión y palidez. Se indicó el suministro de Naloxona, sin mejoría. Por deterioro, se indica intubación orotraqueal sin complicaciones. En cambio de posición presentó asistolia, por lo que se inició reanimación cardio cerebro pulmonar consistente en aplicación de adrenalina. Se reanima por 20 minutos, con adrenalina, se indica calcio, bicarbonato y se prescribe dobutamina por *eco focus* que muestra corazón aturdido.

Se toman paraclínicos y se evidencia Hb 5,4 y se indica trasfusión de dos unidades de glóbulos rojos.

Paciente con acidosis severa, requerimientos de terapia de reemplazo renal, soporte vasoactivo a dosis altas.

Finalmente, el paciente falleció.

III. Estado del arte

3.1. Definiciones

Enfermedad renal crónica: anormalidades en la estructura o función renal presentes por más de 3 meses con complicaciones para la salud. Está clasificada con base a la causa, categoría de tasa de filtración glomerular y albuminuria. Va de G1 a G5 siendo el G5 la falla renal completa.

Terapia de reemplazo renal: Técnicas de purificación de sangre extracorpórea que reemplaza la función renal.

Diálisis peritoneal: Técnica de terapia de reemplazo renal en la que se usa el peritoneo (cubierta interna del abdomen), para la filtración de las sustancias que se producen en el cuerpo.

Catéter de diálisis peritoneal: Catéter en la parte abdominal conectada al peritoneo por la que cada día se realiza recambio de líquidos para la excreción de sustancias que normalmente son eliminadas por la orina y cuyo acumulo de sustancias toxicas para el sistema cardiovascular, muscular y neurológico.

Infección asociada a catéter de diálisis peritoneal: infección del líquido peritoneal asociado a la posibilidad que el catéter de diálisis esté contaminado o colonizado por gérmenes.

***Clostridium tertium*:** bacteria bacilo gram positive anaeróbico.

***Escherichia Coli* inductora de betalactamasa:** Enterobacteria gran negativa con patrón de resistencia para antibióticos betalactámicos.

Bacteriemia: Infección bacteriana que se disemina a través de la sangre.

Choque séptico: situación en la que los órganos del cuerpo no reciben suficiente oxígeno o nutrientes lo que lleva a muerte progresiva de las células y fallo en la función de los diferentes órganos.

Soporte vasoactivo: Medicamentos que se utilizan para intentar mejorar la presión arterial y así garantizar la entrega de oxígeno a los órganos para su funcionamiento.

Hidromorfona: Opioide sintético. Medicamento que se usa para el manejo del dolor.

Parada cardiorrespiratoria: Cese de la respiración y del latido cardiaco de un individuo.

Reanimación cardiopulmonar: Medidas para reestablecer el latido cardiaco y el flujo sanguíneo durante una parada cardiorrespiratoria.

Intubación orotraqueal: Colocación de tubo en la vía respiratoria para mantener la respiración cuando el individuo es incapaz de realizar respiraciones que garanticen el aporte de oxígeno al organismo.

Anemia: Hemoglobina menor de 12 g/dl en mujeres y 13g/dl en hombres.

3.2. Argumento de autoridad

La enfermedad renal crónica tiene impacto en la morbilidad y mortalidad de los pacientes, la cual se incrementa con el estadio en el que se encuentra el paciente, siendo mayor para la enfermedad, el estadio G5. El riesgo relativo, medida utilizada en estadística para determinar cuántas veces mayor riesgo tiene un paciente con una determinada condición, de morir, comparada con el resto de la población, para pacientes con enfermedad renal crónica G5, está entre 5.3 - 6.6 para todas las causas de mortalidad, 8,1 - 14 para la mortalidad cardiovascular. [(1)]

El choque séptico, es decir, la presencia de disfunción orgánica e hipoperfusión secundaria a una infección y que se caracteriza por la clínica que presentaba el paciente y la necesidad de soporte vasoactivo y antibióticos para tratar la infección, tiene una mortalidad que oscila entre el 24,2 al 32% en casos de pacientes no seleccionados, esto es, en la población general sin tener en cuenta comorbilidades.

La edad, la presencia de neutropenia y el desarrollo de isquemia de órganos intrabdominales como el intestino, secundaria a alteraciones de la perfusión por el choque empeoran el pronóstico de los pacientes ingresados por choque séptico. (2)

Un subestudio de la cohorte NHANES, (corte prospectiva de seguimiento poblacional, más grande del mundo), determinó que la mortalidad asociada a infecciones en la población con enfermedad renal crónica es más alta, especialmente, en aquellos pacientes con menor tasa de filtración glomerular, es decir, pacientes en estado V pueden llegar a tener un Hazard Ratio (riesgo de presentar un evento en comparación de otra población) de 1.36 veces, es decir 36% más que las personas con Tasa de filtración glomerular mayor del 60% y esto empeora en el caso de bacteriemia donde 11.7% de los pacientes en hemodiálisis y 9,4% de los pacientes en diálisis peritoneal tienen al menos un episodio de bacteriemia en su vida con una mortalidad 100 a 300 veces mayor para los pacientes en diálisis crónica que en la población en general.(3)

Cabe anotar que la presencia de episodios infecciosos en estos pacientes también incrementa su riesgo de readmisiones por infección en los siguientes 30 días del evento con tasas que llegan a ser del 21-34% e incremento del riesgo de eventos cardiovasculares subsecuentes. (4)

Las infecciones por *Escherichia coli* son la causa más frecuente de bacteriemia; su frecuencia aumenta con la edad con tasas mayores a 300 en pacientes entre los 74 a 85 años (no hay datos por encima de esta edad), con una fatalidad del 12% con fuente primaria en el 53% de los casos en el tracto genitourinario. (5)

Los patrones de resistencia son cada vez más frecuentes en el mundo, causando aumento en la morbilidad y mortalidad; la presencia de esta enzima significa una capacidad reducida en las opciones antimicrobianas y que el riesgo de incrementar la resistencia con nuevos episodios infecciosos sea mayor (6).

Al comparar las infecciones por gérmenes no resistentes, con gérmenes con patrón de resistencia, la mortalidad es más alta en los pacientes con betalactamasas, especialmente, en pacientes ancianos, con leucocitosis y tratados con carbapenémicos [(7)].

La infección por *clostridium tertium* es infrecuente en las personas con estado inmunológico adecuado. Los reportes de esta infección son escasos, algunos infectólogos no consideran en condiciones normales este microorganismo un patógeno (es decir un microorganismo causante de enfermedad), los pocos casos de enfermedad registrados son en pacientes en quienes su sistema inmune no está en la capacidad de defenderlo de agresiones, por ejemplo pacientes con neutropenia severa asociada a leucemia, enfermedad en la que se encuentran reportados el 91% de los casos, y el restante son casos en pacientes con enfermedades gastrointestinales [(8)].

IV. Uso de opioides en pacientes con enfermedad renal crónica

En Estados Unidos se ha reportado que el 43.8% de los pacientes con enfermedad renal crónica han recibido alguna vez un medicamento opioide para el control del dolor.

La morfina el principal representante de esta familia de medicamentos tiene un punto máximo de acción de 30 minutos después de la aplicación intravenosa con una vida media que dura entre 2 a 3 horas después del bolo. Su metabolito, la morfina 6 glucuronamida se acumula en pacientes con enfermedad renal crónica desde dosis de 30 mg, especialmente, en el sistema nervioso central, lo que genera no solo analgesia, sino también sedación y posiblemente neurotoxicidad, por lo que se debe evitar en pacientes con enfermedad renal crónica y de edad avanzada.

La hidromorfona medicamento de corta acción, es el medicamento de elección en los pacientes con enfermedad renal crónica, es tan efectivo como la morfina y 8,5 veces más poderoso por vía endovenosa para el control del dolor, con una baja unión a proteínas y una vida media de 39 horas.

La ventaja de la hidromorfona sobre otros derivados opiáceos en el contexto de enfermedad renal crónica, es que no tiene acumulación renal dado su rápido cambio a su metabolito primario, que no tiene actividad analgésica no relacionada con los eventos adversos típicos de los opioides, por lo que este medicamento es más favorable y seguro que la morfina.

La aparición de efectos adversos de índole neurológica, como la agitación, disfunción cognitiva, mioclonías, y tremor aparecen con dosis repetitivas y crecientes. **La dosis recomendada es de 1-2 mg cada 3 a 4 horas con una vida media normal de 2-5 horas** [9, 10].

No se recomienda el uso de antinflamatorios no esteroideos (AINES) como ibuprofeno, naproxeno dados sus potenciales riesgos gastrointestinales y la interacción de la ciclooxigenasa que puede llevar a hiperkalemia (elevación del potasio en sangre que puede llevar a arritmia) en pacientes renales crónicos. Entre los eventos gastrointestinales que se pueden presentar se encuentra el sangrado digestivo. [10]

V. Análisis valorativo de la praxis médica según la *lex artis y lex artis ad hoc*

De la historia clínica se deduce que se trata de un paciente adulto mayor frágil con una con falla renal en diálisis. La presencia de hospitalización reciente y la persistencia de signos y síntomas durante el período que estuvo ambulatorio habla de la escasa reserva funcional que tenía.

A su ingreso con cuadro de choque, por lo descrito del sangrado, se especuló en hipovolémico, pero, al no encontrarse foco de sangrado que lo explicase (estando pendiente la colonoscopia) y con la aparente estabilidad de la hemoglobina en un par de mediciones, se orientó hacia choque séptico, situación para lo cual igualmente hay antecedentes y factores de riesgo; además, las dos condiciones pueden presentarse simultáneamente.

En la noche, encontrándose en condición crítica, con doble soporte vasopresor, presentó dolor abdominal agudo posterior a un cateterismo que no cedió con analgésico de primera línea (acetaminofén), por lo que se decidió administrar un opioide.

La hidromorfona es uno de los opioides considerados seguros en los pacientes con falla renal, y la dosis administrada fue baja (0.2 mg. de 1 o 2 mg. recomendados) para considerar que ello habría generado el deterioro del cuadro clínico del señor Jauregui Bautista.

No es posible atribuir el deterioro clínico del paciente a la administración de este fármaco, únicamente considerando el periodo transcurrido a partir de su suministro, puesto que ello no está acorde con el comportamiento del medicamento y sus características ya descritas.

Una de las obligaciones del profesional en la medicina se circunscribe al control del dolor del paciente, y para tal propósito existen diversos fármacos que su uso conlleva ciertos riesgos; sin embargo, sus beneficios superan ampliamente los peligros de su formulación.

La depresión respiratoria y el efecto hemodinámico de los opioides es dosis dependiente, esto significa que se da dependiendo de la cantidad de medicamento utilizada y la frecuencia en su administración, y la dosis utilizada en el paciente fue muy baja. Si el fármaco en esa dosis hubiera causado el evento, resultaba imposible de prever y, al tener una necesidad imperativa de aliviar el dolor, el beneficio de la administración superaba ampliamente cualquier riesgo (muy bajo) de su utilización.

La falta de respuesta del paciente ante el antídoto específico (naloxona) genera duda si la hidromorfona hubiera sido la responsable de tal deterioro, puesto que la respuesta de la naloxona después de su administración es inmediata.

La presencia de la hemoglobina de 5,4 es muy llamativa y permite formular la existencia de un episodio de sangrado mayor oculto de origen no evidenciado en los estudios que se alcanzaron a realizar. Tal grado de anemización, en un paciente de su fragilidad, sería escasamente tolerada, lo cual le produciría su muerte.

A pesar de que se realizó trasfusión de hemoderivados y no hubo mejoría clínica, la reanimación se hizo con la plena intención de evitar la muerte, incluso, por un tiempo prolongado y escalando a medidas invasivas como la hemodiálisis continua, lo cual, para un paciente de sus características, no resultaba realmente provechoso.

En otras palabras, el cuadro clínico del paciente al momento de ingresar a la Unidad de Cuidados Intensivos de la clínica Fundación Valle de Lili fue muy precario, y sumado a las preexistencias, como la falla renal en estadio G5, que requería terapia de reemplazo renal, y los antecedentes de infecciones por gérmenes con patrón de resistencia antibiótica y gérmenes que solo afectan a pacientes con compromiso de su estado inmunológico de manera severa y sobre todo, su avanzada edad de 88 años, produjeron su deceso, mas no es posible asociar que el suministro del opioide hidromorfona en una única dosis y en la quinta o décima parte de la cantidad que la literatura médica recomienda suministrar, generó su muerte.

Lo anterior, por cuanto si la hidromorfona, inclusive, en esa cantidad tan baja, hubiera causado el deterioro de las condiciones del paciente, el cuadro clínico habría mejorado con el suministro de la naxolona, fármaco de inmediata acción.

VI. Contraargumentación

El uso de 0.2 mg. de hidromorfona en un paciente de falla renal en estadio G5 causaría eventualmente el deterioro del estado del paciente, eventualmente, si se aplicaría en dosis mayores y de manera recurrente, lo que hubiera causado una acumulación del opioide en el organismo, lo cual es poco probable, considerando la vida media del fármaco y el metabolito que produce.

VII. Limitaciones de la investigación pericial

Del análisis de la historia clínica no es posible establecer los niveles de concentración de los opioides en el organismo del paciente; no obstante, con la evidencia y literatura médica existente se puede demostrar que la única dosis utilizada fue, incluso, más baja que la recomendada en estos pacientes.

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Dr. Leonardo Marín Restrepo

Médico especialista en medicina interna, nefrología y cuidado intensivo

C. C. N.º 94.366.458 de Tuluá

R.M. N.º 760189-97

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The Role of Opioids in Pain Management in Elderly Patients with Chronic Kidney Disease: A Review Article

Sanam Dolati [1, 2], Faezeh Tarighat [1], Fariba Pashazadeh [3], Kavous Shahsavarinia [4], Saina Gholipouri [5] and Hassan Soleimanpour [6, *]

[1] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Physical Medicine and Rehabilitation Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3] Research Center for Evidence-Based Medicine, Health Management and Safety Promotion Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran
[4] Emergency Medicine Research Team, Tabriz University of Medical Sciences, Tabriz, Iran
[5] Department of Medical Sciences, University of Western Ontario, Ontario, Canada
[6] Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran

[*] *Corresponding author*: Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran. Email: h.soleimanpour@gmail.com, soleimanpourh@tbzmed.ac.ir

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Abstract

Chronic kidney disease (CKD) is a global public health problem. Pain is one of the most generally experienced symptoms by CKD patients. Pain management is a key clinical activity; nonetheless, insufficient pain management by health professionals keeps it up. Opioids as pain relievers are a class of naturally-derived and synthetic medications. They act through interactions with receptors in peripheral nerves. Numerous pharmacokinetic alterations happen with aging that influence drug disposition, metabolism, and quality of life. Acetaminophen alone, or combined with low-potency opioid dose is regarded as the safest pain-relieving choice for CKD. Morphine and codeine are probably eluded in renal impairment patients and used with excessive carefulness. Tramadol, oxycodone, and hydromorphone can be used by patient monitoring, while methadone, transdermal fentanyl, and buprenorphine seem to be safe to use in older non-dialysis patients with renal impairment. Consistent with the available literature, the main aim of this review was to explore the occurrence of chronic pain and its opioid treatment in CKD patients. According to this review, more and well-made randomized controlled trials are necessary to find appropriate opioid doses and explore the occurrence of side effects.

Keywords: Pain Management, Opioids, Chronic Kidney Disease, Dialysis

1. Context

Chronic kidney disease (CKD) is described as the perseverance of structural and/or functional anomalies of the kidney for three or more months (1). The overall prevalence of CKD is approximately 13.1% in adults, so that 50% of the patients with CKD are older than 70 years (2). More than 26 million people are affected in the United States (US), and its prevalence will increase to 35% in individuals over the age of 70 years in the next 10 years (3). The majority of CKD patients suffer from mild-to-moderate CKD stages I-III (12.7%); however, severe CKD stages IV and V are rare (0.35% and 0.11%, respectively) (2). There has been a constant rise in the number of older patients with CKD leading to end-stage renal disease (ESRD) in need of dialysis (4). ESRD is described by the National Kidney Foundation as the furthermost stage of renal failure stage V (with estimated glomerular filtration rate (eGFR) < 15 mL/min) (5).

In the US, patients older than 65 years comprise 40% of ESRD patients (6). The causes of CKD consist of diabetes, hypertension, renovascular diseases, primary glomerulonephritis, and inherited kidney diseases. Proteinuria, renal hypertension, anemia, and nerve damages are also developed with the progression of CKD (7). Fatigue is observed in 71% of patients, pruritus in 55%, nervousness in 38%, dyspnea in 35%, nausea in 33%, and depression in 27%, all leading to the decreased quality of life (QoL) of patients (8, 9). Pain is among the most commonly described symptoms, predicted to have impacts on more than 58% of CKD patients, of which 49% is moderate to severe in intensity (10, 11). Common types of pain in dialysis patients include musculoskeletal pain (63%) due to osteoarthritis, neuropathic pain, and pain associated with the dialysis procedure, such as arteriovenous (AV) (12). Other causes of pain comprise peripheral vascular disease, renal osteodys-

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trophy, inflammatory arthritis, and polycystic kidney disease (13). It is predicted that up to 48% of dialysis patients have dialysis-related headaches (DH) (14). The traditional management of CKD includes the control and treatment of hypertension to decrease the progress of CKD, salt restriction, use of statins, diabetes control, home care, oral sodium bicarbonate, anti-aging, antioxidant, and anti-inflammatory agents, and dialysis (15). Kidney transplantation provides older patients with good longstanding transplant endurance and quality of life; nonetheless, it entails a greater risk of malignancy, infection, and car-diovascular disorder (16).

Opioids are also used for pain management in CKD patients (17). The short-term efficiency of opioid use ($\leq$ 12 weeks) has been recognized among older adults (18). Despite evidence about the advantages of opioids and accessibility of these drugs, some studies have suggested that pain is inefficiently cured in patients on hemodialysis (HD), and side effects may be an obstacle to operative pain management (19). The frequency of analgesic use in ESRD patients is very different; nonetheless, it is estimated at 24%, which less than 15% are prescribed opioids, and even acetaminophen use is low at 6% (20). One of the main obstacles to efficient pain control is opioid addiction (21). Opioids can also increase the risk of falls in elderly patients, which is a principal reason for injuries, hospitalization, and deaths among the elderly (22). Opioid therapy worsens the symptoms, including orthostatic hypotension, impaired cognition, nausea, and poor appetite., fatigue, and constipation (21). General practitioners are now unwilling to recommend chronic opioids to patients with CKD due to severe side effects, including depressive effects on the respiratory and central nervous systems and psychological addiction (23, 24). In 2016, more than 42,000 deaths were attributed to opioid overdose, and 40% of them were attributed to prescribed opioids (25). The World Health Organization (WHO) step 1 - 3 pain relievers are essential to pain management (26). Mild pain must be treated by step 1 analgesics, con-taining acetaminophen (paracetamol (1g qds)) or nonsteroidal anti-inflammatory drugs (NSAIDs) (27). Step 2 applies to moderate pain and includes weak opiates such as tramadol (50 - 100 mg qds) and low-dose opioids such as hydromorphone (1 - 2 mg) or oxycodone (2.5 - 5 mg) (28). Step 3 is used for severe pain, with greater doses of oxycodone or hydromorphone and drugs with long-lasting effects, including fentanyl (25 micrograms as initial dose subcutaneously and "25" patch upwards, transdermal every 72 hours) (29). Consistent with the available literature, the main aim of this review was to examine the opioid management of chronic pain in CKD patients and related adverse effects.

2. Opioid Use in Chronic Pain Management

Between September 2001 and July 2002, one study of 205 HD patients in Canada assessed the prevalence, strictness, reasons, and management of pain in this population and establish that 50% of the patients described the pain as a symptom. Patients with pain were on hemodialysis therapy longer than patients without pain were (52.2 months vs. 37.7 months) (30). Of these patients, 32% were prescribed with no analgesics, 29.1% ad-ministered non-opioids, 26.2% were provided with weak opioids, and only 9.7% received strong opioids. The efficiency of therapy was described as acceptable by only 6% of the patients, whereas 74.8% reported their treatment as insufficient (30). In 2006, a cohort study was conducted on 45 patients on chronic HD who had pain. Short-form MPQ (SF-MPQ) was used for pain assessment at baseline, and the patients were then managed according to a WHO analgesic ladder for more than four weeks (31). The mean age was 65 $\pm$ 12.5 years, and 49% of the patients had diabetic nephropathy as a reason for ESRD. Early pain was rated severe by 76% of the patients. In total, 43 patients described sufficient analgesia at four weeks, and there was a numerically substantial decline in the mean pain score compared to baseline (31). From 1995 to 2004 in 12 countries of diverse regions, a systematic review investigated 10 studies reporting opioid use in > 26,000 patients with ESRD, including 90% dialysis patients (19). The described prevalence of opioid use was in the range of 5% to 36%. The most common recommended opioids in Canada were codeine and oxycodone although, in the US, the propoxyphene-acetaminophen combination was the most common recommended opioid (19). A study by Barrantes et al. (32) in 2013 investigated the results of kidney transplants according to the patients' history of chronic opioid use before transplantation. Among 1,064 adult kidney transplant patients, 42.5% described the existence of numerous body pains. This study documented that a history of previous chronic opioid use was individually related to a higher risk of death (adjusted hazard ratio (aHR) = 1.65; 95% CI, 1.04 - 2.60). Therefore, a history of chronic opioid use before transplantation seems to be accompanied by enhanced mortality risk (32). A Swiss survey of 123 patients aged 36 - 90 years on dialysis for 3.5 years found that 68 patients had chronic pain, and the pain intensity in two-thirds of the patients was higher than five on a Visual Analog scale

(VAS) (33). Besides, 35 patients recognized musculoskeletal pain as the most troubling pain (33). In these patients, musculoskeletal pain was a prominent reason for sleep disturbances including problems in awakening, nightmares, interrupted sleep, sleep apnea syndrome, and restless leg syndrome, and it was cured with opioids in only a small number of patients (33). Opioids were suggested for only 21% of these patients; and non-opioid analgesics (principally NSAIDs) were in use by 80% of the patients (34). A study used the data on baseline visits from 308 patients with CKD. The chronic pain severity was evaluated by the Wong-Baker FACES Pain Rating scale (35). In this study, 60.7% of the patients stated chronic pain, and 5.8% with no chronic pain were on NSAIDs (36). Mild and severe chronic pains were related to analgesics with a drug-related problem (DRP), with odds ratios (OR) of 3.04 and 5.46, respectively (35). Olivo et al. (37) examined opioid management approaches in 191 HD patients; 27% of them were long-standing opioid users (more than 90 days). The most usually recommended opioids were paracetamol-comprising opioid drugs (98%), principally, hydrocodone-paracetamol (90%), and oxycodone-paracetamol (42%) (37). The safest opioids, fentanyl, and methadone were recommended in 6% and 4% of the cases, respectively (37). A recent systematic review of 52 studies with an overall of 6,917 patients described a prevalence of acute (82%) and chronic (92%) pain in HD patients (38). A small number of studies investigated the features of pain, but the prevalence of severe pain was described to be up to 76% (38). One cohort study during 2006 - 2010 evaluated opioid treatment and the relationship of opioid recommendation and dose with patient outcomes (39). In the study period, 64% of the dialysis patients received at least one opioid recommendation, 41% of the patients had a short-term prescription, and 23% received a chronic opioid recommendation ($\geq$ 90-day supply) (39). In the 2010 cohort, patients with temporary (1 - 89 days) and chronic opioid treatments showed more hospitalization, dialysis discontinuation, and mortality than did patients without an opioid prescription (39). In a study, among 1,256 opioid users who died of an opioid-associated reason and 4,619 controls who also used opioids, the first experience was simultaneous gabapentin use in 120 days before the index date; a sensitivity analysis studied the effect of simultaneous (NSAID) use in previous 120 days (40). The simultaneous use of opioids and gabapentin was correlated with a considerably enhanced odds of opioid-associated death (approximately 60%) compared to opioid prescription alone (40). There was no substantial link between the simultaneous use of opioids and NSAIDs and opioid-related death (40). Gabapentin is a drug frequently used in combination with opioids, and both of them have revealed to inhibit breathing, which can be lethal (40). The simultaneous opioid use raises the amount of gabapentin absorbed, and it was accompanied by a 49% higher risk of becoming extinct from an opioid overdose (40). One cohort study assessed connotation during opioid use and time to hospitalization or first visit because of falls, fracture, and altered mental status among 140,899 adults on hemodialysis (41). Opioids were related to adverse results in patients on HD; 64% received opioids; besides, fall (7646 events), fracture (4151 events), and episode of altered mental status (15,658 events) happened (41). The prevalence rates of opioid prescriptions (containing methadone, tramadol, and buprenorphine), NSAIDs, and across stages of kidney function in primary care patients were assessed by the Geisinger Health System between 2011 and 2016 and Johns Hopkins Medicine between 2013 and 2016 (42). The NSAID use was less in patients with minor eGFR in both cohorts (42). The proportion of patients who used opioids of methadone and buprenorphine was 0.9% at Geisinger and 0.3% at Johns Hopkins Medicine (42). These results emphasize higher awareness. regarding opioid and gabapentinoid use in CKD patients and the need for further studies to conclude the safety of such drugs in clinical trials (42). Some studies carefully chosen for information on opioids use in chronic pain management are summarized in Table 1.

3. Opioids

The 2018 United States Renal Data System reported that 43.8% of CKD patients were prescribed at least one opioid in 2016 (46). Morphine is used for treating cancer pain. The pain-relieving effect of morphine peaks 90 min after oral administration and 30 min after the intravenous (IV) administration (47). The plasma half-life is two to three hours after an IV bolus (48). Morphine and its metabolites are responsible for a more powerful analgesic effect and accumulate in patients with renal impairment, bringing to bear intense analgesia and sedation and possibly severe neurotoxicity (49). In a case-controlled study, after a single dose of 30 mg of morphine, morphine-6-glucuronide (M6G) was accumulated in patients with renal impairment (50). At 24 h, in the CSF, the concentration of the accumulated metabolite was at least 15 times greater than in those patients with normal renal function (51). These results show that morphine should be avoided in older CKD patients. Codeine is a methyl derivative of morphine and

Table 1. Detailed Description of Studies of Opioid Use in Chronic Pain Management

Study (References)	Therapy	Patient Population	Findings
Opioids Use in Chronic Pain Management			
A small study at a tertiary referral medical center in Los Angeles, California (11)	-	130 patients with CKD	Sources of pain: musculoskeletal (62%); gastrointestinal (13%); genitourinary (10%); hematological/oncological (10%); central and peripheral nervous system (9%); cardiovascular (7%)
A prospective cohort study at the University of Alberta (30)	26.2% were on weak opioids (codeine, propoxyphene, and oxycodone); 9.7% were on strong opioids (hydromorphone, methadone, fentanyl, and morphine)	205 Canadian hemodialysis patients	Musculoskeletal pain was most common (50.5%); peripheral neuropathy; peripheral vascular disease pain; effectiveness of therapy was 6% in the patients
A cohort study (31)	Treatment based on a WHO analgesic ladder/algorithm; Over 4 weeks	45 patients on chronic hemodialysis	40% nociceptive pain; 31% neuropathic; 29% both; 96% of patients reported adequate analgesia at 4 weeks
A retrospective study (32)	Chronic opioid use before transplantation	1064 adult kidney transplant patients	Increased risk of death
A cross-sectional, observational, multicenter study (33)	21% used opioids; 80% used non-opioid analgesics (mainly NSAIDs)	123 patients with CKD stage 5 on dialysis	Asthenia and fatigue
A cohort study between 2011 and 2013 in the Safe Kidney Care in Baltimore, Maryland (35)	Analgesic prescriptions up to 30 days before visits	308 patients with CKD	Mild chronic pain: analgesics with a DRP, with OR of 3.04; severe chronic pain: analgesics with a DRP, with OR of 5.46
A cohort study from a single center (37)	52 patients were long-term opioid recipients; 78 patients had opioid for fewer than 90 days; 8 patients had only a non-opioid prescription	191 HD patients	Findings of this study may not be generalizable to all HD patients due to the small sample size from one setting
A cohort study of the US Renal Data System (39)	Over 60% of dialysis patients received at least one opioid; 20% had chronic opioid prescription ($\geq$ 90-day supply)	671,281 patients on maintenance dialysis	Most prescribed opioids: hydrocodone (11.7%); oxycodone (5.4%); tramadol (2.5%); propoxyphene (1.4%)
A cohort study in Ontario, Canada, between August 1, 1997, and December 31, 2013 (40)	Simultaneous gabapentin use in 120 days; gabapentin dose as low (< 900 mg daily), moderate (900 to 1,799 mg daily), and high (-1,800 mg daily); concomitant (NSAID) use in the preceding 120 days	1,256 opioid users died of an opioid-related cause; 4,619 controls also used opioids	Co-prescription of opioids and gabapentin was correlated with a considerably increased odds of opioid-related death; no significant association between co-prescription of opioids and NSAIDs and opioid-related death
A cohort study using the US Renal Data System (41)	64% of patients received opioids	140,899 adults receiving hemodialysis	Opioid use was associated with a risk of: Altered mental status; fall; fracture
A cohort study in Geisinger Health System, in Pennsylvania, and Johns Hopkins Medicine, in Maryland (42)	31.8% received at least one opioid prescription in Geisinger; -22.7% received at least one opioid prescription in Johns Hopkins Medicine	In 2016; 181,107 patients in Geisinger; 109,219 patients in Johns Hopkins Medicine	Gabapentin and pregabalin prescriptions were less common in the overall cohort at 9.9% of Geisinger and 6.3% of Johns Hopkins Medicine; NSAID use was similar across the two cohorts and was lower in patients with lower eGFR in both cohorts; -prescription opioids: methadone and buprenorphine were 0.9% at Geisinger and 0.3% at Johns Hopkins Medicine
A prospective observational study between May 1996 and September 2001 (DOPPS) (43)	Dialysis patients: 15% were on an opioid; 1.7% on an opioid with acetaminophen; 1.2% on an opioid with COX-2; -0.6% on an opioid with NSAIDs	3749 dialysis patients	The proportion of patients prescribed any analgesic decreased from 30.2% to 24.3%; narcotic prescriptions decreased from 18.0% to 14.9%; propoxyphene and acetaminophen were most commonly prescribed (47.2%)
A prospective cohort study (44)	Chronic opioid derivative	308 patients on thrice-weekly HD	12.7% with a median age of 74.7 years fell at least once during 8 weeks; 3.9% experienced a fall-related fracture during 12 months; 28% who fell were on an opioid derivative; 9.7% were not on opioids
A prospective cohort study (45)	Opioid; benzodiazepines; + opioid; adrenal cortical; steroids; antidepressants	12,782 HD patients	Opioid pain medications; combination opioid medications

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CKD, chronic kidney disease; DOPPS, dialysis outcomes and practice patterns study; DRP, drug-related problem; ESRD, end-stage renal disease; HD, hemodialysis; HRQOL, health-related quality of life; HR, hazard ratio; HTEMS, high-tone external muscle stimulation; IRR, incidence rate ratio; LHID2000, longitudinal health insurance database 2000; NHRI, National Health Research Institutes; NSAID, nonsteroidal anti-inflammatory drugs; OR, odds ratio; QoL, quality of life; RCT, randomized clinical trial; WHO, World Health Organization.

brings to bear powerful cough-suppressant and modest pain-relieving effects (52). Codeine has a very little plasma protein binding (7%) and needs a dose change in patients with renal failure (52). Codeine is usually recommended in combination with acetaminophen (52). Renal clearance of codeine in patients with moderate to severe renal impairment is considerably reduced, and their accumulation causes sedation, respiratory depression, and hypotension (53). Thus, a cautious dose adjustment is necessary when a renal failure exists. Hydromorphone is a chosen short-acting opioid in ESRD patients. It is five times as effective as morphine when assumed through the oral route, and 8.5 times as powerful as morphine when administered intravenously (54). It has low protein binding (19%) (55). A long-lasting half-life of 39.4 $\pm$ 16 hours happens in severe renal impairment as compared to 14.8 $\pm$ 11.3 hours in normal renal function (56). Hydromorphone is not considerably accumulated in renal impairment because of the rapid change to its primary metabolite, which is without pain-relieving activity and typical opioid-related adverse events; therefore, this drug is more favorable in safety than is morphine (57). More than 80% of patients with cancer and kidney failure, who experienced side effects mainly with morphine, improved after a change to hydromorphone (58). In a study of 54 patients with kidney diseases (stage 3 - 5), hydromorphone had little neuroexcitatory signs until its metabolite, hydromorphone-3-glucuronide (H3G), accumulated more than the neurotoxic threshold. In another study, side effects happened with a rising dose or duration, including agitation (48%), cognitive dysfunction (39%), myoclonus (20%), and tremor (20%) (59). Oxycodone is a semi-synthetic opioid with parallel clinical efficiency with morphine. It has fewer adverse events, such as nausea, vomiting, and confusion (60). Oxycodone has a higher protein binding ability (46%) than hydromorphone, suggesting that it may be dialyzed (60). Pain relief from oxycodone starts in one hour and persists for 12 hours after administration (60). A case report of controlled-release oxycodone exhibited that after two hours of dialysis, the plasma levels of the drug and derivatives decreased by 32% - 52% (61). Kirvela et al. (62) administered one dose of oxycodone to 10 patients with severe renal impairment. There was a substantial postponement in the clearance of oxycodone, and the removal of metabolites was elongated. Fitzgerald indicated that normal doses of oxycodone used by patients with severe renal impairment can cause CNS toxicity and sedation (63). Broadbent recommends when CrCl is 10 - 50 mL/min, 75% of the normal dose of oxycodone should be used and when CrCl is < 10 mL/min, 50% of the normal dose of oxycodone could be used, with normal dosing intervals (64). Plasma concentrations of oxycodone and its metabolites reduced within 240 min of dialysis, causing a little enhance in post-dialytic pain intensity (65). Hydrocodone is a recommended opioid in HD patients, predominantly in combination with acetaminophen (66). About 26% of hydrocodone is excreted unchanged or as metabolites in the urine; thus, kidney failure is anticipated to have only an insignificant effect on drug clearance. In a single open-label study, plasma hydrocodone concentrations and mean bio-availability were influenced after a single use of hydrocodone 45 mg in patients with different stages of renal failure; thus, a 50% dose adjustment may be suggested for moderate to severe renal failure (CrCl < 30 mL/min) (67). Tramadol is an unusual pain-relieving compound structurally associated with codeine and morphine. It is suggested that 90% of tramadol is excreted by the kidney after oral administration (68). Dialysis slightly clears (7%) the drug. The occurrence of side effects ranges from 1% to 6% (68). Careful use in dialysis patients entails a decrease in dose and increase in dosing interim, for instance beginning at 50 mg every 12 hours and a maximum dose of 200 mg every day (69). Respiratory depression has been reported in patients with ESRD experiencing HD because of the overdose of tramadol (70). Propoxyphene is structurally associated with methadone and has a pain-relieving effect similar to codeine (71). In renal failure, serum concentrations of propoxyphene will be enhanced, and its accumulation can cause severe and possibly life-threatening side effects such as hypotension, arrhythmias, numerous CNS injuries, and sedation (71). Furthermore, this agent cannot be dialyzed in considerable quantities. Consequently, a suitable dosing adjustment should be considered, and its use should be evaded for pain controlling in elderly patients (72). Methadone is a synthetic opioid, being 5 - 10 folds more effective than morphine and a chosen agent in ESRD patients (73). Methadone exerts a beneficial anti-N-methyl-D-aspartate (NMDA) influence. Consequently, this agent is used for decreasing moderate-to-severe pain and relieving neuropathic pain (73). Methadone has an elongated half-life of 8 to 80 hours in different individuals after recurrent administration; furthermore, the half-life rises with age (74). Methadone is not accumulated in patients with renal impairment, nor is eliminated by HD (75). Meperidine is a synthetic opioid with a half-life of about 3.5 hours; it is metabolized to normeperidine in the liver (76), which is more toxic and durable. Meperidine has been described to cause CNS and respiratory depression, seizures, and psy-

chosis (77). In a study of 48 patients who had meperidine-associated adverse effects, 29% had a renal deficiency. According to the probable neurotoxicity of metabolites of meperidine, the use of a parental agent in patients with ESRD is avoided (77). Buprenorphine is a semisynthetic, extremely lipophilic opioid, and may be a beneficial strong opioid in ESRD (78). Buprenorphine is at least 30 times stronger than morphine (79). One study investigated the disposition of transdermal (TD) buprenorphine and norbuprenorphine in patients with CKD stage IV. There was no rise in the levels of buprenorphine and norbuprenorphine at doses up to 70 lg/h (78). Its properties, including extraordinary protein binding (96%) and great volume of distribution, do not favor elimination in dialysis (80). TD buprenorphine has a greater safety threshold than other opioids; the maximum amount for respiratory depression has been reported when this drug is used in devoid of other CNS depressants (81). Dosing recommendation starts at 5 mg/h transdermally every 7 days (82). Fentanyl is a synthetic drug with highly lipid soluble properties, which is about 80 times more powerful than morphine; it is very common for transdermal administration (83). It can be administered intravenously for acute titration. It is well-tolerated by ESRD patients (84). Its extraordinary protein binding (80%) and little water solubility cause to not be cleared well by dialysis (85). The stable state plasma fentanyl concentrations reach after almost 12 hours and are sustained for nearly 72 hours (86). There is a decline in the clearance of fentanyl in patients with severe renal impairment who are assumed a single bolus dose of the drug. This may cause respiratory depression (87). Han et al. (88) reported two patients experiencing HD receiving transdermal fentanyl at greater doses (up to 500 μg/h) for longstanding treatment (up to 3 years) without suffering substantial side effects. TD buprenorphine was as operative, safe, and acceptable as fentanyl (89). Alfentanil is a fentanyl derivative synthetic molecule. Alfentanil is a very short-acting opioid with a pain-relieving effect, which persists between 5 and 10 min (90). Only a small volume of injection is essential, when a patient needs high pain-relieving doses, constant subcutaneous infusion could be a benefit over fentanyl (91). Tapentadol is an unusual strong opioid. It has a 50-fold lower affinity than morphine (92). In patients with CrCl < 30 mL/min, the plasma levels of tapentadol-O-glucuronide raise up to 6.1 folds. Thus, because of limited evidence about its use in severe kidney deficiency, tapentadol is yet not suggested in patients with ESRD (93).

Daily offered mean doses of opioids include morphine (50 mg), codeine (93.3 mg), hydromorphone (33.6 mg), oxycodone (11.9 mg), propoxyphene (238 mg), methadone (21.7 mg), meperidine (100 mg), and fentanyl (37.5 μg/h) (30, 92). Metabolism and clinical consideration of opioids use in patients with renal failure are summarized in Table 2.

The kidney plays a major role in pharmacokinetics and pharmacodynamics of drugs; consequently, it recommends carefulness with opioids in the treatment of patients with CKD. (94). A decline in renal function in old patients influences the removal of drugs such as opioids, needing dose regulation and careful checking for side effects. Generally, lower doses must be used when starting narcotic therapy in the elderly (95). Acetaminophen was the most usually used pain-relieving (34% of the entire CKD cohort), although the higher doses of acetaminophen used chronically have been accompanied by analgesic nephropathy (96). To avoid toxicity, it is proposed to not exceed 3 g/day of acetaminophen (97). For moderate pain, tramadol is preferred, given its low risk of direct nephrotoxicity (98). The use of fentanyl, alfentanil, and hydromorphone is relatively safe in dialysis patients, but doses should be adjusted to minimize the risk of respiratory depression (97). However, adjuvant medications are useful for improving pain scores, decreasing opioid doses, and treating neuropathic components of pain in dialysis patients (99). The accumulation of opioid metabolites can lead to respiratory and central nervous system depression, hypotension, and seizures in patients with advanced CKD. For severe pain in CKD patients, methadone and fentanyl can be used (100). If a patient's condition worsens, particularly near the end of life, alternatives are necessary, such as subcutaneous fentanyl. With the minimal variations in kinetics in kidney impairment, hydromorphone, fentanyl, methadone, and buprenorphine may be possibly beneficial opioids (101).

Pain is the most common symptom experienced by renal patients (102). Pain controlling in renal patients is challenging, as the space between pain relief and toxicity is minor (103, 104). The most usually recommended opioids in patients with ESRD are hydrocodone and oxycodone, used in 51% and 16% of total treatments, respectively (105, 106). Basic skills for pain management include the acknowledgment of the type of pain syndromes (nociceptive, neuropathic, and mixed pain) and suitable history-taking skills (107). Neuropathic pain is often poorly reactive to opioids, needing doses that are related to intolerable toxicity (108). A meta-analysis described that 72% of patients prescribed opioids such as morphine, hydromorphone, and oxycodone also had risk factors for drug-drug interactions (109). As a consequence of these risks,

Table 2. Metabolism and Clinical Consideration of Opioid Use in Patients Suffering From Kidney Failure

Opioid	Metabolism	Recommended Dosing	T 1/2 Normal, h	T 1/2 Dialysis (ESRD), h	Clinical Considerations	Dosage Consideration Based on Renal Dysfunction and Dialysis
Morphine (47-49)	Morphine and its metabolites (M6G) have moderate water solubility and can be dialyzed	-[a]	2 - 3	Unchanged	Nausea; vomiting; myoclonus; seizures; sedation; respiratory depression	Avoided in patients with severe renal failure of eGFR < 30 mL/min (51)
Codeine (52, 53)	Metabolized via CYP2D6 to: C6G, 81%; morphine, 10%; normorphine, 2%; M6G; M3G	15 - 60 mg every 4 h	2.5 - 4	13 - 18.9	Sedation; respiratory depression; hypotension	Is not recommended in patients undergoing HD because of the accumulation of toxic metabolites (52)
Hydromorphone (54, 56, 57)	Metabolized to: hydromorphone-3-glucuronide; dihydroisomorphine-6-glucoside	1 - 2 mg every 3 - 4 h	2 - 5	3.2 on dialysis; 5.9 non-dialysis days	Tremor; myoclonus; agitation; cognitive dysfunction	A growing AUC with declining renal function at a ratio of 1:2:4 for patients with normal (CrCl > 80 ml/minute); moderate (CrCl 40 - 60 mL/minute); severe (< 30 mL/minute) renal dysfunction (55)
Oxycodone (60, 62-64)	Metabolized to active noroxycodone; oxymorphone; glucuronides	2.5 - 5 mg every 4 - 6 h	2 - 4	3 - 5	Nausea; confusion; hallucinations; CNS toxicity; respiratory depression	Avoided in patients with eGFR less than 60 mL/min; increased the half-life, and metabolites in patients with renal dysfunction (CrCl < 60 ml/minute) (61)
Tramadol (69, 70)	Active metabolites formed; by CYP2D6: M1; O-desmethyl tramadol	25 - 50 mg every 6 h; Age > 75 y: 300 mg/day	6	11	Headaches; dizziness; sweating; dry mouth; respiratory depression	Overdose through an IV dose of 400 mg in a patient undergoing HD (70)
Methadone (73, 75)	Converted to: 2-ethylidene-1; 5-dimethyl-3; 3-diphenylpyrrolidene; 2-ethyl-5-methyl-; 3,3-diphenylpyraline	-[a]	15 - 60	13 - 47	Risk of hypoxemia; No important adverse effects	In ESRD patients, close monitoring is proposed with the beginning doses 50% - 75% of normal post-dialysis (75)
Buprenorphine (78, 79, 81)	Metabolized to: norbuprenorphine; -N-deal kylbuprenorphine	5 μg/h patch every 7 days	30	Unchanged	Sedation; nausea; vomiting; dizziness; headaches	TD buprenorphine has higher safety (81)
Fentanyl (85-87)	Primarily oxidized to; norfentanyl	12 μg/h patch every 72 h	2 -7	Possibly increased	Respiratory depression	TD fentanyl has higher safety (88, 89)

Abbreviations: AUC, area under the curve; CrCl, creatinine clearance; C6G, codeine-6-glucuronide; CKD, chronic kidney disease; CYP2D6, cytochrome P450 2D6 enzyme; GFR, glomerular filtration rate; HD, hemodialysis; IV, intravenous; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; TD, transdermal.
[a]Consult with specialists for the proper dose.

it is significant to accentuate that opioids should be prescribed only to older, non-dialysis chronic kidney disease patients when they are absolutely indicated (110). Furthermore, considering the increasing number of elderly people (over 65 years of age) often afflicted with numerous comorbidities and chronic pain syndromes demanding efficient pain-relieving treatments, the safe and impressive administration of opioids in damaged renal function is the most important issue (111). Also, the physician must monitor the patient's glomerular filtration rate and creatinine to determine the appropriate dosing (112).

4. Conclusions

Pain in patients with CKD should be known as a significant health problem, and the nephrology community should support pain treatment in HD patients as a clinical and research importance to improve the patients' quality of life and pain-related debility. It is probable, according to information on opioid pharmacokinetics, to propose carefulness with particular opioids in the pain management of patients with CKD. Modifications in the dosing or choice of drugs are essential in CKD because of complications due to the decreased removal of drugs or their metabolites. One of the restrictions of this study is that we were attentive only to opioid management and ignored non-opioid studies in patients with CKD. Unfortunately, clinical studies are lacking concerning maintenance opioids' effectiveness and safety, particularly as they are associated with chronic pain management. More randomized controlled trials are critically required evaluating the effectiveness of opioids and other drugs for the proper treatment of chronic pain among patients with CKD.

Footnotes

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Timing and causes of death in septic shock

Fabrice Daviaud[1,2], David Grimaldi[1,2,3], Agnès Dechartres[2,4], Julien Charpentier[1], Guillaume Geri[1,2], Nathalie Marin[1], Jean-Daniel Chiche[1,2,3], Alain Cariou[1,2], Jean-Paul Mira[1,2,3] and Frédéric Pène[1,2,3*]

Abstract

Background: Most studies about septic shock report a crude mortality rate that neither distinguishes between early and late deaths nor addresses the direct causes of death. We herein aimed to determine the modalities of death in septic shock.

Methods: This was a 6-year (2008–2013) monocenter retrospective study. All consecutive patients diagnosed for septic shock within the first 48 h of intensive care unit (ICU) admission were included. Early and late deaths were defined as occurring within or after 3 days following ICU admission, respectively. The main cause of death in the ICU was determined from medical files. A multinomial logistic regression analysis using the status alive as the reference category was performed to identify the prognostic factors associated with early and late deaths.

Results: Five hundred forty-three patients were included, with a mean age of 66 ± 15 years and a high proportion (67 %) of comorbidities. The in-ICU and in-hospital mortality rates were 37.2 and 45 %, respectively. Deaths occurred early for 78 (32 %) and later on for 166 (68 %) patients in the ICU ($n = 124$) or in the hospital ($n = 42$). Early deaths were mainly attributable to intractable multiple organ failure related to the primary infection (82 %) and to mesenteric ischemia (6.4 %). In-ICU late deaths were directly related to end-of-life decisions in 29 % of patients and otherwise mostly related to ICU-acquired complications, including nosocomial infections (20.4 %) and mesenteric ischemia (16.6 %). Independent determinants of early death were age, malignancy, diabetes mellitus, no pathogen identification, and initial severity. Among 3-day survivors, independent risk factors for late death were age, cirrhosis, no pathogen identification, and previous corticosteroid treatment.

Conclusions: Our study provides a comprehensive assessment of septic shock-related deaths. Identification of risk factors of early and late deaths may determine differential prognostic patterns.

Background

The incidence of sepsis is increasing as a result of population's aging and associated comorbidities such as cancer, immunosuppression, diabetes mellitus, or chronic organ dysfunctions. Although the higher number of cases accounted for an overall increase in sepsis-related deaths, the attributable fatality rate significantly dropped at the turn of the century. About 20 years ago, the crude mortality rate of septic shock exceeded 50 % in non-selected populations [1, 2]. Since then, improvement in management of severe sepsis and septic shock translated into increased survival rate in observational studies [3–8]. This is also emphasized by the low mortality rates ranging from 24.2 to 32 % observed in the control arms of recent interventional studies on severe sepsis and septic shock [9–11].

While the literature is plenty of studies with vital status as the main outcome, it is striking that very few data are available about the time to death and the causes that ultimately led to death in septic patients. Nowadays, the combination of anti-infective treatments and aggressive organ failure supports often allows stabilization of the clinical condition, but patients become then exposed to intensive care unit (ICU)-acquired complications that significantly impact on the prognosis. Nevertheless, most epidemiological and interventional studies about septic shock report crude mortality rates that make deaths directly related to the initial septic process or to secondary nosocomial infections hardly distinguishable. The negative results of interventional studies in sepsis despite a robust scientific rationale should then question about

* Correspondence: frederic.pene@cch.aphp.fr
[1]Réanimation médicale, Hôpital Cochin, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France
[2]Faculté de Médecine, Université Paris Descartes, Sorbonne, Paris Cité, France
Full list of author information is available at the end of the article

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the pathophysiological mechanisms leading to death of septic patients. Lastly, a number of ICU patients die after therapeutic limitations as a result of withholding or withdrawing life support decisions that were not accurately reported within studies. With respect to the current trends in epidemiology and outcome of septic shock and to the design of future interventional trials in the field, a better comprehension of the clinical course of septic shock is required beyond the common but gross endpoint of vital status. To this aim, we performed a retrospective study aimed at studying the timing and related causes of death in this setting, as well as respective predictors of early and late deaths.

Methods

Patients and setting

The study took place in a 24-bed tertiary medical ICU with an average of 1600 admissions per year. From January 2008 to July 2013, all adult patients (age ≥18 years old) diagnosed with septic shock within the first 48 h of ICU admission were included. Septic shock was defined by the association of the following: (i) a suspected or proven infection, (ii) at least two criteria of systemic inflammatory response syndrome, (iii) an acute circulatory failure requiring vasopressor support. There were no exclusion criteria other than age below 18 years old. Septic shock was defined as a microbiologically proven or clinically suspected infection, associated with acute circulatory failure requiring vasopressors despite adequate fluid filling [12]. Senior staffing remained stable over the 6-year study period. End-of-life decisions to withhold or withdraw life support were taken on collectively when maintenance or increase of life-sustaining therapies was considered as futile by all participants and that death would irremediably occur in a short-term manner. This procedure is standardized in our unit. Data were computed from medical files and extracted from the patient data management system (Clinisoft, GE Healthcare). The ethics committee of the French Intensive Care Society (Société de Réanimation de Langue Française, CE SRLF #12-402) approved the protocol and waived patient's consent.

Intended care for patients with septic shock

Patients were promptly treated with broad-spectrum antibiotic combination, depending on the site of infection, previous antibiotic treatment, and known colonization with multidrug-resistant bacteria. Antimicrobial treatment was deescalated to narrower spectrum after identification of the responsible pathogen. Source control measures, such as surgery or removal of infected devices, were applied when necessary. Besides, patients were treated according to the 2008 guidelines of the Surviving Sepsis Campaign [13]. Renal replacement therapy was commonly indicated in established acute renal failure but was also performed early in the course of septic shock in case of profound metabolic acidosis.

Collection of data

For each patient, the following data were collected: demographics (age and gender), comorbidities, malignancy under treatment within the year prior to ICU admission. Features of immunosuppression included intravenous chemotherapy during the last 3 months, leuconeutropenia defined by leucocyte count <1000/mm^3 and/or neutrophil count <500/mm^3, HIV infection at any stage, treatment with corticosteroids for more than 3 months at any dosage, or ≥0.5 mg/kg prednisone equivalent per day for more than 7 days, and treatment with other immunosuppressive drugs.

Characteristics of the primary infection were described as follows: community- or healthcare-acquired, source of infection, bacteremia, causing pathogen. The adequacy of initial antibiotic treatment was assessed in microbiologically documented infections and was defined as at least one antimicrobial active against the pathogen. Severity at admission was assessed by Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA) scores during the first 24 h of ICU admission [14, 15].

Characteristics of deaths

The modalities of death were investigated by collecting the date, the location (in-ICU and in-hospital), and the main cause of death. Early and late deaths were a priori defined as occurring within or after 3 days following ICU admission, respectively. This was based on previous works performed in non-cancer critically ill patients and cancer patients with septic shock, for whom trends in organ failures during the first 3 days in the ICU were found accurate predictors of outcome as compared to single assessment on admission [16–18, 8]. Hence, it is our usual policy of full engagement for a 3-day time frame for most septic patients. Allocation of the cause of death was aimed to identify the disease responsible for fatality rather than the final common pathways of terminal organ failures. Disorders responsible for death were determined by analysis of the medical file by two independent physicians (FD and DG), and discrepancies were resolved by consensus. ICU-acquired infections were defined as new infections acquired more than 48 h after ICU admission. Decisions to withholding or withdrawing life support were also collected. Mesenteric ischemia was proven by macroscopic exam during surgery or by digestive endoscopy or was strongly suspected on the basis of clinical symptoms, elevated arterial blood lactate, and/or biological evidence of acute cell lysis (elevated serum levels of lactate dehydrogenase, creatine

phosphokinase, and transaminases) combined to suggestive abdominal CT scan findings such as lack of contrast enhancement of the bowel, pneumatosis intestinalis, and pneumatosis in the intra-hepatic portal vein branches [19].

Statistical analysis

Continuous variables were expressed as mean ± SD or median (interquartile range) and categorical variables as numbers and percentages. The characteristics of patients who died early (≤3 days from ICU admission), lately (>3 days), or who survived were compared using chi-square tests or Fisher exact tests as appropriate for categorical variables and ANOVA for continuous variables. Factors independently associated with early or late in-hospital death were identified using a multinomial logistic regression model using the status alive as the reference category. Variables significantly associated with early or late death in univariate analysis were included in the model. Multicolinearity was checked by calculating the variance inflation factor. A $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.3.

Results

Patients' characteristics

During the study period, 543 patients presented with septic shock during the first 48 h following ICU admission (Fig. 1 and Table 1). Sixty-seven percent of patients had underlying comorbidities and 40 % were immunocompromised. Healthcare-associated infections accounted for 53 % of septic episodes. The main site of primary infection was the lung (53 % of patients). A causing pathogen was identified in 69 % of patients. With respect to organ failure supports, invasive mechanical ventilation and renal replacement therapy were required in 88 and 51 % of patients, respectively.

Timing and causes of deaths

The in-ICU and in-hospital mortality rates were 37.2 and 45 %, respectively, and remained consistent over the study period. Among 244 patients deceased in the hospital, 78 (32 %) died within the first 3 days of ICU admission (early deaths) and 166 (68 %) died thereafter (late deaths) in the ICU ($n = 124$) or in the hospital ($n = 42$) (Fig. 2).

We investigated the primary disorders directly responsible for death in septic patients. With respect to the 42 patients who died after ICU discharge, a comprehensive assessment of the primary cause of death could not be reliably investigated from medical reports. Of note, only six patients who had been transferred to their referent hospital at ICU discharge were readmitted to the local ICU and died there. Definite causes of early and late deaths in the ICU are displayed in Fig. 3. End-of-life decisions precipitated early death in two patients with end-stage comorbidities and previous do-not-resuscitate orders. Late deaths in the ICU also directly resulted from end-of-life decisions in 36 (29 %) patients with fixed multiple organ failure for whom the treating physicians were convinced that meaningful recovery was not possible. Therefore, extensive diagnostic procedures were not carried out in such settings of exclusive palliative care. Besides, most early-onset deaths were directly related to the primary infection through intractable shock and multiple organ failure (82 % of early decedents) (Fig. 3a). In addition, 6.4 % of early decedents were diagnosed with mesenteric ischemia likely to act as a consequence or a contributor of multiple organ failure. Most late deaths were related to ICU-acquired complications such as nosocomial infections (20.4 %) and mesenteric ischemia (16.6 %) (Fig. 3b). Regardless of the time to death, the diagnosis of mesenteric ischemia was proven by surgery (42 %) or endoscopy (5 %) or relied on highly suggestive CT scan findings (53 %).

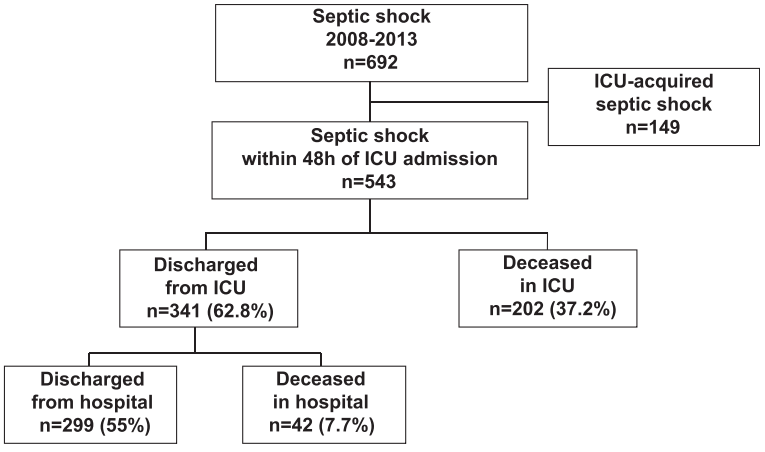


Fig. 1 Flow chart of the study. Percentages were computed from the study cohort of 543 patients

Table 1 Characteristics of survivors and early (≤3 days) and late (>3 days) deceased

Variables	All patients	Alive	Early deaths	Late deaths	*p*
	n = 543	*n* = 299	*n* = 78	*n* = 166	
Demographics					
Age, years	66 ± 15	63 ± 16	70 ± 15	69 ± 13	<0.0001
Male gender	346 (64)	196 (66)	49 (63)	101 (61)	0.64
Comorbidities					
Malignancy	139 (25)	61 (20)	32 (41)	46 (28)	0.0008
Chronic heart failure	126 (23)	59 (20)	18 (23)	49 (29)	0.06
Chronic pulmonary disease	103 (19)	47 (16)	15 (19)	41 (25)	0.06
Diabetes mellitus	96 (18)	46 (15)	22 (28)	28 (17)	0.03
Cirrhosis	65 (12)	28 (9)	9 (11)	28 (17)	0.06
Chronic kidney failure	60 (11)	29 (10)	8 (10)	23 (14)	0.38
Factors of immunosuppression					
Chemotherapy during the last 3 months	64 (12)	33 (11)	13 (17)	18 (11)	0.36
Leuconeutropenia	41 (7)	21 (7)	13 (17)	7 (4)	0.002
Corticosteroid treatment	91 (17)	39 (13)	15 (19)	37 (22)	0.03
Other immunosuppressive drugs	46 (8)	19 (6)	8 (10)	19 (11)	0.14
HIV infection	6 (1)	4 (1)	0 (0)	2 (1)	0.86
Infection characteristics					
Healthcare-related infections	286 (53)	148 (49)	44 (56)	94 (57)	0.26
Source of infection					0.003
Lung	286 (53)	146 (49)	43 (55)	97 (58)	
Abdominal	91 (17)	40 (14)	15 (19)	36 (22)	
Urinary tract	63 (12)	46 (15)	6 (8)	11 (7)	
Catheter	18 (3)	15 (5)	1 (1)	2 (1)	
Skin and soft tissue	33 (6)	22 (7)	2 (3)	9 (5)	
Others[a]	52 (9)	30 (10)	11 (14)	11 (7)	
Microbiological documentation	376 (69)	221 (74)	48 (61)	107 (64)	0.03
Type of microorganism[b]					0.50
Gram-negative bacteria	206 (55)	127 (58)	26 (54)	53 (49)	
Gram-positive bacteria	151 (40)	82 (37)	21 (44)	48 (44)	
Others[c]	19 (5)	11 (5)	1 (2)	7 (6)	
Positive blood cultures	166 (30)	102 (34)	22 (28)	42 (25)	0.12
Admission biological findings					
Leucocytes (G/L)	12.0 [5.6–18.7]	11.3 [6–18.4]	9.2 [1.7–25]	13 [6.7–18]	0.07
Arterial blood lactate (mmol/L)	2.9 [1.5–5.4]	2.2 [1.4–4]	7.8 [4.3–11.8]	2.7 [1.4–5.9]	<0.0001
Creatininemia (μmol/L)	139 [88–215]	129 [82–186]	196 [127–281]	137 [85–214]	0.02
Prognostic scoring systems					
Admission SOFA score	9 [6–12]	9 [5–12]	11 [9–14]	9 [5–12]	0.0005
Admission SAPS II	66 [51–85]	58 [46–80]	86 [77–101]	67 [53–83]	<0.0001

Table 1 Characteristics of survivors and early (≤3 days) and late (>3 days) deceased *(Continued)*

Organ failure supports					
Mechanical ventilation	476 (88)	241 (81)	77 (99)	158 (95)	<0.0001
Renal replacement therapy	277 (51)	101 (34)	65 (83)	111 (67)	<0.0001
Stress-dose corticosteroids	250 (46)	111 (37)	58 (74)	81 (49)	<0.0001

Categorical variables are expressed as numbers (*percentages*) and continuous variables as mean ± SD or median [interquartile range] as appropriate. Comparisons were performed between the three subgroups (alive patients and early and late deceased)
HIV human immunodeficiency virus, *SOFA* Sequential Organ Failure Assessment, *SAPS* Simplified Acute Physiology Score
[a]Meningitis ($n = 7$), bone and joint ($n = 7$), endocarditis ($n = 5$), gynecological ($n = 4$), mediastinitis ($n = 3$), head and neck ($n = 2$), unknown ($n = 24$)
[b]Percentages are computed from patients with microbiological documentation
[c]Fungi ($n = 8$), virus ($n = 9$), mycobacteria ($n = 2$)

Risk factors of early and late deaths

We investigated the determinants of mortality with respect to the timing of death by comparing the characteristics of patients who survived or died either early or lately (Table 1). In addition, most patients (93 %) with microbiologically documented infections received adequate initial antimicrobial treatment, without any difference among survivors and early and late decedents (94, 87, and 91 %, respectively, $p = 0.19$). In multivariate analysis, increasing age, diabetes mellitus, malignancy, lack of pathogen identification, and higher admission SOFA score remained independent risk factors of early death. Among patients who survived the first 3 days, independent determinants of late death included increasing age, cirrhosis, lack of pathogen identification, and previous corticosteroid treatment (Fig. 4). When entered into the model, neither chronic pulmonary disease nor chronic heart failure was associated with early or late death (data not shown).

Discussion

The crude mortality rate is commonly used as the main criterion of outcome in septic shock, but it is clearly limited to assess the prognosis with respect to the clinical diversity of the disorder. Although the visual aspects of survival curves from retrospective or prospective studies provide a gross evaluation of death kinetics in the course of septic shock, specific and reliable data about the timing of deaths are scarce. We herein provided an original comprehensive analysis of modalities of death in septic shock. Because obtaining an accurate etiological diagnosis is of paramount importance in the outcome of critically ill patients, we aimed at describing the primary cause of death as a disease and not as accumulation of organ failures. With respect to the high prevalence of comorbidities and high severity scores on admission, the in-hospital mortality rate of septic shock was 45 % in the present unselected cohort. This is in line with the in-hospital mortality rate of 48.6 % in a recent French cohort of septic shock with similar features, including a similar prevalence of comorbidities (65 %) [5]. The current mortality rate of the ANZICS cohort was reported seemingly lower (22 %), but it encompassed both severe sepsis and septic shock, and the prevalence of comorbidities was only 35 % [4].

The extent of multiple organ failure accounted for the large majority of early deaths in the present cohort. However, the 3-day mortality rate was only 14.3 %, compared to the 3-day mortality rate of 27 % in a cohort of septic shock patients managed in the ICU during the early 1990s [20]. Two French and Spanish multicenter observational studies that included both severe sepsis and septic shock patients in 2001–2002 reported consistent mortality rates of 13.3 and 14.8 %, respectively [21, 22]. Altogether, these data suggest that the overall improvement in the outcome of septic shock is at least

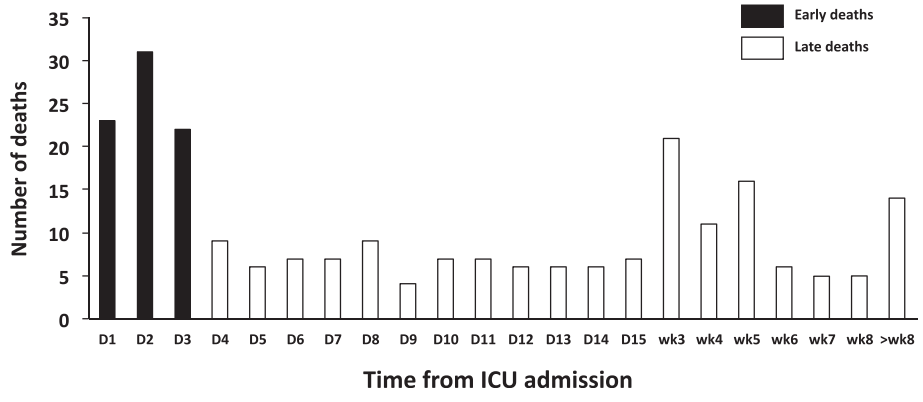


Fig. 2 Distribution of deaths according to time from ICU admission. Numbers of deaths are represented per day during the first 2 weeks and per week thereafter. Early (≤3 days) and late (>3 days) deaths occurred in 78 (32 %) and 166 (68 %) patients, respectively

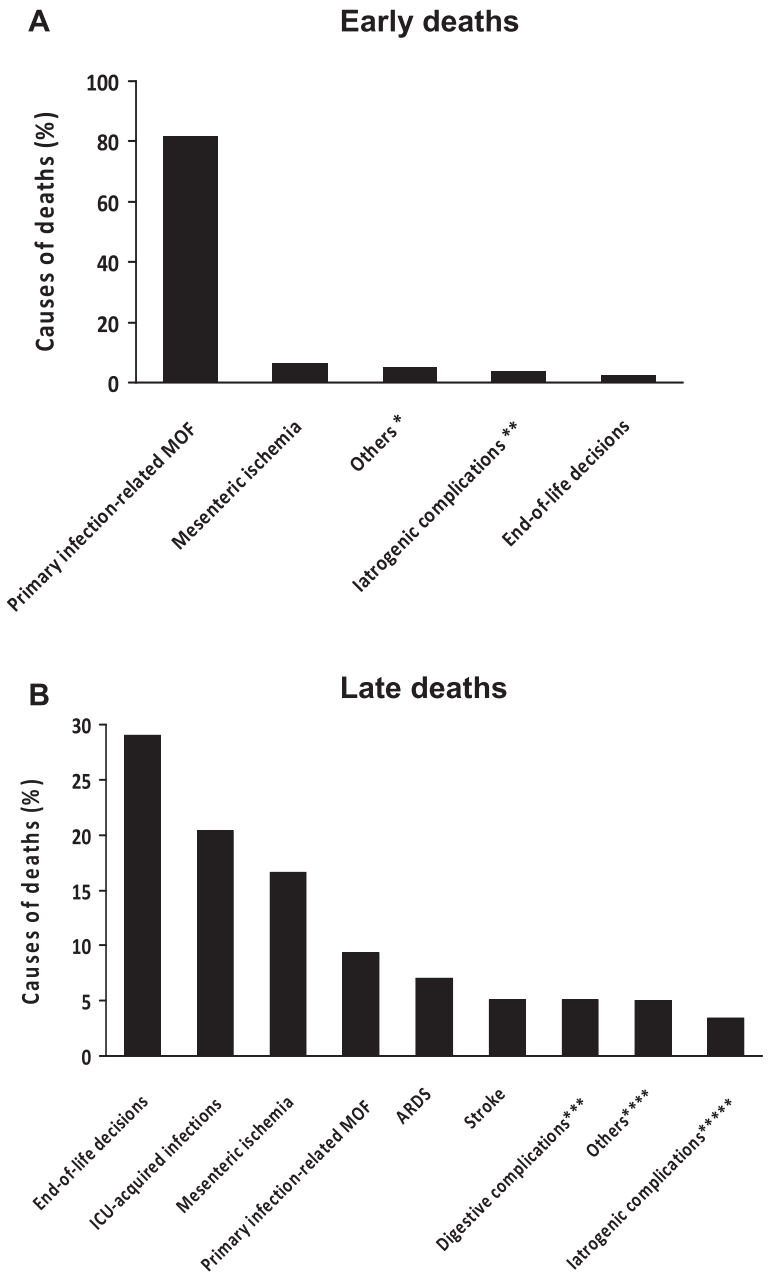


Fig. 3 Definite causes of early (**a**, $n = 78$) and late (**b**, $n = 124$) deaths in the ICU. Others (*one asterisk*): myocardial infarction ($n = 1$), pulmonary embolism ($n = 1$), ARDS-related refractory hypoxemia ($n = 1$), intestinal obstruction ($n = 1$). Iatrogenic complications (*two asterisks*): hypoxemic cardiac arrest complicating emergency endotracheal intubation ($n = 3$). Digestive complications (*three asterisks*): gastrointestinal hemorrhage ($n = 2$), digestive perforation ($n = 3$). Others (*four asterisks*): myocardial infarction ($n = 2$), lymphoma-related tumor lysis syndrome ($n = 2$), extensive limb ischemia ($n = 1$), acute liver failure ($n = 1$). Iatrogenic complications (*five asterisks*) related to chest tube insertion ($n = 1$), catheter insertion ($n = 1$), accidental removal of tracheostomy ($n = 1$), and cardiac arrest at the start of hemodialysis ($n = 1$). *MOF* multiple organ failure, *ICU* intensive care unit, *ARDS* acute respiratory distress syndrome

partially due to a decrease in the early mortality rate. It is likely that the Surviving Sepsis Campaign bundles for early and aggressive resuscitation of severe sepsis and septic shock contributed to decrease the number of early deaths [23, 13]. Interestingly, admission SOFA scores were similar between alive and late deceased patients, suggesting that late deaths were less related to the initial severity, and were rather dependent on subsequent development of lethal ICU-acquired complications and/or therapeutic limitations. Beyond the classical paradigm of sepsis where overwhelming inflammation is responsible for lethal multiple organ failure, the development of

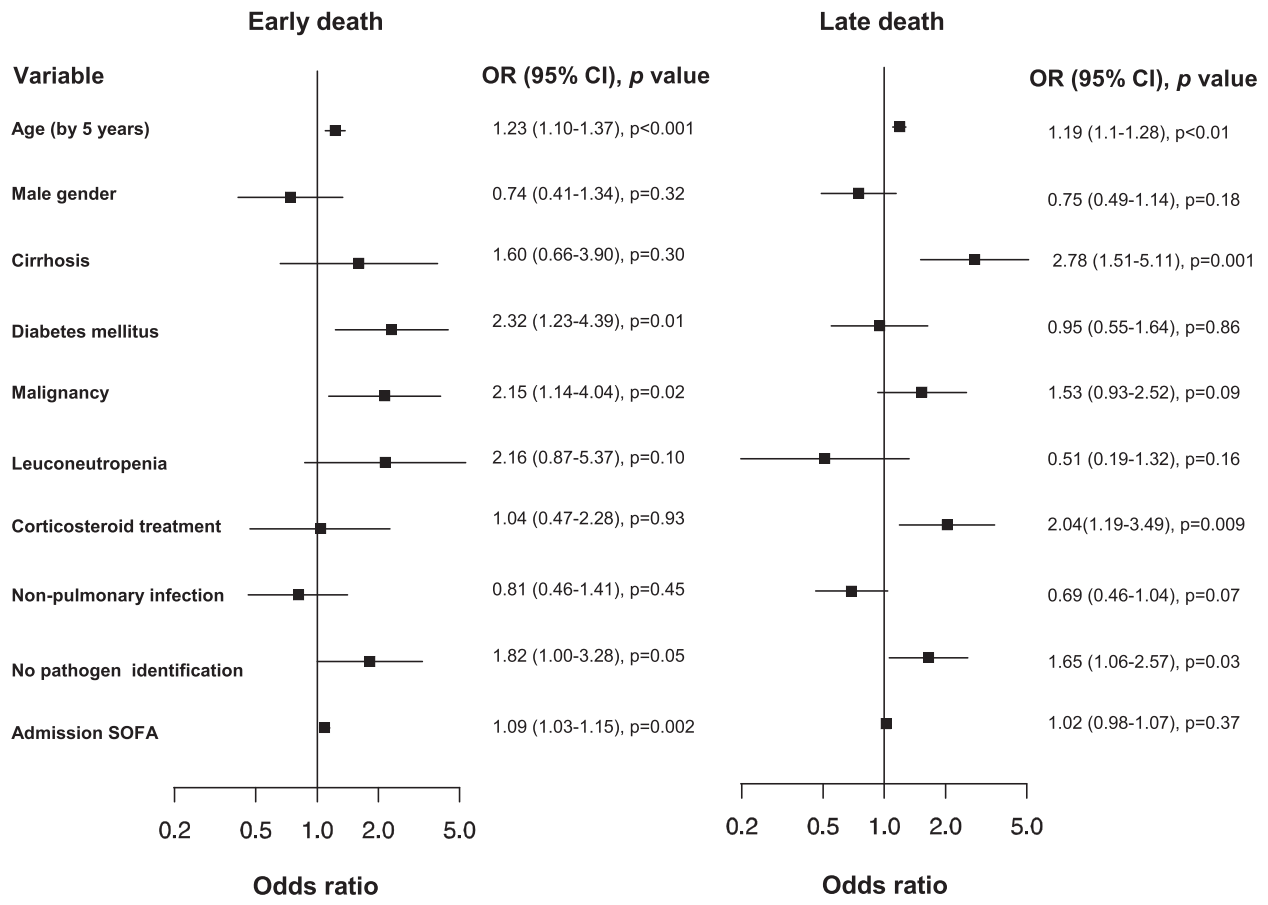


Fig. 4 Prognostic factors of early- (≤3 days) and late-onset (>3 days) mortality. Results of the multivariate multinomial logistic regression analysis. All variables entered into the model are displayed on the figure. The variance inflation factor was less than or around 1 for all variables that denotes a low risk of colinearity

sepsis-induced immunosuppression in patients that survive the primary insult may favor the development of secondary infections in addition to other common risk factors related to severity and requirements for invasive procedures [24–26]. Ventilator-associated pneumonia remains the most dreaded infectious complication in critically ill patients. Although its attributable mortality remains a matter of debate, it is clearly associated with increased duration of mechanical ventilation and increased length of stay in the ICU [27–29].

The identification of mesenteric ischemia as a frequent cause of death both in early and late phases of septic shock is an interesting finding. ICU-acquired mesenteric ischemia is most often associated with microvascular abnormalities. Non-occlusive mesenteric ischemia is a common complication of shock regardless of the underlying etiology and is often considered as the main contributor to terminal multiple organ failure in relation with breaches in the digestive mucosal barrier [30]. Thus, mesenteric ischemia might reflect the severity of shock, and individualizing it as an alternative or independent cause of death is debatable. Yet, the diagnosis is often difficult and is based on the combination of clinical manifestations, biological markers of cell lysis, and suggestive abdominal CT scan findings. A definite diagnosis might be confirmed by digestive endoscopic examination, even up to exploratory laparotomy when highly suspected. In a recent multicenter study of 780 critically ill patients with mesenteric ischemia, the diagnosis was based on CT scan findings in 58 % of patients while it could be proven by surgery and digestive endoscopy in 27 and 15 % of patients, respectively. The outcome was poor as assessed by a mortality rate of 58 % and was dependent on severity but also on the possibility of surgical treatment [19].

Most interestingly, the underlying comorbidities and especially the patterns of immunodeficiency determined differential prognostic patterns in patients with septic shock [31]. Cancer was a predictor of early death, presumably related in part to leuconeutropenia imposed by chemotherapy or bone marrow infiltration. Neutropenia is a major risk factor for fulminant sepsis. In addition, neutropenic sepsis is often associated with non-infectious

conditions likely to contribute to mortality in the ICU [32]. Diabetic patients are often affected by chronic organ dysfunctions likely to affect their response to aggression [33]. Altogether, these results highlight the pejorative impact of quantitative or functional defective phagocytosis on early outcome of septic shock. In contrast, patients with previous corticosteroid treatment seemed relatively preserved from early mortality but were more likely to die later. This finding is intriguing but could be related to the impact of corticosteroids on maintenance of vascular response to vasopressors or immunomodulatory properties toward the overwhelming inflammatory response of septic shock [34–36]. Cirrhosis is well known to be associated with a high mortality rate in case of septic shock and was rather found to be associated with late mortality. Aggressive management of septic shock clearly resulted in improved early survival in cirrhotic patients, who then become exposed to secondary infectious and non-infectious complications [37, 38].

This study has several limitations. The major limit certainly lies in the retrospective design of the study. However, we included all consecutive patients within the study period, and the collection of data was almost exhaustive. The characteristics of our cohort, such as the high prevalence (40 %) of immunosuppression, were highly dependent on our hospital environment comprising large departments of oncology, hematology, and internal medicine, and our findings may not fully apply to other centers. In the same way, most patients are admitted to our unit for medical reasons, which limits the generalization to surgical patients. The cut-off between early (≤3 days) and late (>3 days) deaths is debatable but is relevant for refining the prognostic assessment of critically ill patients with septic shock [18, 8]. Furthermore, it allows comparability to previous observational studies [20–22]. In the present study, the distribution of deaths over time clearly exhibited a high mortality rate over the first 3 days, suggesting that this time frame is clinically relevant. We reported the seemingly primary cause of death unambiguously diagnosed at the bedside, but we cannot rule out that some additional disorders might have contributed to the lethal process in such complex clinical settings. A number of patients died in the ICU as a result of end-of-life decisions and therefore did not undergo exhaustive diagnostic procedures. In addition, the primary cause of death of patients deceased after ICU discharge could not be reliably addressed. However, the low rate of ICU readmission (6 out of 42) suggests that most patients had been subjected to therapeutic limitations in the wards. Finally, autopsy was rarely performed in the present cohort because of logistic limitations in our hospital. A number of studies have emphasized that autopsy findings substantially contributed to the diagnosis of critically ill patients [39, 40]. Specifically, an autopsic study in patients who died from sepsis has revealed continuous septic foci that may have contributed to multiple organ failure and death [41].

Conclusions

We herein provided a comprehensive assessment of septic shock-related deaths. It clearly identifies subgroups of patients with different prognostic patterns in the ICU. Our findings carry several potential implications including early identification of high-risk patients that would require early and aggressive management in the ICU, as well as prevention and detection of secondary complications. In addition, the risk stratification of early or late deaths may also impact on the design and the therapeutic goals of future interventional studies in septic shock.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

FD is the guarantor of the integrity of the data and the accuracy of the data analysis. FD, DG, and FP designed the study. AD performed the statistical analysis. FD, DG, AD, JC, GG, NM, JDC, AC, JPM, and FP contributed substantially to the collection of data, data analysis, and interpretation and to the writing of the manuscript. All authors read and approved the final manuscript.

Author details

[1]Réanimation médicale, Hôpital Cochin, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France. [2]Faculté de Médecine, Université Paris Descartes, Sorbonne, Paris Cité, France. [3]Institut Cochin, INSERM U1016, CNRS UMR8104, Paris, France. [4]Centre d'épidémiologie et de recherche clinique, Hotel-Dieu, AP-HP, Paris, France.

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Case Report

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Infection & Chemotherapy

소장폐색증을 동반한 비호중구감소 환자에서 발생한 *Clostridium tertium*균혈증 1예

구남수[1] · 정혜선[2] · 이재길[3] · 김선빈[1] · 한상훈[1] · 최준용[1] · 이경원[2] · 김준명[1]
연세대학교 의과대학 내과학교실 에이즈연구소[1], 진단검사의학교실 세균내성연구소[2], 외과학교실[3]

Clostridium tertium Bacteremia in a Non-neutropenic Patient with Small Bowel Obstruction

Clostridium tertium-induced bacteremia is a rare condition seen predominantly in neutropenic patients and/or patients with gastrointestinal disease. In this report, we describe a non-neutropenic, 72-year-old patient with a small bowel obstruction who presented with *C. tertium* bacteremia. *Clostridium tertium* is aerotolerant and resistant to broad-spectrum cephalosporins. The aerotolerant nature of *C. tertium* is resulted in delayed identification and reporting since it is not initially considered a candidate for infection.

Key Words: *Clostridium tertium*, Non-neutropenic, Small bowel obstruction

Nam Su Ku[1], Hae-Sun Chung[2], Jae Gil Lee[3], Sun Bean Kim[1], Sang Hoon Han[1], Jun Yong Choi[1], Kyungwon Lee[2], and June Myung Kim[1]

Departments of [1]Internal Medicine and AIDS Research Institute, [2]Laboratory Medicine and Research Institute of Bacterial Resistance, [3]Surgery, Yonsei University College of Medicine, Seoul, Korea

Introduction

The genus *Clostridium* is a diverse group of Gram-positive, spore-forming, anaerobic bacilli found in soil and the guts of many animals, including humans. *Clostridium*-induced bacteremia is a rare condition seen primarily in intra-abdominal infections associated with surgical trauma. It has also been associated with underlying gastrointestinal disorders, pregnancy, and malignancies [1].

Clostridium tertium was not recognized as a human pathogen until 1963 [2]. It is most frequently isolated from blood cultures, although it can also cause spontaneous bacterial peritonitis, brain abscesses, and pneumonia [3-5]. Most cases of *C. tertium*-induced bacteremia occur in neutropenic patients without a definite source of infection [3, 5]. Here, we describe a case of *C. tertium* bacteremia in a 72-year-old non-neutropenic patient with an intestinal obstruction.

Case report

A 72-year-old male was admitted with diffuse abdominal pain, which had started four days earlier. He had a history of colon cancer, diagnosed in 1998,

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Correspondence to Sang Hoon Han
Department of Internal Medicine and AIDS Research Institue, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea
Tel: +82-2-2228-1991, Fax: +82-2-393-6884
E-mail: shhan74@yuhs.ac

and had been treated with a left hemicolectomy. Two years prior to admission, he was diagnosed with a hepatocellular carcinoma (B-viral) and had undergone five rounds of transcatheter arterial chemoembolization. Upon admission, his body temperature was 38.3°C, his heart rate was 93 beats per minute, his respiratory rate was 20 per min, and his blood pressure was 123/75 mmHg. Physical examination revealed increased bowel sounds and direct/rebound tenderness on the entire abdomen. His initial white blood cell count was 8,320/mm^3 (86.5% neutrophils), his hemoglobin level was 12.6 g/dL, his platelet count was 6,800/mm^3, and his C-reactive protein level was 246 mg/L. Abdominal CT revealed fluid-filled, dilated small bowel loops, most likely at the proximal ileum (Fig. 1).

With a preliminary diagnosis of small bowel obstruction, a nasogastric tube was inserted for decompression. Intravenous antibiotic therapy was initiated with piperacillin-tazobactam (4.5 g every 8 h). However, the small bowel obstruction did not improve with intravenous antibiotic therapy and supportive care. The patient had a persistent fever and severe abdominal pain. His blood leukocytes were also elevated (16,650/μL). These clinical findings, combined with a subsequent plain radiograph, led to suspicion of strangulation (Fig. 2).

On the fifth day after admission, laparotomy and segmental resection of the small bowel with end ileostomy were performed to confirm the strangulation. Tigecycline (50 mg every 12 h after an initial 100 mg dose) was administered intravenously due to a persistent fever, despite the use of piperacillin-tazobactam. On the seventh day after admission, a blood culture revealed *C. tertium*.

Upon admission, three sets of aerobic and anaerobic blood cultures were set up using the BacT/Alert 3D system (bioMérieux, Durham, NC, USA). The two anaerobic bottles yielded bacterial growth on the first day of incubation, while the corresponding aerobic bottles revealed growth three days later. Staining showed Gram-variable bacilli lacking spores. Sub-culturing from all of the

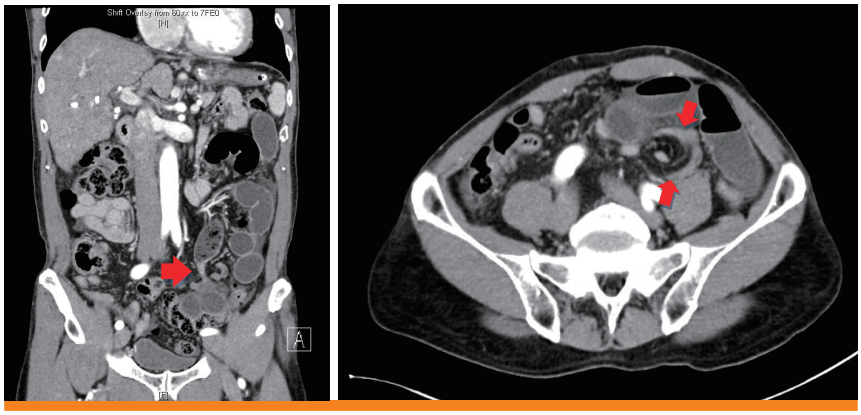


Figure 1. Abdominal computed tomography (CT) at admission shows fluid-filled, dilated small bowel loops at the proximal ileum. An adhesion band is a possible cause of the obstruction (red arrows).

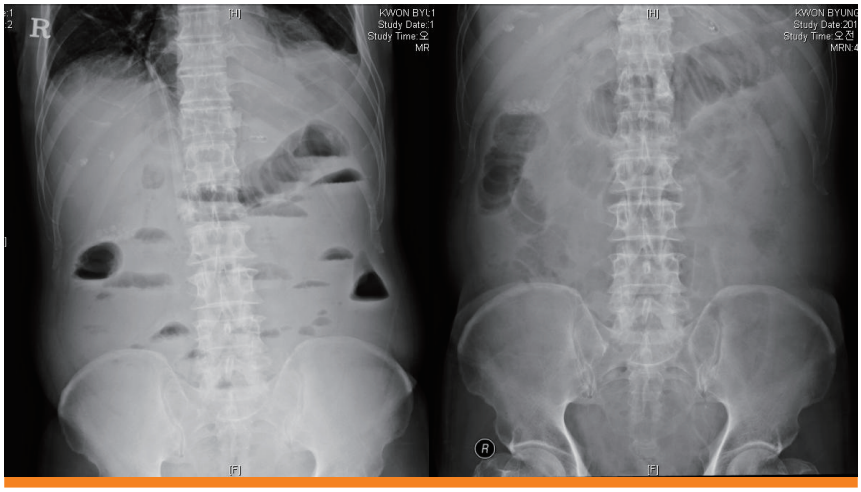


Figure 2. The simple plain X-ray on the fifth day after admission shows distended small bowel loops with air fluid level.

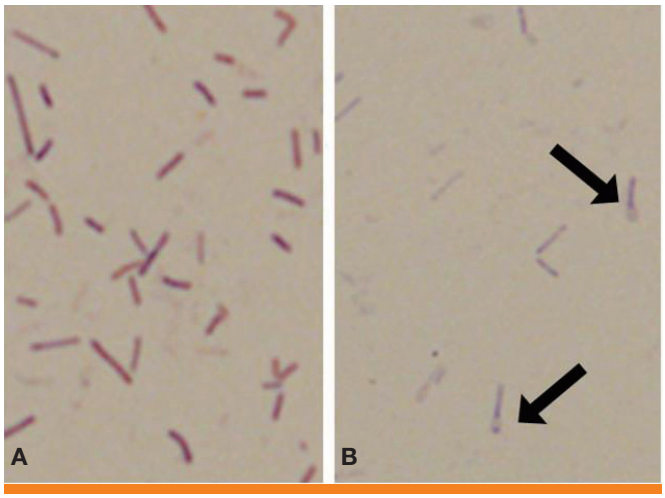


Figure 3. Morphology of Gram-stained *Clostridium tertium* on blood agar plates incubated aerobically (A) and anaerobically (B) (X1,000). A stained smear from an anaerobic blood agar plate shows occasional Gram-positive bacilli with oval terminal spores (black arrows) (X1,000).

positive bottles yielded colonies, but those on anaerobic plates were larger, suggesting that the organism was aerotolerant. Gram staining of the colonies from the anaerobic subculture revealed occasional terminal spores (Fig. 3). Bacterial identification using both the Rapid ID 32A system and ANI card (bioMérieux, Marcy l'Étoile, France) revealed *C. tertium*. The strain was confirmed by PCR and nucleotide sequencing of the bacterial 16S rRNA gene. The sequences were compared with known sequences in the EzTaxon server database (http://www.eztaxon.org; accessed 2 Mar 2011), which revealed 100% homology with *C. tertium* (GenBank accession number Y18174.1).

Three days post-operation, intra-abdominal bleeding was observed, and oliguric acute renal failure developed. Explorative laparotomy revealed active bleeding from the inferior epigastric artery in the left rectus muscle, and suture ligation was performed. In the presence of tigecycline, the same organism was observed at follow-up blood cultures on days 6 and 8, but not on day 13. The patient gradually deteriorated despite aggressive treatment and eventually died 19 days after admission due to multi-organ failure and acute respiratory distress syndrome.

Discussion

Clostridium tertium bacteremia is a rare condition mainly associated with neutropenia in critically ill patients [6-8]. Miller et al. [3] reported that 91% (29/32) of cases of *C. tertium*-related bacteremia occurred in neutropenic patients. Several other studies have also reported neutropenia as a major factor in *C. tertium* bacteremia [6, 8-12]. The exact role of neutropenia in the pathogenesis of *C. tertium* is unclear. However, it may enable *C. tertium* to enter the systemic circulation and facilitate the organism's growth by dampening the innate immune response [3].

In non-neutropenic patients, *C. tertium* bacteremia is associated with intestinal abnormalities. Three distinct cases of *C. tertium* bacteremia in non-neutropenic patients have been described [3]. Of these, one had severe liver disease and spontaneous bacterial peritonitis, one recently had a percutaneous gastrostomy tube implanted, and one had Crohn's disease [3]. A case of *C. tertium* bacteremia in non-neutropenic post-operative patients with a mechanical ileus has also been reported [13]. *Clostridium tertium* bacteremia in non-neutropenic patients is promoted by various abdominal disorders (e.g., chronic inflammatory bowel disease), as well as by the administration of anti-cancer drugs [7, 9]. In the current case, the patient was non-neutropenic but had a small bowel obstruction with strangulation. The obstruction damaged the intestinal mucosa, allowing *C. tertium* to enter the systemic circulation.

Clostridium tertium is not significantly pathogenic, and some authors claim that *C. tertium* is not a true pathogen, but merely a contaminant [14]. However, our patient was at risk (severe sepsis with intestinal obstruction) for *C. tertium* bacteremia, and *C. tertium* was isolated from all three blood cultures. Thus, *C. tertium* bacteremia, in this case, was not likely a result of culture contamination.

Clostridium tertium is not histotoxic, lipolytic, or toxin-producing. When *C. tertium* bacteremia is treated with appropriate antimicrobial therapies, the mortality rate is quite low [1]. In several studies, most patients with *C. tertium* bacteremia survived after appropriate antibiotic therapy [2, 3]. In this case, *C. tertium* did not grow in the blood cultures after the administration of tigecycline. The patient's cause of death was classified as multi-organ failure and acute respiratory distress syndrome due to post-operative bleeding.

Clostridium tertium is resistant to many beta-lactams, and it is often resistant to expanded-spectrum cephalosporins with enhanced activity against gram-positive bacteria [7]. A penicillin-resistant strain has also been reported [10]. Metronidazole, which is commonly used to treat anaerobic infections, may be effective [6, 10], but resistant *C. tertium* isolates have been described [11]. *In vitro*, tigecycline has been shown to have potent inhibitory activity against *C. tertium* [15].

Tigecycline was used to successfully treat patients with complicated intra-abdominal infections in several studies [16, 17]. Tigecycline is not significantly toxic and has a wide spectrum

of antibiotic activities. We applied tigecycline as an alternative antimicrobial.

In conclusion, we describe a case of *C. tertium* bacteremia in a non-neutropenic patient with small bowel obstruction. *Clostridium tertium* rarely causes bacteremia in non-neutropenic patients. However, pre-existing intestinal mucosal injury increases susceptibility to *C. tertium* bacteremia. Furthermore, because of the aerotolerant nature of the isolate, *Clostridium* species were not initially considered, resulting in delayed identification and reporting.

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Clinical Infectious Diseases

MAJOR ARTICLE

Epidemiology of *Escherichia coli* Bacteremia: A Systematic Literature Review

Marc Bonten,[1,a] James R. Johnson,[2,a] Anita H. J. van den Biggelaar,[3,a] Leonidas Georgalis,[3] Jeroen Geurtsen,[4] Patricia Ibarra de Palacios,[5] Stefan Gravenstein,[6] Thomas Verstraeten,[3] Peter Hermans,[4] and Jan T. Poolman[4]

[1]Julius Center, UMC Utrecht, Utrecht University, Utrecht, The Netherlands, [2]Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA, [3]P95 Pharmacovigilance and Epidemiology Services, Leuven, Belgium, [4]Bacterial Vaccines Discovery and Early Development, Janssen Vaccines and Prevention B.V., Leiden, The Netherlands, [5]Clinical Development, Janssen Vaccines, Bern, Switzerland, and [6]Brown University and Providence Veterans Administration Hospital, Providence, Rhode Island, USA

Background. *Escherichia coli* is the most common cause of bacteremia in high-income countries. To enable the development and implementation of effective prevention strategies, a better understanding of the current epidemiology of invasive *E. coli* infections is needed.

Methods. A systematic review of literature published between 1 January 2007 and 31 March 2018 on the burden and epidemiology of *E. coli* bacteremia in populations that include adults in high-income countries was conducted. Meta-analysis was performed for descriptive purposes.

Results. During the studied time interval, the estimated incidence rate of *E. coli* bacteremia was 48 per 100 000 person-years, but this increased considerably with age: rates per 100 000 person-years were >100 in 55-to-75-year-olds and >300 in 75-to-85-year-olds. Overall, *E. coli* accounted for 27% of documented bacteremia episodes: 18% if hospital acquired, 32% if community-onset healthcare associated, and 33% if community acquired. The estimated case fatality rate was 12%. Approximately 44% of episodes were community acquired, 27% community-onset healthcare associated, and 27% hospital acquired. Urinary tract infection (UTI) was the primary source for 53% of episodes.

Conclusions. This systematic review confirms the substantial burden of *E. coli* bacteremia in older adults and justifies the implementation of community-level programs to prevent *E. coli* bacteremia and ideally UTI in this age group.

Keywords. *Escherichia coli*; bacteremia; epidemiology; systematic literature review; ExPEC.

Escherichia coli are gram-negative bacteria within the family *Enterobacteriaceae* that can harmlessly colonize the human gut or cause intestinal or extraintestinal infections, including severe invasive disease such as bacteremia and sepsis. *E. coli* is the most common cause of bacteremia in high-income countries, exceeding other leading bacteremia-causing pathogens such as *Staphylococcus aureus* and *Streptococcus pneumoniae*, and is a leading cause of meningitis in neonates [1–7].

Emerging multidrug-resistant *E. coli* strains are more challenging to treat and confer a higher risk of bacteremia and death [8–11]. Vaccines that can prevent invasive *E. coli* infections such as bacteremia are currently unavailable but are in clinical development [12, 13]. To inform the development and implementation of effective prevention strategies, a better understanding is needed of the current epidemiology of invasive *E. coli* infections. To this end, we conducted a systematic literature review, and describe here the evidence published between 1 January 2007 and 31 March 2018 on the burden and epidemiology of *E. coli* bacteremia in high-income countries.

METHODS

The objectives of this review were to consolidate and describe the available evidence regarding the burden and epidemiology of *E. coli* bacteremia in populations that include adults in high-income countries. Specific topics of interest included the following: (1) incidence rates, (2) proportion of all bacteremia episodes attributable to *E. coli*, (3) risk factors, (4) setting of acquisition, (5) primary source of infection, and (6) mortality rates and case fatality rates (CFRs).

Identification of Studies

A systematic literature review was performed for the broader clinical outcome of invasive *E. coli* infections, including any infection in which *E. coli* was isolated from a normally sterile body site, or from urine in a patient with clinical sepsis and no other identifiable source of infection. We searched MEDLINE (PubMed), LILACS, SciELO, and EMBASE for relevant articles published between 1 January 2007 and 31 March 2018. Search terms included those for *Escherichia coli*

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[a]M. B., J. R. J., and A. H. J. v.d.B. contributed equally to this work.

Correspondence: J. T. Poolman, Janssen Vaccines and Prevention B.V., Archimedesweg 4–69, 2333 CN Leiden, The Netherlands (jpoolman@its.jnj.com).

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(including the terms *Escherichia coli*, *E. coli*, extraintestinal pathogenic *Escherichia coli*, and ExPEC) and invasive disease (including terms for bacteremia, sepsis, urosepsis, meningitis, encephalitis, pneumonia, empyema, septic arthritis, osteomyelitis, peritonitis, and hepatitis) (described in detail in Supplementary File 1). The systematic literature review and meta-analysis were performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

Selection Criteria

Studies had to meet the following inclusion criteria: include subjects aged 18 years or older; conducted in Western Europe, the United States, Canada, Japan, Australia, or New Zealand; published between 1 January 2007 and 31 March 2018; and in English, Dutch, French, Italian, Spanish, or Portuguese. The following types of studies were excluded: those limited to pediatric populations, non–human studies, case reports, case series, intervention trials, reviews, and conference abstracts. No distinction was made as to whether studies included only monomicrobial or also polymicrobial infection, because this information was rarely reported and was not expected to significantly affect results.

Selection Process and Data Extraction

Reports identified through the electronic searches were first screened for eligibility by 2 independent reviewers based on titles and abstracts to make a first selection of reports potentially meeting the selection criteria. The initially selected reports then underwent full-text review to make a final selection of eligible reports to be included in the study and to undergo definitive data extraction. Data were extracted into a Microsoft Access database by a single reviewer. The selection process was documented electronically, with each report's fulfillment/nonfulfillment of the inclusion and exclusion criteria recorded in accordance with PRISMA guidelines [15]. We here report on data extracted for bacteremia and sepsis (confirmed by culture of *E. coli* from blood).

Statistical Analyses

To describe the identified evidence, a random-effects, inverse-variance–weighted meta-analysis [16] was used to calculate pooled estimates for incidence rates, proportion of documented episodes attributable to *E. coli*, proportions of episodes acquired in different settings, proportions of episodes with a urogenital tract infection as primary source, and CFR. Incidence rates were analyzed on log scales and proportions on a logit scale. The Cochrane Q statistic was determined, with P values < .05 indicating a significant amount of heterogeneity, and the I^2 statistic indicating the proportion of total variation attributable to heterogeneity between studies. Results were summarized in forest plots. All analyses were performed in R (version 3.2.0), using the metafor package for meta-analyses [17, 18]. Because of the observational and descriptive nature of the research questions, study quality was not assessed formally.

Sensitivity Analysis

Two types of sensitivity analysis were conducted. First, to assess the effect of including data from studies restricted to patients with clinical sepsis (as defined by the study's authors), meta-analysis results were compared for data pertaining to (1) bacteremia per se (ie, a positive blood culture, irrespective of associated clinical manifestations) and (2) bacteremic sepsis (ie, clinical sepsis, plus a positive blood culture). Second, to assess whether CFR estimates might be influenced by the study's time-to-death criterion, meta-analysis outcomes were compared for data from studies using a 30-day time-to-death criterion, studies without a specified time-to-death criterion, and all studies.

Meta-regression Analysis

To study potential sources of heterogeneity, random-effects meta-regression was conducted. First, univariate analyses were performed to assess the effects of selected study characteristics (calendar year [continuous], geographic region, study design, number and type of study centers, lower age limit, inclusion of multiple episodes, and case definition) on key effect measures, including incidence rates, proportions of bacteremia due to *E.coli*, and CFRs. Next, bivariate analyses were performed for the same effect measures, including in the model calendar time (identified in univariate analysis to have the strongest effect) and other potential sources of heterogeneity, one at a time. A ratio greater than 1 indicates that the effect measure is larger for the category of interest compared with the reference category. We used permutation tests to control for the risk of spurious findings [19].

RESULTS

Available Evidence

The search identified 210 studies (listed in the Supplementary References) that addressed the study objectives regarding *E. coli* bacteremia (Figure 1). For all study objectives for which we conducted meta-analysis, the overall between-study heterogeneity of available evidence was high (I^2 > 50%). Consequently, pooled estimates included in this report are descriptive and cannot be interpreted as predictive values.

Incidence Rates in Time and by Age, Sex, and Setting of Acquisition

The overall incidence rate of *E. coli* bacteremia (as cases per 100 000 person-years) was 48.0 (95% confidence interval [CI], 40.2–57.2) (Figure 2) (Supplementary Table 1). Sensitivity analysis showed that the inclusion of data pertaining to bacteremic sepsis did not appreciably change outcomes (data not shown).

Incidence rate increased significantly with age (Supplementary Figure 1 and Supplementary Table 2). Incidence rates were above the population average in older adults, with estimated rates of 110, 154, and 319 episodes per 100 000 person-years

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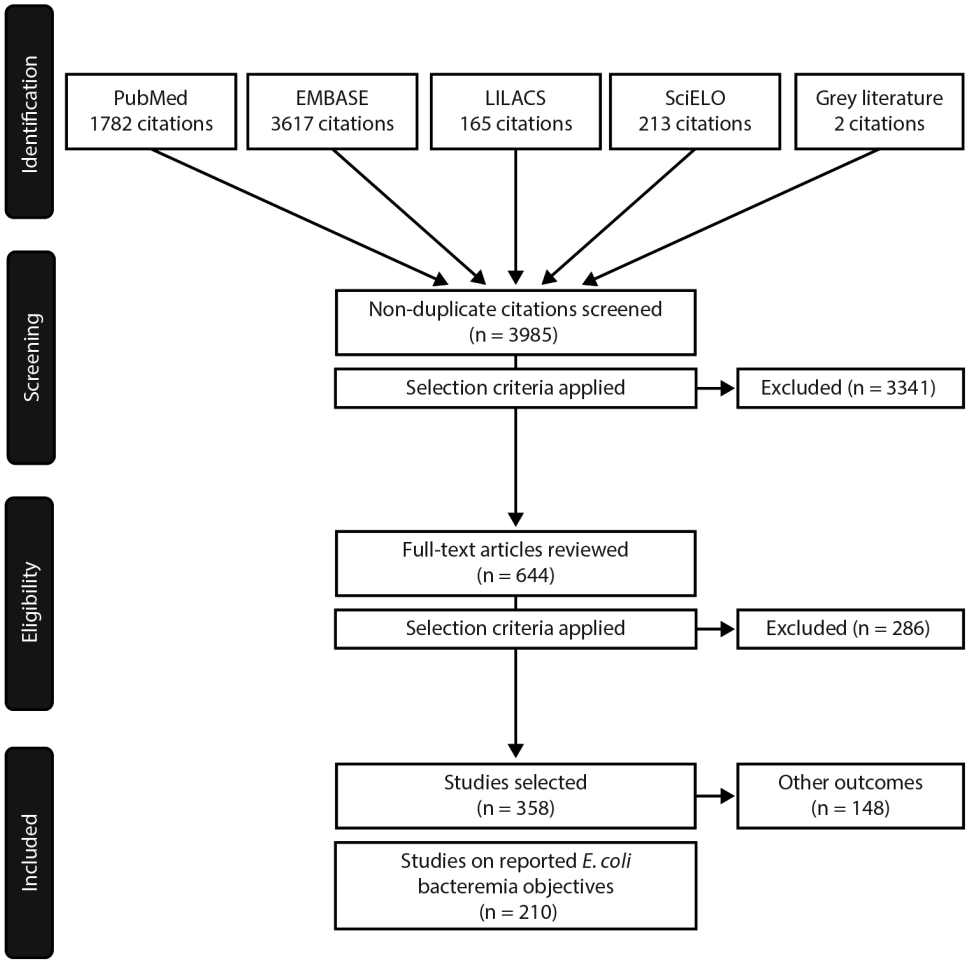


Figure 1. PRISMA diagram of selection process of reports included in this review. A systematic literature search identified 3985 unique studies published between 1 January 2007 and 31 March 2018 reporting on the burden and epidemiology of invasive *E. coli* infections in populations that include adults in high-income countries. After a first screening based on abstracts and titles, 644 reports underwent full-text review, of which 358 met the selection criteria, including 210 that included data on *E. coli* bacteremia pertaining to incidence rates, risk factors, setting of acquisition, primary source of infection, and/or mortality, and CFR, and 148 that reported on other outcomes or manifestations of invasive *E. coli* infections (not reported here). Abbreviation: CFR, case fatality rates; *E. coli, Escherichia coli*; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

among those aged 60-to-69 years old, 70-to-79 years old, and 80 years and older, respectively.

The overall incidence rate of *E. coli* bacteremia was higher among women than men. Stratification by age group showed that this association was limited to young and middle-aged adults; in adults older than 60 years, women and men had similar incidence rates. In the few studies that reported incidence rates in relation to setting of acquisition, rates for hospital-acquired *E. coli* bacteremia were 0.1 and 0.17 per 1000 patient-days [20, 21] (ie, 3650 and 6205 per 100 000 patient-years), whereas for community-onset, healthcare-associated *E. coli* bacteremia they were 25.8 and 32 per 100 000 person-years [22, 23].

Proportion of All Documented Bacteremia Episodes Caused by *Escherichia coli*, Overall and According to Setting of Acquisition

The *E. coli*–specific proportion of all bacteremia episodes was 27.1% overall (95% CI, 24.5–29.8) (Figure 3 and Supplementary Table 2), but varied widely by study, from 6.5% [24] to 57% [25]. It also varied significantly by setting, namely 18.1% (95% CI, 15.1–21.7%) for hospital-acquired episodes as compared with 33.0% (95% CI, 29.1–37.3%) for community-acquired episodes and 31.5% (95% CI, 28.0–35.1%) for community-onset healthcare-associated episodes (Figure 4 and Supplementary Table 3). By contrast, no differences were apparent in relation to year (Figure 3), age, or geographic region. Sensitivity analysis confirmed that results were unaffected by the inclusion of bacteremic sepsis-related episodes (data not shown).

Proportion of *Escherichia coli* Bacteremia Episodes Acquired in Different Settings

Of all documented *E. coli* bacteremia episodes, an estimated 26.6% (95% CI, 21.7–32.2%) were hospital acquired, whereas 44.3% (95% CI, 36.6–52.3%) were community acquired,and 26.5% (95% CI, 22.4–31.0%) were community-onset healthcare

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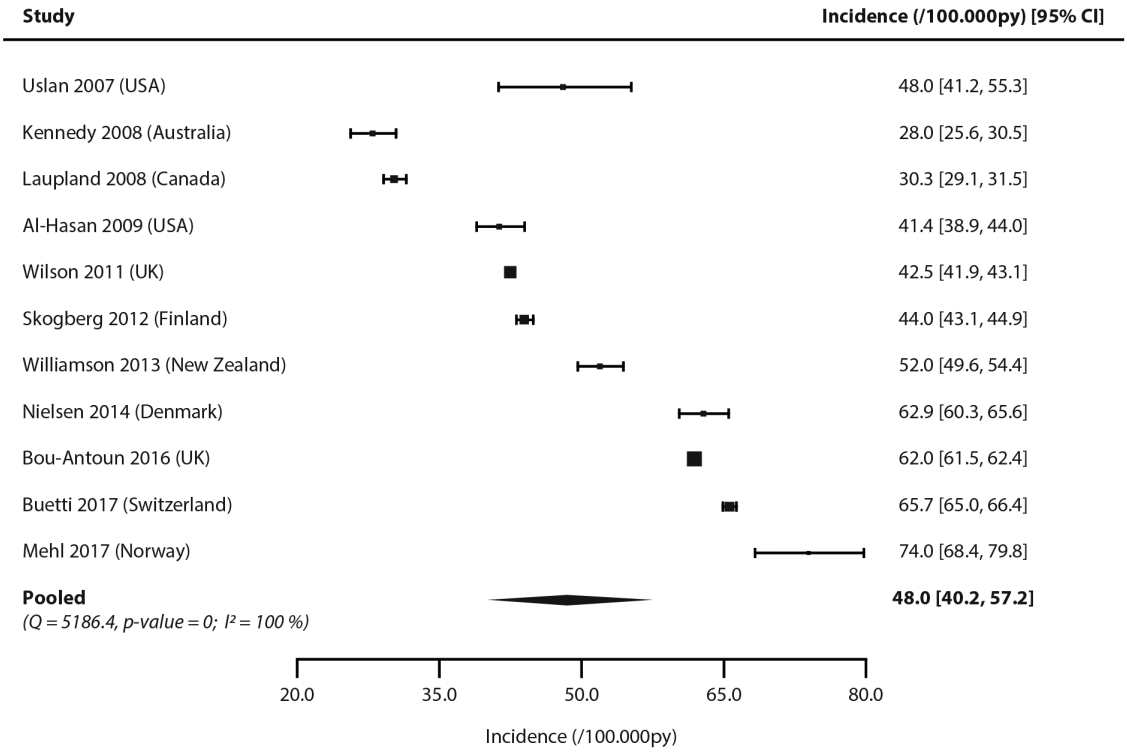


Figure 2. Incidence rate of *E. coli* bacteremia in the general population. Data on the incidence rate of *E. coli* bacteremia (per 100 000 person-years) were pooled and analyzed on log-scales to estimate an overall incidence rate. Data were summarized in a forest plot. Studies are listed in order of publication year. The reference for each study listed can be found in the Supplementary References. Abbreviations: *E. coli*, *Escherichia coli*; CI, confidence interval; *E. coli, Escherichia coli*; py, person-years.

associated. For studies not distinguishing between community-acquired and community-onset healthcare-associated infections, 62.0% (95% CI, 49.9–72.7%) of episodes were community onset (Supplementary Table 4 and Supplementary Figure 2).

Primary Source of *Escherichia coli* Bacteremia

Urogenital infection accounted for more than half of all *E. coli* bacteremia episodes (pooled estimate, 52.6%; 95% CI, 47.0–58.1%; range by study, 31–80%) (Supplementary Table 5 and Supplementary Figure 3). Of the diverse other sources, the most common were biliary infection (range, 11–27%) and other intra-abdominal infections (range, 4–48%).

Relative Risk for *Escherichia coli* Bacteremia According to Medical Conditions and Procedures

Among the various reported medical conditions or procedures, the highest relative risks (RRs) of developing *E. coli* bacteremia compared with the general population were associated with renal dialysis (RR, 26.9), solid-organ transplantation (RR, 20.3), and neoplastic disease (RR, 14.9). In hospitalized individuals, indwelling vascular and urinary catheters increased the risk of *E. coli* bacteremia: by 10-fold and 7.5-fold for central and peripheral venous catheters, respectively, and by 6-fold and 3-fold for suprapubic and urethral urinary catheters, respectively.

Incidence Proportion of *Escherichia coli* Bacteremia in Specific Patient Groups

The proportion of patients who developed *E. coli* bacteremia varied in association with specific underlying medical conditions (Supplementary Table 6), although the RR compared with the general population is unknown due to the absence of control groups. The highest values were for patients with chronic lymphocytic leukemia and multiple myeloma (12–13%) (Supplementary Table 6).

Proportion of Bacteremia Episodes Caused by *Escherichia coli* in Relation to Specific Medical Conditions

Supplementary Tables 7 and 8 show the *E. coli*–specific proportion of all bacteremia episodes in which *E. coli* was isolated among patients with specific medical conditions or following certain surgical interventions. The highest values occurred with transrectal ultrasound-guided prostate needle biopsy (79–100%) and kidney transplantation (23–55%).

Escherichia coli Bacteremia Mortality Rate and Case Fatality Rate

Annual mortality rates for *E. coli* bacteremia ranged from 2.9 to 10.3 per 100 000 persons (Supplementary Table 9). The pooled estimated CFR for *E. coli* bacteremia was 12.4% (95% CI, 10.7–14.3%; range, 2.8–28.5%) (Figure 5 and Supplementary Table 10). Based on limited data, CFRs for specific patient subsets did

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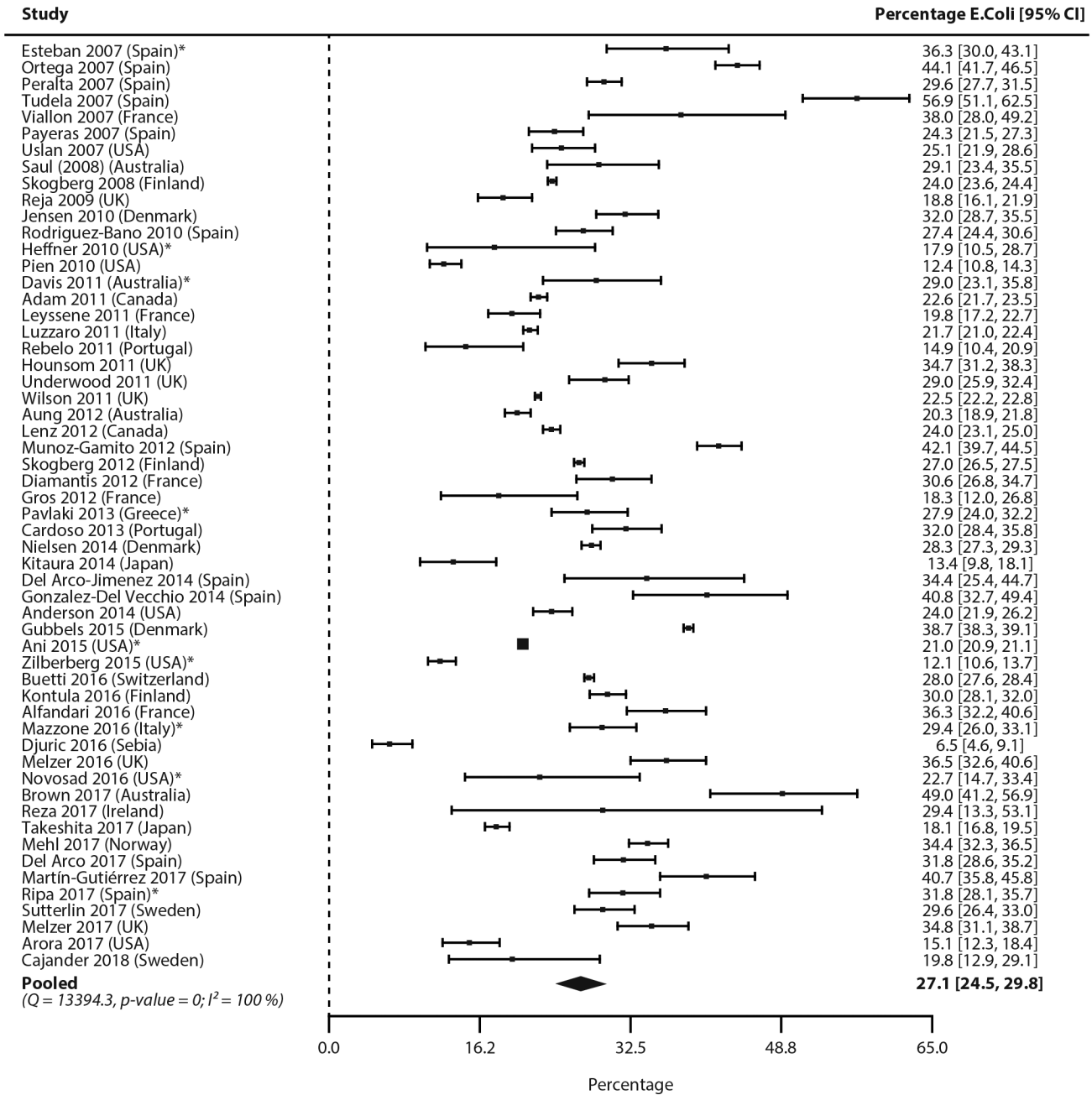


Figure 3. Proportion of all documented bacteremia episodes caused by *E. coli*. Data are from the 56 studies that reported the proportion (%) of all documented bacteremia episodes attributable to *E. coli* (*including data from 9 studies reporting on bacteremic sepsis as a clinical outcome only). Data were pooled and analyzed on a logit scale to calculate an overall estimate and were summarized in a forest plot. Studies are listed in order of publication year. The estimate was unchanged without the 9 studies that reported on bacteremic sepsis only (27.5%; 95% CI, 24.7–30.6%). The reference for each study listed can be found in the Supplementary References. Abbreviations: CI, confidence interval; *E. coli*, *Escherichia coli*.

not differ appreciably from those in the general population (Supplementary Table 11). Sensitivity analysis showed that a study's time-to-death criterion did not influence CFR estimates (data not shown).

Potential Sources of Heterogeneity

Univariate meta-regression analysis found that the incidence of *E. coli* bacteremia was affected most significantly by calendar year, with an estimated 7% (95% CI, 2–11%) increase by year (Supplementary Table 12). According to both univariate and bivariate analyses, the inclusion of children in a study population (lower incidence) and conducting a study in a single center (higher incidence) significantly affected estimates of *E. coli* bacteremia incidence rates. The proportion of bacteremia episodes due to *E. coli* was significantly influenced by geographic region, being only half as large (.52; 95% CI, .36–.76) in North

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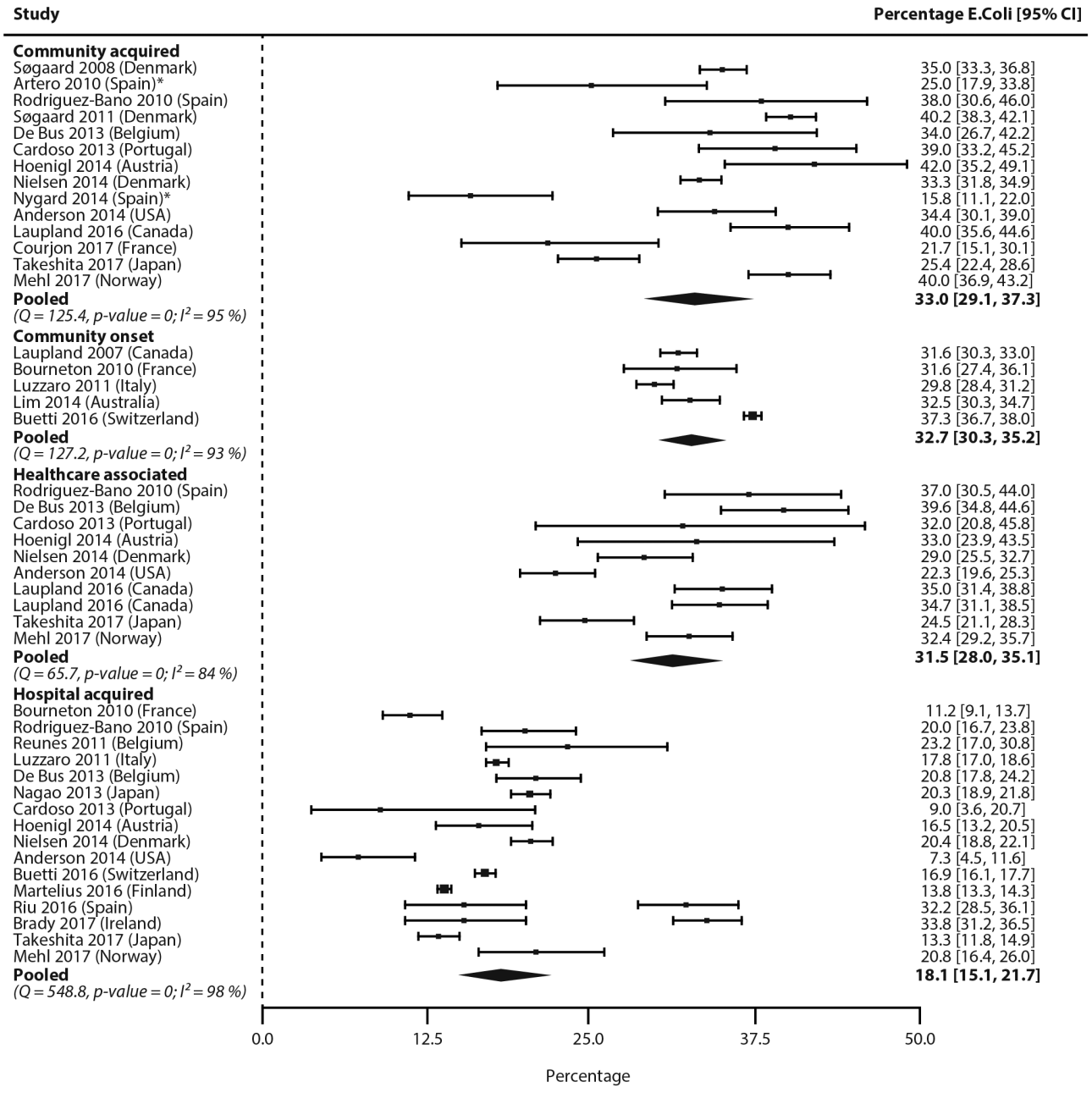


Figure 4. Proportion of bacteremia episodes caused by *E. coli* according to setting of acquisition. Data on the proportion (%) of documented bacteremia episodes attributable to *E. coli* (*including studies reporting on bacteremic sepsis) were categorized as community acquired, community onset and healthcare associated, and hospital acquired. The community-onset category includes studies that did not specify whether patients were receiving outpatient care, so likely contains data for both community-acquired and community-onset healthcare-associated bacteremia episodes. Stratified data were analyzed on a logit scale to calculate a pooled estimate per setting. Data were summarized in a forest plot; studies within each category are listed in order of publication year. The reference for each study listed can be found in the Supplementary References. Abbreviations: CI, confidence interval; *E. coli*, *Escherichia coli*.

America as in Europe. No significant associations were found for CFRs.

DISCUSSION

To our knowledge, this is the first systematic review regarding the epidemiology of *E. coli* bacteremia in high-income countries. This consolidation of data published between 1 January 2007 and 31 March 2018 yielded 3 key findings regarding the current burden of *E. coli* bacteremia, which provide important epidemiological evidence to inform the development and implementation of effective preventive strategies.

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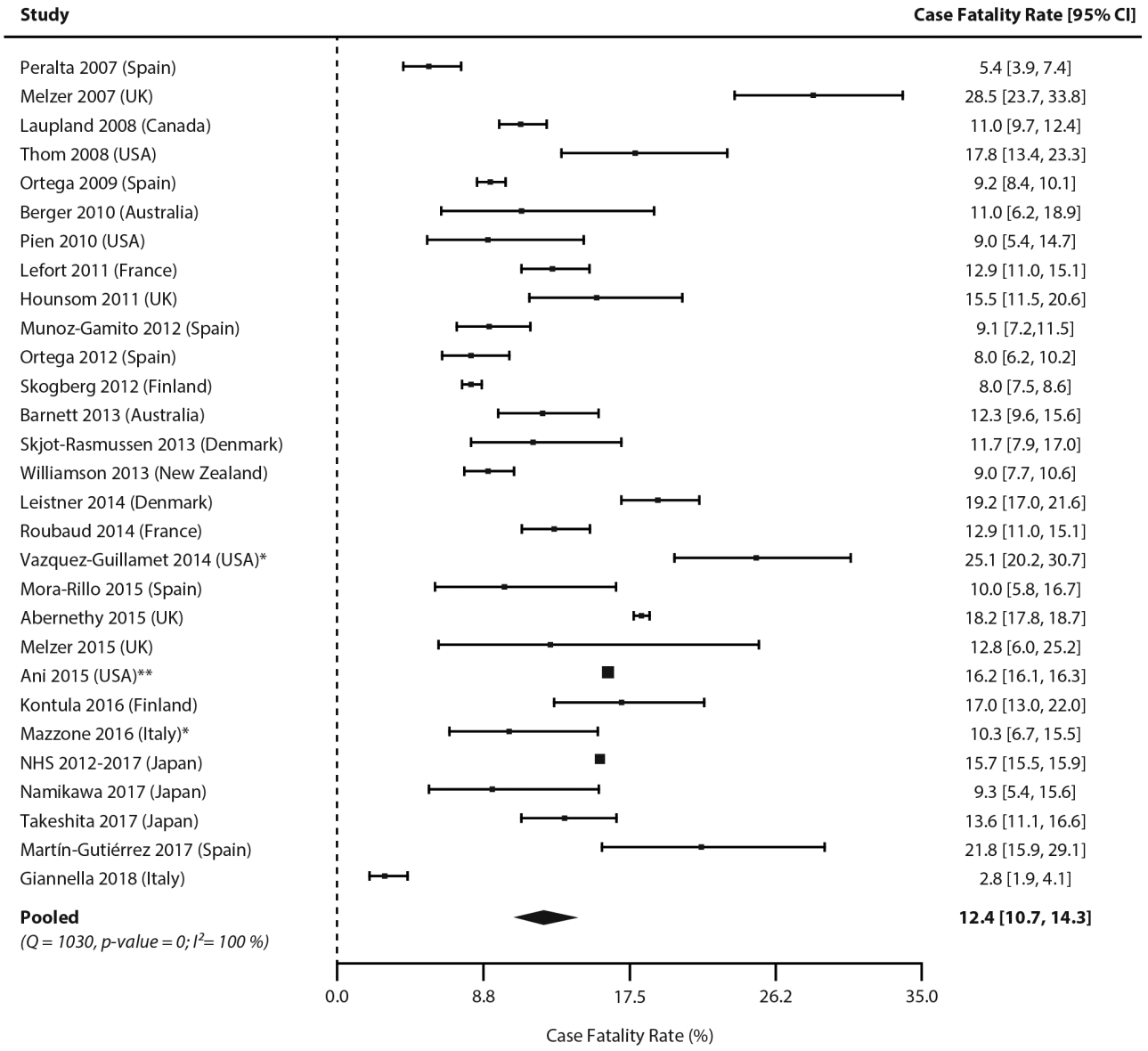


Figure 5. Case fatality rate of *Escherichia coli* bacteremia and sepsis. Data from 29 studies reporting on the case fatality rate (%) in patients with *E. coli* bacteremia (including studies reporting on *bacteremic sepsis or **severe bacteremic sepsis) were pooled and analyzed on a logit scale to calculate an overall estimate. Data were summarized in a forest plot; studies are listed in order of publication year. The estimate was unchanged without the studies reporting on bacteremic sepsis (12.0%; 95% CI, 10.3–13.9%). The reference for each study listed can be found in the Supplementary References. Abbreviation: CI, confidence interval.

First, the burden of *E. coli* bacteremia is substantial, especially among the elderly. Although *E. coli* bacteremia occurs in adults of all ages, its incidence rate rises progressively after age 55–60 years. Because the world's elderly population continues to increase at an unprecedented rate, with the number of individuals aged 65 and older predicted to increase from 617 million in 2015 to 1 billion by 2030 and to 1.6 billion by 2050 [26], the number of *E. coli* bacteremia cases can be expected to increase accordingly, unless preventive action is undertaken. Most episodes will occur in 65- to 74-year-olds, who currently account for most adults aged 65 years and older, and will continue to do so [26, 27]. This implies that, for immunization programs to reduce *E. coli* bacteremia most effectively, adults should be targeted preferably before age 65. By analogy, some high-income countries already follow an age-related approach to routine vaccination for other infectious diseases with a high burden in older adults, such as seasonal influenza, pneumococcal infections, and herpes zoster [28].

A second finding is that approximately three-quarters of *E. coli* bacteremia episodes occur in persons who at the time

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of onset or acquisition are community residents; only approximately one-quarter of episodes are hospital acquired. This, plus the limited evidence for specific risk factors other than age, suggests that for preventive interventions to have the greatest impact on reducing *E. coli* bacteremia they may need to be implemented at the community level and target the near-elderly.

Third, urinary tract infection (UTI) is the leading source for *E. coli* bacteremia, accounting for more than 50% of cases. The risk of UTI increases with age due to physiological changes that lead to bladder dysfunction and urinary catheter use, which increase the risk of bacterial colonization and infection. Consequently, UTI is the most frequent bacterial infection in the elderly, with an incidence rate of 30–100 per 1000 person-years among persons aged 60–90 years [29]. *Escherichia coli* is the most common cause of UTI in all settings [30]. As such, interventions that prevent *E. coli* UTI should also significantly reduce the burden of *E. coli* bacteremia. Importantly, such interventions are also likely to prevent infections caused by antimicrobial-resistant organisms, a growing problem in which *E. coli* features prominently [31].

Other common sources of *E. coli* bacteremia are biliary tract infection caused by bacteria ascending from the gastrointestinal tract and other intra-abdominal infections. *Escherichia coli* biliary tract infection occurs mostly in patients with underlying structural abnormality, normally choledocholithiasis or malignancy [32, 33], whereas other intra-abdominal infections are predominantly complications of surgeries and procedures, often those done on an emergency basis of the gastrointestinal or urogenital tract [34, 35].

This review has several limitations. First, incidence rate data came mainly from small, short-term, single-institution studies; were lacking (except from the United Kingdom) for sequential time periods; and were sparse or lacking from North America after 2007, and from Japan, Australia, and New Zealand. Second, most reports provided only total population incidence, without stratification by age, precluding accurate incidence estimates for older adults. Because *E. coli* bacteremia affects mainly older adults, rates for the total adult population predictably underestimate the disease burden in the elderly. Third, few studies addressed risk factors for *E. coli* bacteremia other than UTI and indwelling urinary catheters. Such data are essential to guide the development and deployment of effective intervention strategies and to measure their impact. Fourth, the review is limited to high-income countries; results may differ in low- and middle-income countries. Fifth, results varied considerably between studies, as indicated by the high I^2 values in the meta-analysis, indicating that the pooled estimates do not represent predictive values. This heterogeneity can be explained partly by between-study differences in time periods, geographic regions, and possibly age groups. The meta-regression results support the notion that the incidence of *E. coli* bacteremia is increasing over time. The 7% annual increase estimated here corresponds to the 6% increase observed in England between 2012 and 2013–2014 [36]. The lower relative proportion of bacteremia attributed to *E. coli* found in North America may be related to higher blood culturing rates that may result in a higher variety of pathogens being detected, or from a higher proportion of patients already receiving antibiotics at the time of taking the blood cultures.

In summary, this review consolidates recent evidence regarding the epidemiology of *E. coli* bacteremia in populations that include adults in high-income countries, as needed to guide the development and implementation of preventive strategies. Its findings suggest that immunization programs should target adults at or before age 65, after which the incidence of *E. coli* bacteremia rises; should be implemented at the community level; and, ideally, should prevent also UTI, the primary source for most *E. coli* bacteremia episodes. To identify optimal target populations for future interventions and to measure their impact, surveillance programs for *E. coli* bacteremia are needed, as are additional studies regarding risk factors and sequelae.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Pain management in patients with chronic kidney disease and end-stage kidney disease

Payel J. Roy[a], *Melanie Weltman*[b], *Laura M. Dember*[c,d], *Jane Liebschutz*[a], *Manisha Jhamb*[e], *on behalf of the HOPE Consortium*

Purpose of review
This review evaluates current recommendations for pain management in chronic kidney disease (CKD) and end-stage kidney disease (ESKD) with a specific focus on evidence for opioid analgesia, including the partial agonist, buprenorphine.

Recent findings
Recent evidence supports the use of physical activity and other nonpharmacologic therapies, either alone or with pharmacological therapies, for pain management. Nonopioid analgesics, including acetaminophen, topical analgesics, gabapentinoids, serotonin–norepinephrine reuptake inhibitors, and TCA may be considered based on pain cause and type, with careful dose considerations in kidney disease. NSAIDs may be used in CKD and ESKD for short durations with careful monitoring. Opioid use should be minimized and reserved for patients who have failed other therapies. Opioids have been associated with increased adverse events in this population, and thus should be used cautiously after risk/benefit discussion with the patient. Opioids that are safer to use in kidney disease include oxycodone, hydromorphone, fentanyl, methadone, and buprenorphine. Buprenorphine appears to be a promising and safer option due to its partial agonism at the mu opioid receptor.

Summary
Pain is poorly managed in patients with kidney disease. Nonpharmacological and nonopioid analgesics should be first-line approaches for pain management. Opioid use should be minimized with careful monitoring and dose adjustment.

Keywords
buprenorphine, chronic kidney disease, end-stage kidney disease, opioids, pain

INTRODUCTION

Chronic pain is a common symptom experienced by patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) [1,2]. Untreated pain in this population negatively impacts health-related quality of life, dialysis adherence, healthcare utilization, and mortality [3–5]; and may contribute to other physical and psychosocial symptoms such as depression, anxiety, and fatigue [6].

There is a disproportionately high use of opioids in this population due to limited availability of nonpharmacological treatment options or safe non-opioid pharmacological options. In a study of over 400 000 ESKD patients, over half had received an opioid prescription, 3.2 times the rate in the US population [7] and 20% were on long-term opioid therapy (LTOT) [8]. Chronic opioid use in patients with kidney disease has been associated with increased risk of altered mental status, falls, fractures, hospitalizations, and mortality, in a dose-dependent manner [9–11,12▪▪]. However, closely monitored LTOT may be warranted in some patients who fail to respond to other pain treatments. This requires careful consideration of risks and benefits.

[a]Division of General Internal Medicine, Department of Medicine, University of Pittsburgh School of Medicine, [b]Department of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy, Pittsburgh, [c]Renal, Electrolyte and Hypertension Division, Department of Medicine, [d]Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia and [e]Division of Renal-Electrolyte, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Correspondence to Manisha Jhamb, MD, MPH, UPMC Presbyterian, 200 Lothrop St. Suite C1100, Room C1103, Pittsburgh, PA 15213, USA. Tel: +1 412 647 7062; e-mail: jhambm@upmc.edu

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KEY POINTS

- Pain management in patients with kidney disease is challenging due to multiple patient, provider, and structural factors.
- Nonpharmacologic management of pain includes behavioral-based and physically-oriented interventions.
- Preferred nonopioid analgesia in CKD and ESKD include acetaminophen, topical analgesics, gabapentinoids, serotonin–norepinephrine reuptake inhibitors, and TCA.
- Before starting opioids, providers should have risk/benefit discussions regarding opioid analgesia, including complete psychosocial assessment and regular monitoring for benefits and adverse effects with evidence-based tools and urine or oral drug screening.
- Preferred opioid analgesics include oxycodone, hydromorphone, fentanyl, methadone, and buprenorphine.

Pain management in kidney disease is a top research priority, and is being fostered in the nephrology community by enterprises such as the Kidney Health Initiative, a public–private partnership between the American Society of Nephrology and US Food and Drug Administration [13,14]. In addition, the recently established Hemodialysis Opioid Prescription Effort (HOPE) Consortium, funded by the National Institutes of Health's Helping to End Addiction Long-term mission and the National Institute of Diabetes and Digestive and Kidney diseases (NIDDK), will address pain management and opioid safety in this population [15].

The goal of the current review is to provide practical guidance for treating pain, summarize evidence on nonpharmacological and pharmacological options for pain, and focus on safety and efficacy of medications including opioids.

APPROACH TO PAIN MANAGEMENT

Multiple patient, provider, and healthcare-system factors make pain management challenging in this population (Fig. 1) [16]. The multifactorial causes of pain and common comorbid conditions in patients with kidney disease result in varying types of pain (neuropathic, nociceptive, or both) [17–21]. Provider-related and system-related factors relate to lack of training for nephrologists in treating pain, fragmentation of care, and most importantly lack of scientific evidence and guidelines around pain management in CKD and ESKD [22,23].

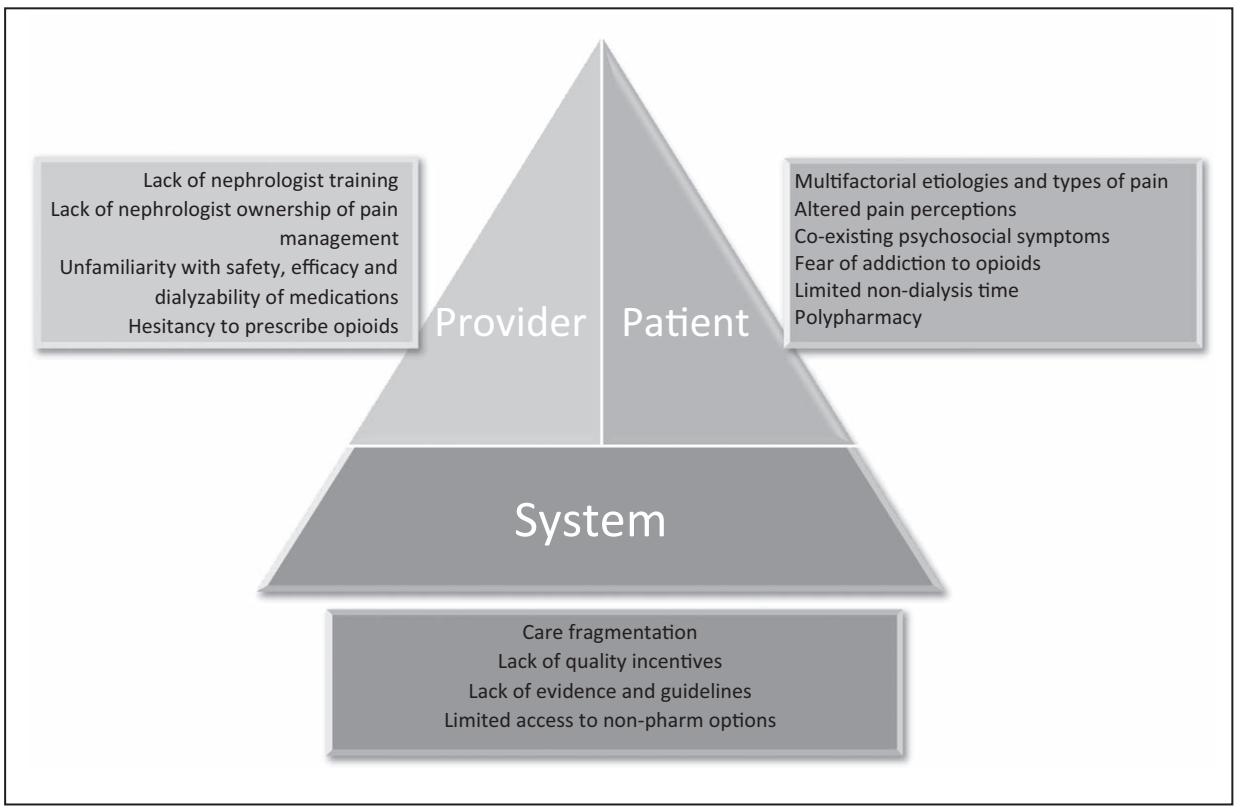


FIGURE 1. Challenges in pain management in patients with kidney disease.

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Pain assessment

This should start with assessment of pain severity using various standardized tools, most common of which is the numerical rating scale [24]; pathophysiologic evaluation into mechanism of injury and type of pain; psychosocial evaluation of co-occurring factors that contribute to pain or make treatment of pain more challenging, such as depression, anxiety, and a history of substance use disorder [25]; and overall impact of pain using tools such as the PEG, a validated, three-item tool assessing Pain intensity, interferences with Enjoyment in life, and General activity [26].

Prior to initiating treatment, discussions should include realistic expectations for improvements in pain and function, which can strengthen the therapeutic alliance between patient and provider [27]. When patients' anticipated pain relief does not align with their experience it requires calibration of expectations [28].

NONPHARMACOLOGIC APPROACHES

Nonpharmacologic options range from psychosocial or behavioral-based interventions [e.g., cognitive behavioral therapy (CBT), acceptance and commitment therapy, relaxation, music therapy, mindfulness] to physically-oriented interventions (e.g., exercise, physical therapy, yoga, acupuncture, electrical stimulation). Psychosocial interventions are supported by robust evidence from the general population as effective approaches for reducing pain severity, interference, pain-related disability and psychological distress, and have limited but promising evidence for reduction in opioid use, and even opioid misuse behaviors [29–35]. Currently, such evidence in kidney disease is very limited and of poor quality [36–39]. Two NIDDK-funded trials (Technology Assisted Collaborative Care and the HOPE Consortium trial [15]) are currently testing telemedicine-delivered CBT-based interventions for pain in patients receiving hemodialysis [40]. Physical therapy or exercise-based interventions have been successful in improving pain in the general population [41]. Few studies of exercise, physical therapy, yoga, or acupuncture in patients with kidney disease have included pain as an outcome but show promising results [42–45]. Given that nonpharmacological interventions are generally safe, further research should test the effectiveness, feasibility, and acceptability of them for patients with kidney disease.

PHARMACOLOGICAL APPROACHES

Review the available evidence on pharmacokinetic, efficacy, and safety profiles of analgesics in patients with kidney disease is provided in Supplementary Tables 1, http://links.lww.com/CONH/A20 and 2, http://links.lww.com/CONH/A20. Summary of dose recommendations are provided in Tables 1 and 2.

Nonopioid therapy for nociceptive pain

Acetaminophen

Acetaminophen, a common over-the-counter analgesic, and can be tried as scheduled doses for mild to moderate pain, although a Cochrane review found that efficacy in the general population may be limited [51]. It requires no dose adjustment and is generally safe in kidney disease, although may rarely cause analgesic nephropathy with long-term use [52].

NSAIDs

Potential risks of NSAIDs include gastrointestinal, cardiovascular, and renal adverse events [53]. NSAIDs inhibit prostaglandin synthesis by interfering with the cyclo-oxygenase pathway, which may increase risk of acute kidney injury, sodium retention, hypertension, hyperkalemia, and heart failure. They may also increase cardiovascular events via vasoconstriction and platelet aggregation [54]. Gastrointestinal and bleeding risks are lower with COX-2 selective agents such as celecoxib [55,56]. Recent epidemiological evidence suggests association of chronic NSAID use with increased risk of CKD progression and hospitalization in patients with CKD, albeit less than that with opioid use [12▪▪]. Similarly, in ESKD, NSAID use has been associated with increased mortality, but these findings are confounded by limitations of observational data [57].

Most of these adverse effects are rare, related to cumulative dose and likely modified by an individual's underlying risk factors, such as comorbidities and concomitant medications. Thus, short-term, cautious use of NSAIDs with consideration of individual risk factors, careful side effect monitoring, and risk/benefit discussion may be appropriate [58]. We agree with recommendations outlined by in a recent review that suggests short-acting NSAIDs could be used short-term (≤5 days) in patients with CKD Stages 1–3; judiciously in patients with CKD Stage 4; and avoided in CKD 5 [59▪▪]. A similar case can be made for cautious use of NSAIDs in ESKD patients, in whom gastrointestinal toxicity and loss of residual renal function are the most concerning side effects. In anuric ESKD patients, there is no effect on glomerular blood flow or tubular function, thus NSAID-mediated electrolyte disturbances, volume retention, and hypertension are of less concern [59▪▪].

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Table 1. Recommended nonopioid medications in patients with kidney disease

Medication	Metabolism and PK comments	Dosing in CKD	Dosing in ESKD	Comments
Medications for nociceptive pain				
Acetaminophen	Hepatic, excreted in the urine primarily as nontoxic metabolites High oral bioavailability 85–98% Median onset 11 min and median duration of action ~4 h after 1000 mg oral dose [46]	Cl_{Cr} 10–50 ml/min: 650 mg q 6 h prn Max daily dose 4000 mg	Cl_{Cr} < 10 ml/min or dialysis: 650 mg q 8 h prn Max daily dose 4000 mg [47]	Use scheduled doses instead of as needed for continuous pain control Use with caution and Lower max daily dose (2000 mg) if liver disease or daily alcohol
NSAIDs, preferably COX-2 selective agents such as celecoxib		Reduce dose and increase dosing interval, use for short-term (≤5 days only) Contraindicated in CKD stage 5	No dose adjustment, use for short term only	Monitor for volume retention, cardiotoxicity, renal, and gastrointestinal toxicity
Topical analgesics (NSAIDs, lidocaine, capsaicin)	Systemic exposure with topical NSAIDs is ~5% than with oral, but increases with higher dose applied to larger surface area [48]			Avoid high-dose topical NSAID use over large surface area
Medications for neuropathic pain				
Pregabalin	Negligible, 90% excreted renally as unchanged drug High oral bioavailability ≥90% Onset of pain relief ~1 week	Max daily dose: Cl_{Cr} 30–60 ml/min: 300 mg daily (2–3 divided doses) Cl_{Cr} 15–30 ml/min: 150 mg daily (1–2 divided doses) Cl_{Cr} < 15 ml/min: 75 mg daily (single dose)	Start at 25 mg once daily, maximum dose 75 mg once daily Well dialyzed, dose post-HD	Start at low dose and uptitrate every 1–2 weeks, monitor for altered mental status and falls
Gabapentin	Not metabolized, excreted renally as unchanged drug Bioavailability is dose dependent: is upto 80% with 300 mg/day but decreases as dose increases to <50% above 1200 mg/day	Max daily dose: Cl_{Cr} 50–79 ml/min: 1800 mg daily (3 divided doses) Cl_{Cr} 30–49 ml/min: 900 mg/day (2–3 divided doses) Cl_{Cr} 15–29 ml/min: 600 mg/day (1–2 divided doses) Cl_{Cr} < 15 ml/min: 300 mg/day (single dose)	Maximum dose 300 mg once daily Well dialyzed, dose post-HD	Start at low dose and uptitrate every 1–2 weeks, monitor for altered mental status and falls
Duloxetine	Extensively metabolized in the liver via CYP1A2 and 2D6 to inactive metabolites, Oral bioavailability 30–80%, >90% protein bound Excretion: renal 70%, fecal 20%	Start with 20 mg daily Max daily dose: 60 mg Cl_{Cr} 30–80 ml/min: no dose adjustment necessary Cl_{Cr} < 30 ml/min: avoid use	Avoid use (limited data)	Monitor for hyponatremia, can rarely cause serotonin syndrome
Venlafaxine	Hepatically metabolized via CYP2D6 to active metabolite, O-desmethylvenlafaxine. Bioavailability is ~13% for immediate release and 45% for extended release, primarily excreted renally	Extended release: start at 37.5 mg once daily Max daily dose: Cl_{Cr} 30–89 ml/min: 150 mg daily Cl_{Cr} < 30 ml/min: 112.5 mg daily	Extended release: Start at 37.5 mg once daily Max daily dose: 112.5 mg daily Poorly dialyzed	Monitor for hyponatremia, can rarely cause serotonin syndrome
Desvenlafaxine (active metabolite of venlafaxine)	Hepatically metabolized Oral bioavailability approximately 80% Excreted renally approximately 45% as unchanged drug and 24% as metabolites	Max daily dose: Cl_{Cr} 30–50 ml/min: 50 mg once daily Cl_{Cr} < 30 ml/min: 25 mg once daily or 50 mg every other day	Max daily dose: 25 mg once daily or 50 mg every other day Poorly dialyzed	Monitor for hyponatremia, can rarely cause serotonin syndrome
Amitriptyline	Hepatically metabolized to nortriptyline (active metabolite) Oral doses are completely and rapidly absorbed, > 90% protein bound Excreted renally as metabolites, 18% as unchanged drug	Start at 10 mg once daily at bedtime, No dose adjustment recommended Maximum dose 150 mg daily	Start at 10 mg once daily at bedtime, No dose adjustment recommended Maximum dose 150 mg daily Poorly dialyzed	Limited evidence in CKD The Beers Criteria recommends avoidance in older adults (strong anticholinergic properties, sedation, orthostatic hypotension, urinary retention)

CKD, chronic kidney disease; ESKD, end-stage kidney disease; PK, pharmacokinetics.

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Table 2. Recommended opioid medications in patients with kidney disease

Medication	Metabolism and PK comments	Dosing in CKD	Dosing in ESKD	Comments
Oxycodone (short-acting)	Hepatically metabolized via mainly CYP3A4 to noroxycodone (weakly active) and some by CYP2D6 to oxymorphone (strongly active), High oral bioavailability of 50–87%, $t_{1/2}$ prolonged to ~7 h in ESKD [49]	Start at 2.5–5 mg every 12 h, recommend prolonged dosing interval in severe renal impairment	Start at 2.5–5 mg every 12 h, recommend prolonged dosing interval in ESKD Poorly dialyzed	Caution should be used with long acting formulations and when used concurrently with medications that affect CYP3A4 or CYP2D6 metabolism [50]
Hydromorphone	Hepatically metabolized, oral bioavailability is low to moderate	Start at 2.5–5 mg every 6–8 h	Start at 2.5–5 mg every 6–8 h, well dialyzed but no supplemental dose required post-HD	Use caution with high doses
Fentanyl (transdermal)	Hepatically metabolized, 10–20% excreted renally, low oral bioavailability	Dose based on equivalent dose of patient's oral narcotics, wean oral opioids after 1–2 days	Dose based on equivalent dose of patient's oral narcotics, wean oral opioids after 1–2 days Poorly dialyzed	Do not start in opioid naïve patient
Methadone	Hepatically metabolized to inactive metabolites, >80% oral bioavailability	Start 1–2 mg once or twice a day	Start 1–2 mg once or twice a day Poorly dialyzed	Do not start in opioid naïve patient. Obtain a baseline EKG and a follow-up EKG 2–4 weeks after starting to monitor for prolonged QT interval. Monitor and correct electrolyte abnormalities
Buprenorphine	Hepatically metabolized to B3G (inactive) and norbuprenorphine (active but does not cross blood brain barrier), low oral bioavailability but effective as sublingual or transdermal formulation, excreted mostly fecally (bile)	See Table 3	See Table 3 Poorly dialyzed	Do not start in opioid naïve patient. Lesser risk of overdose and respiratory and CNS depression as compared with other opioids

CKD, chronic kidney disease; CNS, central nervous system; EKG, electrocardiogram; ESKD, end-stage kidney disease; HD, hemodialysis; PK, pharmacokinetics.
*EKF was a typo.

Topical agents

Topical agents (e.g., topical NSAIDs, lidocaine patch, high-dose capsaicin patch) may provide localized pain relief [60–63]. Topical NSAIDs are efficacious in both acute and chronic pain, have minimal systemic exposure (5% of oral dose), and are safe in patients with kidney disease when used over limited surface area [48].

Skeletal muscle relaxants

Skeletal muscle relaxants such as baclofen, methocarbamol, and tizanidine, do not have a role in chronic pain conditions and are only recommended for short-term use in some acute pain conditions such as spasticity and spasms [64]. All skeletal muscle relaxants may cause significant sedation, muscle weakness and dizziness and should be avoided in advanced CKD and ESKD. For example baclofen, which is renally cleared, can cause severe neurotoxicity and muscle paralysis in advanced CKD and ESKD, and should be avoided.

Cannabis

While cannabis may improve some painful conditions, it has not been tested in persons with kidney disease, and its role and safety in this population is unclear [65–67].

Nonopioid therapy for neuropathic pain

In the general population, evidence supports the use of gabapentinoids (pregabalin and gabapentin), tricyclic antidepressants (TCA), and serotonin–norepinephrine reuptake inhibitors (SNRI) as first-

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line treatments for neuropathic pain [62]. The clearance of both gabapentin and pregabalin decreases and half-life ($t_{1/2}$) increases proportionately with worsening renal function, requiring renal dose adjustment (Table 1 and Supplementary Table 1, http://links.lww.com/CONH/A20). Both medications should be dosed hemodialysis (HD). These agents have been associated with increased risk of altered mental status, falls, and fractures in ESKD patients [68], and concomitant use with opioids is associated with increased hospitalization and mortality [69▪▪]. They have been associated with potential misuse and addiction and should be used with caution and close monitoring [70].

Little evidence exists regarding use of TCAs and SNRIs for patients with kidney disease (Table 1 and Supplementary Table 1, http://links.lww.com/CONH/A20). TCAs are associated with dose-related anticholinergic and antihistaminic side effects; SNRIs are generally better tolerated. Both of these classes may cause or exacerbate syndrome of inappropriate antidiuretic hormone secretion. The use of the SNRI duloxetine in patients with Cl_{Cr} less than 30 ml/min or on dialysis is not recommended by current Food and Drug Administration guidance; however, guidelines from the European Union and Canada suggest its use in severe CKD and ESKD with lower starting doses and cautious monitoring [71].

Opioid therapy for pain

Although the main indication for opioids is for nociceptive pain, they have also been shown to be effective in improving neuropathic pain, especially diabetic neuropathy, either alone or as adjuvants to gabapentinoids [72,73]. The decision to initiate LTOT should be made through a careful risk–benefit evaluation and shared decision-making. Opioids should be avoided if other options are effective, and should be used sparingly at the minimum effective doses. We recommend a similar approach to the Centers for Disease Control and Prevention (CDC) guidelines, including maximizing nonpharmacologic therapy and nonopioid analgesia, establishing clear therapeutic goals, initiating treatment with immediate-release opioids rather than long-acting, starting with low doses, and uptitrating gradually with close monitoring of side effects [8].

The benefits of treatment may include improved quality of life and better functioning. This should be balanced with the increased risks of opioids in kidney disease such as altered mental status, falls, fractures, hospitalizations, and mortality, which occurs in a dose-dependent manner and can be seen even at lower doses [9–11,12▪▪]. These risks may be more pronounced in the older adults, and those with concomitant sedating medications such as gabapentinoids and benzodiazepines [69▪▪,74]. LTOT can also have additional adverse effects such as hyperalgesia, sedation, overdose, and progression to opioid use disorder (OUD). An evidence-based tool to help evaluate risk of opioid misuse before initiating treatment is the Revised Opioid Risk Tool, which creates a risk category based on personal and family history of substance misuse, age, and psychological disease [75]. If OUD is suspected, we recommend referral to an addiction treatment provider.

Monitoring of long-term opioid therapy

A cornerstone of LTOT is ensuring proper monitoring. CDC guidelines recommend checking statewide prescription drug monitoring programs to identify controlled medications prescribed by other providers [8]. In addition, periodic drug screens are important to ensure prescribed medication use and evaluate for illicit substance use. Urine drug testing is the preferred method of screening due to high sensitivity and specificity [76]. However, this may be challenging in patients with ESKD who produce little or no urine. Oral buccal swabs or saliva testing offer a reasonable alternative but may have logistic issues with specimen collection as these patients frequently have xerostomia.

Specific opioid medications

The pharmacokinetic evidence of commonly used opioid medications in patients with kidney disease is summarized in Supplementary Table 2, http://links.lww.com/CONH/A20. Opioids that are safer to use in kidney disease include oxycodone, hydromorphone, fentanyl, methadone, and buprenorphine. Oxycodone is one of the most commonly prescribed opioids for kidney disease patients in the United States [9]. It has predominantly hepatic elimination and is poorly dialyzed (Table 2). Caution should be used with long-acting formulations and when prescribed concurrently with medications that affect CYP3A4 or CYP2D6 metabolism [50]. Similarly, hydromorphone has a reasonable safety profile in kidney disease at lower doses and is dialyzed by HD, but supplemental doses are usually not needed post-HD. Fentanyl appears to be safe in kidney disease, although evidence is limited. On the other hand, morphine and hydrocodone have high risk of accumulation and systemic exposure, thus are contraindicated in patients with CKD or ESKD.

Tramadol is an atypical, centrally acting opioid with dual action as a weak mu-opioid receptor agonist and SNRI. Tramadol and its active M1 metabolite are renally excreted. Its metabolism can vary unpredictably depending on an individual's cytochrome P450 genetic profile [77]. Tramadol also has multiple drug interactions that may result in serotonin

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syndrome or seizures. Thus, we recommend it be used with extreme caution and at reduced doses, but preferably avoided.

SPECIAL CONSIDERATION: BUPRENORPHINE AND METHADONE

Less commonly used opioid medications for pain are methadone (full agonist at mu-opioid receptor) and buprenorphine (partial agonist). They are more commonly used for the treatment of OUD where they reduce cravings, abate withdrawal symptoms, and prevent overdose. However, there are formulations for methadone and buprenorphine that can be used to treat chronic pain, as discussed below.

Methadone

Methadone functions as an N-methyl-D-aspartate (NMDA)-receptor antagonist-receptor antagonist, giving it additional efficacy for neuropathic pain. The analgesic half-life is 6–8 h, requiring multiple daily doses. Methadone and its metabolites do not accumulate in CKD or ESKD, thus no dose adjustment is needed and it is not dialyzed out by HD (Table 2 and Supplementary Table 2, http://links.lww.com/CONH/A20). Because it can prolong the QTc interval, the electrolyte abnormalities such as hypo/hyperkalemia or hypo/hypermagnesemia that are frequently present in kidney disease may exacerbate its arrhythmia potential.

For patients without OUD, methadone as an analgesic can be prescribed by any provider with an active Drug Enforcement Administration license, does not require patients to attend a clinic with an Opioid Treatment Program license, and can be legally filled at commercial pharmacies. In contrast, for patients with OUD, methadone is highly regulated, must be dispensed from a federally licensed Opioid Treatment Program, is dosed once a day, and initially requires patients to travel daily to receive observed dosing.

Buprenorphine

Buprenorphine is an efficacious treatment of pain in the general population [78]. Due to its partial agonism, it has a 'ceiling effect' which reduces the risks of respiratory sedation and overdose. It is metabolized in the bile duct, requires no dose adjustment in CKD, and is not dialyzed (Table 2). Given its better safety profile compared with full agonist opioids and steady state in CKD/ESKD, it may provide a therapeutic advantage and a safer alternative for pain management in patients with kidney disease who have a physiologic dependence to opioids [79▪,80,81].

Buprenorphine prescribing for chronic pain remains low due to barriers depicted in Fig. 2; potential solutions are offered. Barriers include provider

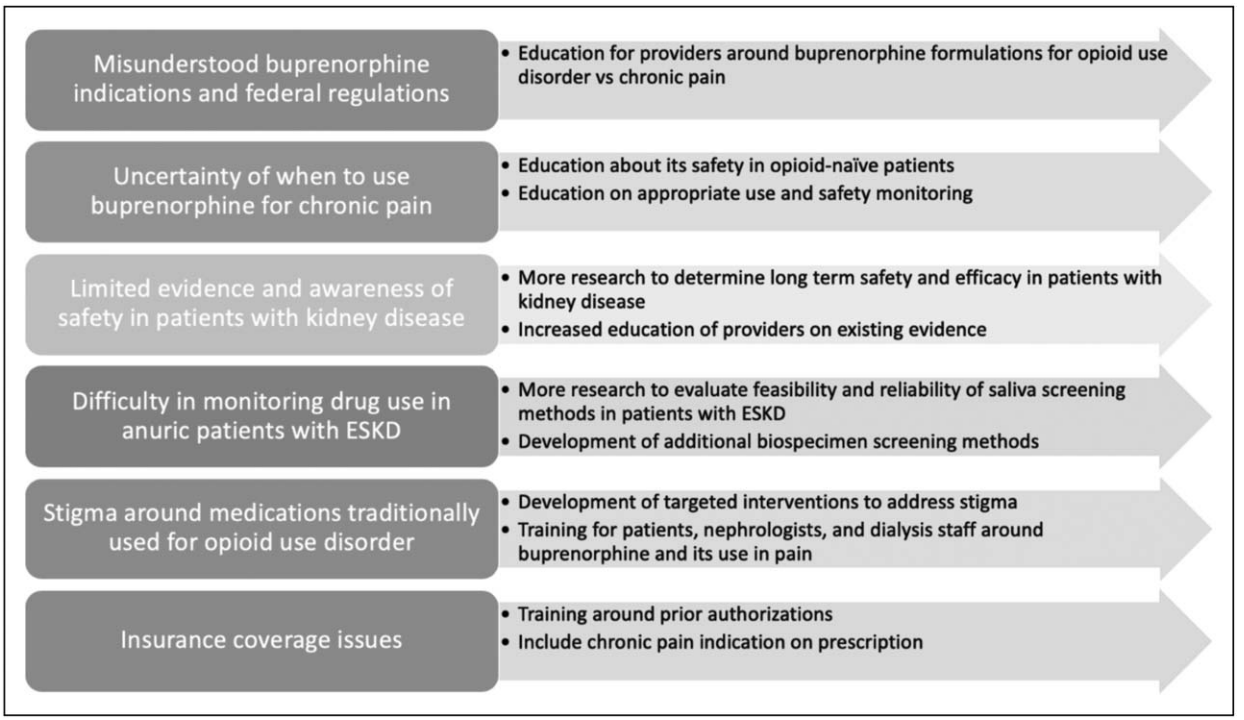


FIGURE 2. Barriers and potential solutions for increasing use of buprenorphine for chronic pain in patients with kidney disease.

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Table 3. Comparison of commonly prescribed buprenorphine products

Trade name	Generic name	Route	FDA indication	X-waiver required?	Starting dose
Butrans[a]	Buprenorphine	Transdermal patch	Chronic pain	No	5 μg/h once weekly
Belbuca[b]	Buprenorphine	Buccal tablet	Chronic pain	No	75 μg once daily
Suboxone[c]	Buprenorphine-naloxone[d]	Sublingual film or tablet	Opioid use disorder	Yes[e]	2 mg–0.5 mg
Subutex[c]	Buprenorphine	Sublingual tablet	Opioid use disorder in patients who cannot tolerate naloxone	Yes	2 mg

[a]Purdue Pharma L.P., Stamford, CT, USA.
[b]BioDelivery Sciences International, Inc, Raleigh, NC, USA.
[c]Reckitt Benckiser Pharmaceuticals Incorporation, Richmond, VA, USA.
[d]When taken sublingually, the effect of buprenorphine predominates; if injected however, the effect of naloxone predominates.
[e]No X-waiver needed if used off-label for treatment of pain [83].

confusion about available buprenorphine formulations, their indications, and federal regulations for X-waiver (Table 3) [82]. Notably, although sublingual buprenorphine-naloxone can be prescribed off-label as an analgesic, several logistical hurdles make that difficult, including requiring documentation of indication [83]. Insurance authorization may also be required for transdermal or buccal formulations of buprenorphine [84,85]. Lastly, given its traditional use as a treatment for OUD, buprenorphine may be stigmatized by patients and providers, similar to methadone [86]. The ongoing HOPE Consortium trial will provide valuable insight into the acceptability, tolerability, and efficacy of buprenorphine in patients on dialysis.

CONCLUSION

Pain is highly prevalent and challenging to treat among patients with kidney disease. Pain management requires careful assessment, continuous monitoring, and shared decision-making of risks and benefits of different pharmacological and non-pharmacological therapeutic options with patients. Long-term therapy with full agonist opioid treatment is associated with significantly higher adverse effects in this population, thus more research into safer alternatives such as buprenorphine is warranted.

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Conflicts of interest

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- ■■ of outstanding interest

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Infection in Advanced Chronic Kidney Disease and Subsequent Adverse Outcomes after Dialysis Initiation: A Nationwide Cohort Study

Chih-Hsiang Chang[1,2], Pei-Chun Fan[1,2], George Kuo[1], Yu-Sheng Lin[3], Tsung-Yu Tsai[1,2], Su-Wei Chang[4,5], Ya-Chung Tian[1,2] & Cheng-Chia Lee[1,2*]

It remains unclear whether infection events before entering end stage renal disease (ESRD) have a long-term negative impact on patients with advanced chronic kidney disease (CKD) who survive to permanent dialysis. We enrolled 62,872 patients with advanced CKD who transitioned to maintenance dialysis between January 1, 2004 and December 31, 2013. We used multivariable Cox as well as Fine and Gray models to determine the association of pre-dialysis infection exposure with all-cause mortality after starting dialysis. Compared with no infection during advanced CKD, the presence of infection exposure during that period was independently associated with a higher risk of all-cause mortality in the first year of dialysis (hazard ratio [HR] 1.34, 95% confidence interval [CI] 1.27–1.42) and also during the entire follow-up period (HR 1.19, 95% CI 1.16–1.22). The increased risks of all-cause mortality increased incrementally with higher annual number of infections during advanced CKD. Similar results were found for all other adverse outcomes, e.g. post-ESRD infection-related hospitalization and major cardiac and cerebrovascular events. In conclusion, infection events during advanced CKD was associated with increased risks of adverse outcomes after dialysis has been started. Timely interventions in such a vulnerable group may help attenuate these risks.

Advanced chronic kidney disease (CKD) is associated with a marked increase in the risk of all-cause mortality and morbidity, frequently necessitating hospitalization[1,2]. Other than cardiovascular causes, approximately 50% of mortality in patients with CKD can be attributed to non-cardiovascular causes; infection is now increasingly recognized as one of these causes, particularly as some such infection events may be preventable[2–5]. Infection is also a common cause of hospitalization in patients with CKD and studies have shown a strong graded association between the incidence of infection and reduced kidney function[6–9].

Infection events in patients receiving dialysis not only contributes to a higher risk of death but is also associated with substantial morbidity. For example, research has reported that 15.3% of patients with infection-related hospitalization (IRH) required an intensive care unit stay while 28.6% required prolonged hospitalization[10] and 21%–34% were readmitted within 30 days[11–13], and even that IRH increased the risk of subsequent cardiovascular events[14], cumulatively constituting a substantial burden on the health care system. Hence, identifying dialysis patients at risk of IRH is of paramount importance.

Few studies have addressed the consequences of an infection event in non-dialysis patients with advanced CKD. A recent analysis of the Canadian prospective cohort (CanPREDDICT) comprising 2,370 patients with advanced CKD showed that an infection episode was independently associated with an increased risk of

[1]Kidney research center, Department of Nephrology, Chang Gung Memorial Hospital, Chang Gung University, College of Medicine, Taoyuan, Taiwan. [2]Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan. [3]Department of Cardiology, Chang Gung Memorial Hospital, Chiayi branch, Chiayi, Taiwan. [4]Clinical Informatics and Medical Statistics Research Center, Chang Gung University, Taoyuan, Taiwan. [5]Division of Allergy, Asthma, and Rheumatology, Department of Pediatrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan. *email: chia7181@gmail.com

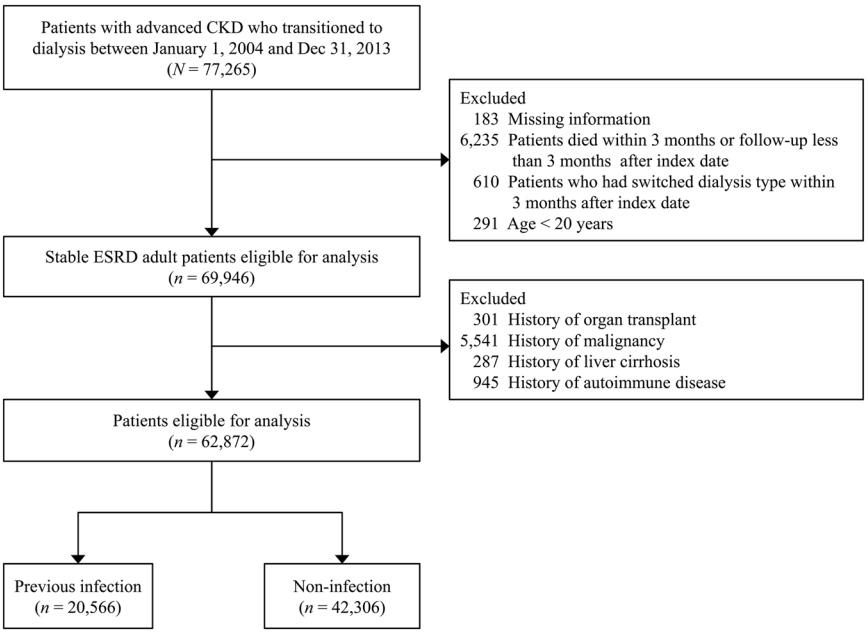


Figure 1. Flowchart of patient inclusion.

end-stage renal disease (ESRD) or other adverse outcome before dialysis, such as cardiovascular events and death[15]. However, it remains unclear whether infection events before entering ESRD have a long-term negative impact on patients with advanced CKD who survive to permanent dialysis. To address this knowledge gap, we investigated the association of infection exposure during advanced CKD and adverse outcomes, e.g. all-cause mortality, recurrent IRH, major cardiac and cerebrovascular events (MACCE), after dialysis initiation by using a nationwide representative population with advanced CKD transitioning to ESRD. We hypothesized that infection exposure in advanced CKD might not only lead to a higher risk of adverse outcomes before ESRD but also have a persistently negative impact after transitioning to permanent dialysis.

Results

Study population characteristics. The study population selection process is shown in Fig. 1. We identified 77,265 patients with advanced CKD who started permanent dialysis (either peritoneal dialysis or hemodialysis) between January 1, 2004 and December 31, 2013. We excluded patients who switched dialysis type within 3 months of starting dialysis (n = 610) in order to investigate the impact of different dialysis modalities. Patients were also excluded if they had a history of organ transplant, malignancy, liver cirrhosis, or autoimmune disease because they represented a substantially different population with varying susceptibility to infection than our target population. Ultimately, a study population of 62,872 patients with advanced CKD who entered permanent dialysis were eligible for analysis.

Table 1 shows the baseline characteristics of the study population, stratified by infection exposure status during pre-dialysis advanced CKD. The mean age was 63.1 ± 13.7 years, 51.6% of patients were male, and 58.8% of patients had diabetes. Of the patients, 20,566 (32.7%) had at least one infection episode whereas 42,306 (67.3%) had no infection. Compared with the non-infection group, the infection group was older, was more likely to be female, and had a higher prevalence of diabetes, ischemic heart disease, history of heart failure and myocardial infarction, prior cerebrovascular disease, hypoalbuminemia, and dementia at baseline. The follow-up duration was shorter in the patients with infection than in those without infection (3.2 vs. 3.8 years, $P < 0.001$). Other detailed baseline characteristics including some of comorbidities and 14 medications between two groups are available in Supplementary Table S1.

Figure 2 exhibited the nature of the infectious events during advanced CKD. Of the 20,566 patients with prior infection, the most frequent infections were urinary tract infection (41.9%) and pulmonary infection (41.5%), followed by septicemia (23.5%), central venous catheter-related infection (12.4%) and soft tissue infections (11.9%). The average time and standard deviation in years from an infection event during advanced CKD to ESRD, post-ESRD IRH, post-ESRD MACCE, and all-cause mortality were 0.4 ± 0.8, 1.7 ± 1.8, 2.5 ± 2.1, and 3.0 ± 2.3, respectively (data not shown).

Association of infection exposure during advanced CKD with post-ESRD all-cause mortality and IRH. There were 25,475 (40.5%) deaths during a mean follow-up of 3.6 years (standard deviation: 2.4 years) following dialysis initiation. As shown in Table 2, the infection and non-infection groups had 9,556 (46.5%) deaths and 15,919 (37.6%) deaths, respectively. After the covariates were controlled for, the presence of infection exposure during advanced CKD was independently associated with a higher risk of all-cause mortality (hazard ratio [HR] 1.19, 95% CI 1.16–1.22) compared with the absence of any infection episodes. This increased risk was higher in the first year after starting dialysis (HR 1.34, 95% CI 1.27–1.42) than later during follow-up.

Variable	All (n = 62,872)	Infection (n = 20,566)	Non-infection (n = 42,306)	P value
Demographic				
Age (y)	63.1 ± 13.7	65.6 ± 13.6	61.9 ± 13.6	< 0.001
Female	30,404 (48.4)	11,322 (55.1)	19,082 (45.1)	
No. of nephrologist outpatient visits in the previous year	11.7 ± 9.1	12.1 ± 9.0	11.5 ± 9.1	< 0.001
Modality				< 0.001
Hemodialysis	54,291 (86.4)	18,206 (88.5)	36,085 (85.3)	
Peritoneal dialysis	8,581 (13.6)	2,360 (11.5)	6,221 (14.7)	
Initial dialysis access type for hemodialysis				< 0.001
Fistula	34,651 (63.8)	9,428 (51.8)	25,223 (69.9)	
Graft	6,155 (11.3)	2,602 (14.3)	3,553 (9.8)	
Tunneled-catheter	13,485 (24.8)	6,176 (33.9)	7,309 (20.3)	
Comorbidity				
Hypertension	56,987 (90.6)	18,699 (90.9)	38,288 (90.5)	0.090
Diabetes mellitus	36,952 (58.8)	12,489 (60.7)	24,463 (57.8)	< 0.001
Ischemic heart disease	16,908 (26.9)	5,964 (29.0)	10,944 (25.9)	< 0.001
Dementia	1,924 (3.1)	901 (4.4)	1,023 (2.4)	< 0.001
History of heart failure	15,675 (24.9)	6,209 (30.2)	9,466 (22.4)	< 0.001
Previous ischemic stroke	10,315 (16.4)	4,056 (19.7)	6,259 (14.8)	< 0.001
Old myocardial infarction	4,189 (6.7)	1,658 (8.1)	2,531 (6.0)	< 0.001
Hypoalbuminemia	2,794 (4.4)	1,754 (8.5)	1,040 (2.5)	< 0.001
Follow-up duration (y)	3.6 ± 2.6	3.2 ± 2.4	3.8 ± 2.6	< 0.001

Table 1. Selected baseline characteristics of patients stratified by infection exposure status during pre-dialysis advanced CKD. Data are presented as frequency (percentage) or mean ± standard deviation.

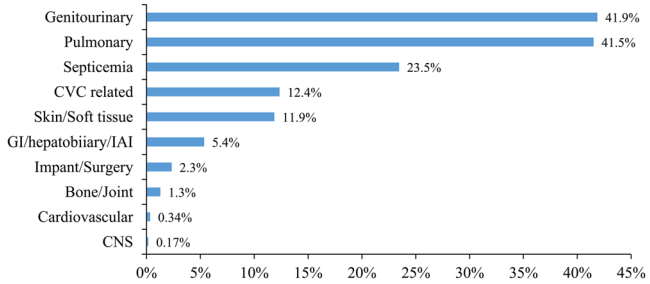


Figure 2. Types of infection during advanced CKD. Abbreviations: CVC, central venous catheter; GI, gastrointestinal; IAI, intra-abdominal infection; CNS, central nervous system.

After starting dialysis, 34,711 (55.2%) patients experienced at least one IRH during the entire follow-up, with a crude incidence rate of 22.9 events per 100 person-years. Among the patients who experienced IRH, 17,342 (50%) of them had it during their first year of dialysis. The infection group had significantly higher cumulative incidences (subdistribution HR [SHR] 1.28, 95% CI 1.25–1.31, Fig. 3a) of post-ESRD IRH than the non-infection group did. Similarly, the increased risk of post-ESRD IRH was higher in the first year of dialysis therapy (SHR 1.44, 95% CI 1.39–1.48) than later during follow-up. Notably, the risk of infection-related death was also significantly higher in the infection group than in the non-infection group (HR 1.26, 95% CI 1.21–1.31).

Furthermore, to test the robustness of our results, we categorized the study population with at least one infection episode (infection group, N = 20,566) into four quartiles based on annual number of infections during pre-dialysis advanced CKD. As shown in Table 3, the rate of all-cause mortality increased with the frequency of pre-ESRD infection exposure (P for trend < 0.001), regardless of whether the follow-up was restricted to the first year or the entire follow-up period. The annual number of previous infections during advanced CKD was also incrementally associated with the cumulative incidence of post-ESRD IRH, with significantly higher post-ESRD IRH risks correlated with higher numbers of previous infection events (P for trend < 0.001, Table 3 and Supplementary Fig. S1a).

In subgroup analyses, the pattern of associations between pre-ESRD infection exposure and post-ESRD IRH was generally consistent across selected subgroups. However, age and dialysis modalities significantly modified this association: the effect of pre-ESRD infection exposure on the risk of post-ESRD IRH was significantly greater among the older patients and those with hemodialysis, particularly among patients with tunneled-catheter as their initial dialysis access (Fig. 4a).

Outcome	No. of events (%)			Infection vs. non-infection[b]			
	All	Infection	Non-infection	Univariate		Multivariable[c]	
	(n = 62,872)	(n = 20,566)	(n = 42,306)	HR (95% CI)	P value	HR (95% CI)	P value
1-year follow-up							
All-cause mortality	5,637 (9.0)	2,681 (13.0)	2,956 (7.0)	1.94 (1.84, 2.04)	<0.001	1.34 (1.27, 1.42)	<0.001
IRH	17,342 (27.6)	7,645 (37.2)	9,697 (22.9)	1.80 (1.75, 1.86)	<0.001	1.44 (1.39, 1.48)	<0.001
Infection death	3,016 (4.8)	1,629 (7.9)	1,387 (3.3)	2.48 (2.31, 2.67)	<0.001	1.58 (1.46, 1.70)	<0.001
MACCE[a]	6,444 (10.2)	2,680 (13.0)	3,764 (8.9)	1.50 (1.43, 1.57)	<0.001	1.17 (1.11, 1.23)	<0.001
At the end of follow-up							
All-cause mortality	25,475 (40.5)	9,556 (46.5)	15,919 (37.6)	1.49 (1.46, 1.53)	<0.001	1.19 (1.16, 1.22)	<0.001
IRH	34,711 (55.2)	12,795 (62.2)	21,916 (51.8)	1.48 (1.44, 1.51)	<0.001	1.28 (1.25, 1.31)	<0.001
Infection death	11,766 (18.7)	4,834 (23.5)	6,932 (16.4)	1.60 (1.54, 1.66)	<0.001	1.26 (1.21, 1.31)	<0.001
MACCE[a]	20,472 (32.6)	7,245 (35.2)	13,227 (31.3)	1.23 (1.19, 1.26)	<0.001	1.07 (1.03, 1.10)	<0.001

Table 2. Follow-up outcomes of primary interest in patients with and without infection history during pre-dialysis advanced CKD. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; IRH, infection-related hospitalization; MACCE, major adverse cardiac and cerebrovascular event. [a]Any patient with acute myocardial infarction, acute ischemic stroke, intracerebral hemorrhage, heart failure, or cardiovascular death. [b]Except for all-cause mortality, the outcomes were estimated using a subdistribution hazard model that considered all-cause mortality a competing risk. [c]Adjusted for the variables listed in Supplementary Table S1 except primary renal disease; the follow-up duration was replaced with the index year.

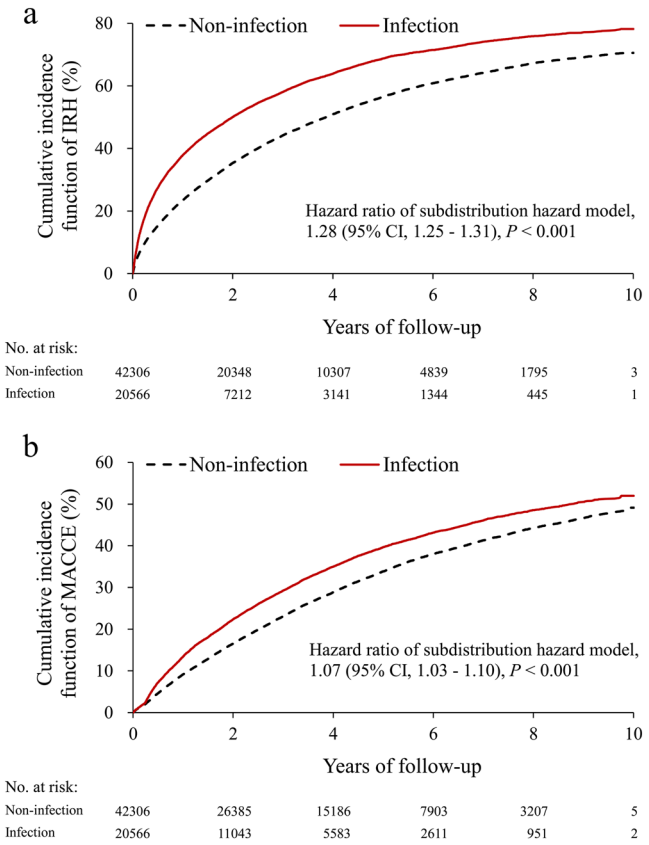


Figure 3. Cumulative incidence of IRH (**a**) and MACCE (**b**) in patients with and without infection during pre-dialysis advanced CKD. Abbreviations: CKD, chronic kidney disease; IRH, infection-related hospitalization; MACCE, major adverse cardiac and cerebrovascular event.

Association of infection exposure during advanced CKD with post-ESRD MACCE. During follow-up, 20,472 (32.6%) patients experienced MACCE, including 13,072 cardiovascular deaths. The presence of pre-ESRD infection exposure was associated with a slightly higher risk of MACCE compared with the absence of any infection episodes (SHR 1.07; 95% CI 1.03–1.10, Table 2 and Fig. 3b). However, as the number of previous infections during advanced CKD increased, there was still a stepwise increase in the incidence of MACCE during

Outcome	No. of events (%), categorized by annual number of previous infections				P trend	P trend[c]
	Group 1 (n = 5,142)	Group 2 (n = 5,154)	Group 3 (n = 5,122)	Group 4 (n = 5,148)		
1-year follow-up						
All-cause mortality	396 (7.7)	554 (10.7)	778 (15.2)	953 (18.5)	<0.001	<0.001
IRH[b]	1,374 (26.7)	1,793 (34.8)	2,106 (41.1)	2,372 (46.1)	<0.001	<0.001
Infection death[b]	222 (4.3)	305 (5.9)	483 (9.4)	619 (12.0)	<0.001	<0.001
MACCE[a,b]	435 (8.5)	635 (12.3)	752 (14.7)	858 (16.7)	<0.001	<0.001
At the end of follow-up						
All-cause mortality	1,930 (37.5)	2,306 (44.7)	2,514 (49.1)	2,806 (54.5)	<0.001	<0.001
IRH[b]	2,789 (54.2)	3,100 (60.1)	3,380 (66.0)	3,526 (68.5)	<0.001	<0.001
Infection death[b]	950 (18.5)	1,088 (21.1)	1,308 (25.5)	1,488 (28.9)	<0.001	<0.001
MACCE[a,b]	1,465 (28.5)	1,857 (36.0)	1,864 (36.4)	2,059 (40.0)	<0.001	0.003

Table 3. Follow-up outcomes of primary interest stratified by annual number of infections during pre-dialysis advanced CKD. Abbreviations: CKD, chronic kidney disease; IRH, infection-related hospitalization; MACCE, major adverse cardiac and cerebrovascular event. The median number of previous infection events was 0.7, 1.8, 4.1, and 12.2 in groups 1, 2, 3, and 4, respectively. [a]Any patient with acute myocardial infarction, acute ischemic stroke, intracerebral hemorrhage, heart failure, or cardiovascular death. [b]Except for all-cause mortality, the outcomes were estimated using a subdistribution hazard model that considered all-cause mortality a competing risk. [c]Adjusted for the variables listed in Supplementary Table S1 except primary renal disease; the follow-up duration was replaced with the index year.

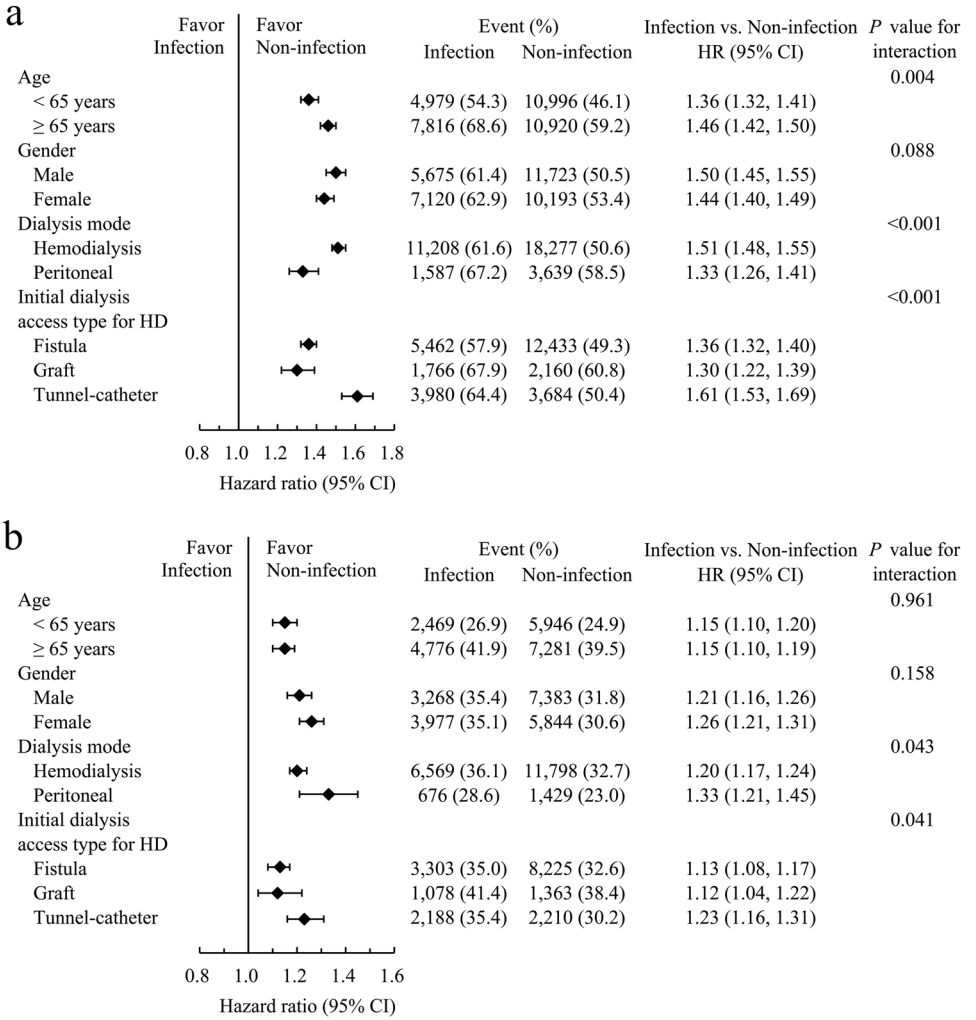


Figure 4. Pre-specified subgroup analysis comparing patients with and without infection during pre-dialysis advanced CKD with IRH (**a**) and MACCE (**b**). Abbreviations: CKD, chronic kidney disease; IRH, infection-related hospitalization; MACCE, major adverse cardiac and cerebrovascular event.

both the first year (P for trend < 0.001, Table 3) and the entire follow-up period (P for trend = 0.003, Table 3 and Supplementary Fig. S1b). In subgroup analyses, the association between increased risk of MACCE and infection exposure remained consistent across different age and sex groups (Fig. 4b).

Infections in advanced CKD start a vicious cycle, leading a higher risk of post-ESRD IRH. As shown in Table 4, multivariate logistic regression analysis, after adjustment for related variables, revealed that the presence of pre-ESRD infection exposure was independently associated with a higher risk of post-ESRD IRH in both patients on hemodialysis (SHR 1.35, 95% CI 1.32–1.38) and peritoneal dialysis (SHR 1.30, 95% CI 1.23–1.38). Other factors associated with an at least 20% increased risk of post-ESRD IRH for both dialysis types included older age, hypoalbuminemia, diabetes, chronic obstructive pulmonary disease, prior cerebrovascular disease, and dementia. Notably, a higher number of cumulative nephrology visits during advanced CKD was independently associated with a lower risk of IRH for both dialysis types after starting dialysis.

Sensitivity analysis. The sensitivity analysis yielded similar results to that of the primary analysis by excluding patients with AKI during advanced CKD period that potentially had rapid decline of renal function (Supplementary Table S2).

Discussion

This national population-based cohort study of 62,872 patients with advanced CKD revealed that approximately one-third of the patients experienced at least one infection event before transitioning to permanent dialysis. As hypothesized, we found that pre-ESRD infection exposure was associated with higher risks of all-cause mortality, IRH, and MACCE after dialysis initiation. These increased risks were higher in the first year but remained significant throughout the entire follow-up period. These results are strengthened by a dose-dependent relationship observed between annual number of pre-ESRD infection episodes and post-ESRD adverse outcomes, suggesting that infections in advanced CKD start a vicious cycle.

Accumulating evidence indicates that infection is a frequent event in patients with non-dialysis advanced CKD and that reduced estimated glomerular filtration rate (eGFR) is associated with a higher risk of subsequent short-term mortality. In a study of 25,675 participants from a single Canadian health region, individuals with eGFRs of less than 30 mL/min/1.73 m^2 were found to have a 3.5-fold higher risk of bloodstream infection and more than 4-fold higher risk of subsequent 30-day mortality compared with those with eGFRs of 60 mL/min/1.73 m^2 or higher[6]. A recent analysis of the Atherosclerosis Risk in Communities cohort also demonstrated that participants with eGFRs of 15–29 mL/min/1.73 m^2 showed an approximately 3.5-fold higher risk of infection compared with those with eGFRs of 90 mL/min/1.73 m^2 or more[9]. Moreover, recurrent IRH was more frequent among participants with lower eGFRs (8.9%, 11.5%, 22.5%, and 42.1% in those with eGFRs $\geq$ 90, 60–89, 30–59, and 15–29 mL/min/1.73 m^2, respectively). Little is known about the long-term negative impact of infection events or recurrent infections among advanced CKD patients who survive to permanent dialysis, particularly among Asians, who appear to have higher rates of entering permanent dialysis[16]. Herein, we provide further evidence of an association between infection exposure during advanced CKD and post-ESRD adverse outcomes irrespective of all-cause mortality, IRH, or MACCE.

Our finding regarding the substantial burden of infection in dialysis patients is consistent with the results of a previous analysis of 333,453 incident dialysis patients from the U.S. Renal Data System, which showed a 31% cumulative incidence rate of IRH in the first year and 52.5% at 3 years[17]. Therefore, early identification of patients with a higher risk of IRH would likely minimize the overall health care expenditure on dialysis patients, as each IRH can spiral into a vicious cycle resulting in substantial adverse consequences, including worsening nutritional status[18], readmission[11–13], and cardiovascular event[14]. Similar to previous studies, we found that older age, diabetes, heart failure, chronic obstructive pulmonary disease, and prior cerebrovascular disease are risk factors for IRH in incident dialysis patients irrespective of their initial dialysis modality[2,19,20]. The finding that catheter as initial vascular access was associated with a higher risk of IRH is also consistent with previous observations[2,21]. In addition, our results extend observation of Drew *et al.*[22], showing that dementia can independently contribute to a higher risk of not only death but also IRH. Furthermore, we report the novel finding that after adjustment for relevant confounders, the presence of any infection event during advanced CKD was associated with a 30% higher risk of post-ESRD IRH.

Our findings for the short- and long-term negative impact of infection events during advanced CKD on post-ESRD outcome expand on the emerging theory that pre-ESRD conditions, such as blood pressure control[23], cardiovascular medication nonadherence[24], and abrupt decline in kidney function[25], have a sustained impact on post-ESRD outcome. Our report adds to this literature by elucidating the impact of pre-dialysis infection. The aggravated negative impact of infection exposure we identified in the first year of dialysis therapy also supports the notion that incident dialysis patients experience the highest morbidity and mortality within the first year after starting dialysis[26]. This observation raises the possibility that infection events during advanced CKD directly affects clinical outcomes or that infection events are simply a surrogate marker for the severity of uremia that itself affects clinical outcomes. However, our study showed that the negative impact of infection exposure was not only restricted to the first year of dialysis but remained significant throughout the entire mean 3.6 years of follow-up period, indicating that uremia alone is not sufficient to interpret our whole results. Notably, Fig. 3 shows steeper slope in infection group was observed during the first to second year. Therefore, the negative impact of infection exposure may mainly impact on the early phase after dialysis initiation. Prior studies also demonstrated that rapid loss of kidney function before ESRD had an increased risk of death within the first year of ESRD[25,27]. As infection or other cause related AKI might confound our findings, we repeated our primary analysis excluding patients who had AKI during advanced CKD period and the effect estimates of the infection exposure were similar.

Variable	Patients with hemodialysis		Patients with peritoneal dialysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Infection during pre-dialysis advanced CKD	1.35 (1.32, 1.38)	<0.001	1.30 (1.23, 1.38)	<0.001
Age (per 10 y)	1.29 (1.27, 1.30)	<0.001	1.21 (1.18, 1.24)	<0.001
Female	0.99 (0.97, 1.01)	0.412	1.04 (0.98, 1.09)	0.227
CKD duration (per 1 y)	0.998 (0.995, 1.002)	0.373	0.995 (0.987, 1.003)	0.197
No. of prior nephrologist outpatient visits	0.987 (0.986, 0.989)	<0.001	0.994 (0.991, 0.997)	<0.001
Dialysis access				
Fistula	1 (Reference)	—	—	—
Graft	1.28 (1.24, 1.32)	<0.001	—	—
Tunneled-catheter	1.40 (1.36, 1.44)	<0.001	—	—
Hypoalbuminemia	1.35 (1.28, 1.42)	<0.001	1.27 (1.09, 1.47)	0.002
Polycystic kidney disease	1.05 (0.97, 1.14)	0.251	1.25 (1.03, 1.51)	0.025
Hypertension	0.97 (0.93, 1.01)	0.127	0.94 (0.86, 1.03)	0.185
Diabetes mellitus	1.42 (1.38, 1.46)	<0.001	1.52 (1.43, 1.61)	<0.001
Chronic obstructive pulmonary disease	1.29 (1.24, 1.34)	<0.001	1.22 (1.06, 1.41)	0.007
Peripheral arterial disease	1.18 (1.11, 1.24)	<0.001	0.99 (0.82, 1.19)	0.902
Ischemic heart disease	1.03 (0.99, 1.06)	0.060	1.13 (1.05, 1.22)	0.002
Dementia	1.41 (1.33, 1.49)	<0.001	1.55 (1.24, 1.92)	<0.001
History of heart failure	1.21 (1.17, 1.24)	<0.001	1.14 (1.05, 1.24)	0.001
Previous ischemic stroke	1.26 (1.23, 1.30)	<0.001	1.32 (1.21, 1.45)	<0.001
Previous hemorrhage stroke	1.28 (1.19, 1.37)	<0.001	1.24 (1.01, 1.51)	0.039
Old myocardial infarction	1.11 (1.06, 1.17)	<0.001	0.95 (0.82, 1.09)	0.440

Table 4. Associations between baseline characteristics at dialysis initiation and infection-related hospitalization during follow-up. CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

The underlying mechanisms linking infection events during advanced CKD to a higher risk of post-ESRD IRH or other adverse outcomes are likely to be multifactorial. In our study, the patients with advanced CKD who experienced at least one infection event had a higher prevalence of comorbidities. The progression of these comorbidities may conceivably serve as a link between pre-dialysis infection event and post-ESRD adverse outcomes. Alternatively, any infection event during advanced CKD may serve as a marker for patients with particularly poor control of these comorbidities. However, after adjustment for all the studied comorbidities, the risk of post-ESRD adverse outcomes was attenuated but remained statistically significant, supporting the idea that infections may trigger other risk factors, such as hypercatabolic state or chronic inflammation, leading to worse outcomes. Systemic inflammation has been shown to contribute to the link between infection and cardiovascular events[28,29]. Notably, this link is further supported by another finding of the current study, namely the independent association between pre-dialysis infection exposure and MACCE after dialysis initiation.

Another factor involved in the higher risk of post-ESRD adverse outcomes might be the result of insufficient handling of these advanced CKD patients after an infection event, potentially highlighting the importance of early intervention for these populations. Early referral to a nephrologist after any infection event in a patient with advanced CKD might be necessary because nephrologists are more likely to comprehensively manage worsening nutritional status, anemia, and volume status complicated by an infection event. Several observational studies have demonstrated that the quality of pre-dialysis CKD care independently predicts post-dialysis mortality[30,31]. Notably, our study found that a higher number of nephrologist visits during advanced CKD was associated with a lower risk of post-ESRD IRH, irrespective dialysis modality. Our finding that a higher risk of post-ESRD IRH is linked with pre-dialysis infection exposure among older patients and patients using tunneled-catheter is also supported by previous reports[19,21], suggesting timely arteriovenous fistula creation. Moreover, incident dialysis patients with infection exposure or recurrent infections during advanced CKD appear particularly vulnerable to infections or other adverse events and may benefit from timely preventive strategies, such as nutrition resilience assessment[32] and/or nutrition supplementation[33], immunization against influenza and pneumococcus[34,35], blood stream infection prevention collaborative interventions[36], or appropriate management of comorbidities[37]. Further research is needed to confirm the beneficial effect of the aforementioned multifaceted interventions for such high-risk patients. Although this study provides novel information on the relationship between pre-dialysis infection exposure and post-ESRD adverse outcomes, they must be weighed against the potential limitations of the investigation. First, we excluded advanced CKD patients with a malignancy, an autoimmune disease, liver cirrhosis, or history of organ transplant because they may have had other factors linking infection and post-ESRD adverse outcomes. Therefore, our results may not be generalizable to the entire dialysis population. Second, our study design raises the possibility of selection bias as patients needed to survive those infection events and initiate dialysis to be included in the study. Third, we defined infection events by identifying only hospitalization and emergency department visits but some patients with a mild infection may have been treated in the outpatient setting, which led to underestimate the infection events. However, some disease can mimic a mild infection at initial presentation and those cases are difficult to ascertain due to either uncertain diagnostic accuracy or lack

of definite information of infection type, potentially introducing misclassification bias. Fourth, our study was limited by the use of only principal discharge diagnoses to define infections; the true incidence of infection events may have been underestimated. We used diagnostic codes rather than validated clinical criteria to ascertain infection types, potentially resulting in some misclassifications. However, the primary objective of this study was to heighten awareness among clinicians regarding the significance of pre-dialysis infection events, like pre-dialysis cardiovascular disease, as potential risk factors for post-ESRD adverse outcomes and thus deserving of routine assessment. As such, misclassifications may not affect the relevance or accuracy of our results. Finally, although we adjusted for a large number of patient characteristics, we cannot rule out the possibility of residual confounding such as baseline nutritional status, exact eGFR at enrollment and speed of eGFR decline, or vaccination status. The observational nature of the study also makes it impossible to prove a causal link between the occurrence of infections and adverse outcome later on, meaning that the results should be regarded as hypothesis generating only and require further investigation.

In conclusion, the results of this study indicated that infection is a frequent event in patients with non-dialysis advanced CKD and that infection exposure during advanced CKD can lead to higher risks of post-ESRD adverse outcomes irrespective of all-cause mortality, IRH, or MACCE. Timely multifaceted preventive strategies among such high-risk incident dialysis patients may lead to improved outcomes and a lower burden on the health care system.

Methods

Ethics statement. This study was conducted in accordance with the Declaration of Helsinki. Because no identifiable personal information is included in the NHIRD, the Research Ethics Committee agreed that no informed consent was required. All experimental protocols were performed following the relevant guidelines and was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No.201701186B0).

Data source. We analyzed longitudinal data from Taiwan's National Health Insurance Research Database (NHIRD), which contains anonymized health care information collected prospectively from approximately 99.9% of Taiwan's population. Only patients who had advanced CKD and then started permanent dialysis were included as the source population. Hence, we selected individuals who had a primary diagnosis of CKD and received erythropoiesis-stimulating agent (ESA) treatment. According to the reimbursement regulations of Taiwan's National Health Insurance program, ESA is to be initiated when patients with CKD have an eGFR of 15 mL/min/1.73 m^2or less and a hematocrit level below 28%. This definition of advanced CKD has been widely reported in previous NHIRD-based studies[38,39]. In addition, when patients with advanced CKD start permanent dialysis, they can receive a catastrophic illness certificate verified by the Bureau of National Health Insurance, exempting them from related copayments. Thus, the ESRD registry in the NHIRD is notably comprehensive and our selected cohort was highly representative of patients with advanced CKD who entered permanent dialysis.

Exposure ascertainment. The primary exposure of interest was the number of infection episodes during pre-dialysis advanced CKD. An episode of infection was ascertained by identifying either hospitalizations or emergency department visits with a principal discharge diagnosis of selected infection-related International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes as indicated previously (Supplementary Table S3)[12]. To avoid double counting of the same infection, the infections recorded in emergency departments and those recorded for hospitalization were combined into one single infection episode if the admission date was within two weeks of the emergency visit date.

Outcome and covariate assessment. The covariates we examined were age, sex, CKD duration, number of nephrologist outpatient visits in the previous year, dialysis modality, 11 baseline comorbidities, and 14 medications. Comorbidities were defined as at least 2 outpatient visits or one inpatient stay in the previous year. Most of the diagnostic codes used for these comorbidities have been validated in previous studies[40]. We obtained inpatient records only to ascertain history of heart failure, stroke, and myocardial infarction. Medications were identified by the filling of a prescription at least once or refilling a prescription for a chronic illness at least once within 3 months of the index date. The primary outcomes of interest were all-cause mortality and IRH after starting permanent dialysis. We identified first IRH event by using the same ICD-9-CM codes as for ascertaining infection exposure during advanced CKD. In addition to all-cause mortality, we also examined infection-related death by examining the cause of death in the main diagnosis in the discharge records for inpatient hospital deaths, the primary diagnosis of the last emergency visit, or hospitalization within 7 days of death for out-of-hospital deaths[41]. The secondary outcomes investigated were MACCE, comprising acute myocardial infarction, acute ischemic stroke, intracerebral hemorrhage, heart failure, and cardiovascular death, most of the diagnostic codes for which have been previously studied and validated[42,43]. The observation period was from the index date to death, first IRH or MACCE, or the end of the study, whichever occurred first. In addition, other events were analyzed, including sepsis death, catheter-related infection requiring catheter removal, readmission for any cause, and each MACCE component (Supplementary Tables S4 and S5). Death prior to the occurrence of IRH or MACCE was considered a competing risk event.

Statistical analysis. We compared the continuous variables between groups (infection vs. non-infection) by using the independent sample t test. The categorical data between groups were compared using the chi-square test. The association between infection exposure prior to ESRD transition and risk of all-cause mortality was investigated using univariate and multivariable Cox proportional hazard models. The association between infection exposure and risk of other time to event outcomes (i.e., MACCE) was studied using a Fine and Gray

subdistribution hazard model in which all-cause mortality during follow-up was a competing risk. Furthermore, to determine the robustness of our results and as a sensitivity analysis, we analyzed the risk of post-ESRD adverse outcomes according to four quartiles based on the annual number of infection episodes during pre-dialysis advanced CKD. We then examined linear trends by modeling the quartiles of these infection exposures as a continuous variable with and without adjustment for covariates. To compare the effect of pre-dialysis infection exposure on early and late post-ESRD adverse outcomes, the analyses were performed with the follow-up time restricted to the first year or with the entire follow-up period. The covariates adjusted for in the multivariable analyses were age, sex, CKD duration, number of nephrologist outpatient visits in the previous year, dialysis modality, 11 baseline comorbidities, 14 medications, and the index year (the year of dialysis initiation).

A sensitivity analysis was done by excluding patients who had AKI during advanced CKD because rapid decline of renal function caused by infection or other etiology might confound the primary analysis. At last, we also conducted subgroup analyses to examine whether the hazard of pre-dialysis infection exposure was consistent across different levels of the 4 pre-specified subgroups (sex, age, dialysis modality, and initial dialysis access type for hemodialysis). A two-sided P value of less than 0.05 was considered statistically significant and no adjustment for multiple testing (multiplicity) was made. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), including the procedure 'phreg' for survival analysis and the macro '%cif' for cumulative incidence functions.

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Author contributions

Conceptualization: C.C.L., C.H.C., P.C.F.; Methodology: G.K., Y.S.L., T.Y.T.; Software: S.W.C.; Validation: P.C.F., T.Y.T.; Formal Analysis: C.C.L., S.W.C., Y.S.L.; Investigation: C.H.C., G.K.; Writing-Original Draft Preparation: C.H.C., C.C.L.; Writing- Review & Editing: P.C.F., G.K.; Supervision: Y.C.T., C.C.L. All the authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to C.-C.L.

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Elena Zakharova, MD, PhD

NKF-KDIGO GUIDELINE DEVELOPMENT STAFF

Kerry Willis, PhD, Senior Vice-President for Scientific Activities

Michael Cheung, MA, Guideline Development Director

Sean Slifer, BA, Guideline Development Manager

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Reference Keys

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1**, **Level 2**, or **Not Graded**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

	Implications		
Grade*	**Patients**	**Clinicians**	**Policy**
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

ADULT GFR ESTIMATING EQUATIONS

2009 CKD-EPI creatinine equation: $141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age}$ [$\times$ 1.018 if female] [$\times$ 1.159 if black], where SCr is serum creatinine (in mg/dl), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min is the minimum of SCr/κ or 1, and max is the maximum of SCr/κ or 1.

Equations expressed for specified sex and serum creatinine level

Gender	Serum creatinine	Equation for estimating GFR
Female	$\leqslant$ 0.7 mg/dl ($\leqslant$ 62 μmol/l)	$144 \times (SCr/0.7)^{-0.329} \times 0.993^{Age}$ [$\times$ 1.159 if black]
Female	$>$ 0.7 mg/dl ($>$ 62 μmol/l)	$144 \times (SCr/0.7)^{-1.209} \times 0.993^{Age}$ [$\times$ 1.159 if black]
Male	$\leqslant$ 0.9 mg/dl ($\leqslant$ 80 μmol/l)	$141 \times (SCr/0.9)^{-0.411} \times 0.993^{Age}$ [$\times$ 1.159 if black]
Male	$>$ 0.9 mg/dl ($>$ 80 μmol/l)	$141 \times (SCr/0.9)^{-1.209} \times 0.993^{Age}$ [$\times$ 1.159 if black]

2012 CKD-EPI cystatin C equation: $133 \times \min(SCysC/0.8, 1)^{-0.499} \times \max(SCysC/0.8, 1)^{-1.328} \times 0.996^{Age}$ [$\times$ 0.932 if female], where SCysC is serum cystatin C (in mg/l), min indicates the minimum of SCysC/0.8 or 1, and max indicates the maximum of SCysC/0.8 or 1.

Equations expressed for serum cystatin C level

	Serum cystatin C	Equation for estimating GFR
Female or male	$\leqslant$ 0.8 mg/l	$133 \times (SCysC/0.8)^{-0.499} \times 0.996^{Age}$ [$\times$ 0.932 if female]
Female or male	$>$ 0.8 mg/l	$133 \times (SCysC/0.8)^{-1.328} \times 0.996^{Age}$ [$\times$ 0.932 if female]

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2012 CKD-EPI creatinine–cystatin C equation: $135 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-0.601} \times \min(SCysC/0.8, 1)^{-0.375} \times \max(SCysC/0.8, 1)^{-0.711} \times 0.995^{Age}$ [× 0.969 if female] [× 1.08 if black], where SCr is serum creatinine (in mg/dl), SCysC is serum cystatin C (in mg/l), κ is 0.7 for females and 0.9 for males, α is −0.248 for females and −0.207 for males, min(SCr/κ, 1) indicates the minimum of SCr/κ or 1, and max(SCr/κ, 1) indicates the maximum of SCr/κ or 1; min(SCysC/0.8, 1) indicates the minimum of SCysC/0.8 or 1 and max(SCysC/0.8, 1) indicates the maximum of SCysC/0.8 or 1.

Equations expressed for specified sex, serum creatinine, and serum cystatin C level

Gender	Serum creatinine	Serum cystatin C	Equation for estimating GFR
Female	⩽0.7 mg/dl (⩽62 μmol/l)	⩽0.8 mg/l	$130 \times (SCr/0.7)^{-0.248} \times (SCysC/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
		>0.8 mg/l	$130 \times (SCr/0.7)^{-0.248} \times (SCysC/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
Female	>0.7 mg/dl (>62 μmol/l)	⩽0.8 mg/l	$130 \times (SCr/0.7)^{-0.601} \times (SCysC/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
		>0.8 mg/l	$130 \times (SCr/0.7)^{-0.601} \times (SCysC/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
Male	⩽0.9 mg/dl (⩽80 μmol/l)	⩽0.8 mg/l	$135 \times (SCr/0.9)^{-0.207} \times (SCysC/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
		>0.8 mg/l	$135 \times (SCr/0.9)^{-0.207} \times (SCysC/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]
Male	>0.9 mg/dl (>80 μmol/l)	⩽0.8 mg/l	$135 \times (SCr/0.9)^{-0.601} \times (SCysC/0.8)^{-0.375} \times 0.995^{Age}$ [× 1.08 if black]
		>0.8 mg/l	$135 \times (SCr/0.9)^{-0.601} \times (SCysC/0.8)^{-0.711} \times 0.995^{Age}$ [× 1.08 if black]

PEDIATRIC GFR ESTIMATING EQUATIONS

Creatinine-based equations

$41.3 \times (height/SCr)$
$40.7 \times (height/SCr)^{0.64} \times (30/BUN)^{0.202}$

BUN, blood urea nitrogen in mg/dl; height in meters; SCr, serum creatinine in mg/dl

Cystatin C-based equations

$70.69 \times (SCysC)^{-0.931}$

SCysC, serum cystatin C in mg/l.

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CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health and CKD is classified based on cause, GFR category, and albuminuria category (CGA).

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m^2) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

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CONVERSION FACTORS OF METRIC UNITS TO SI UNITS

Parameter	Metric units	Conversion factor	SI units
Albumin (serum)	g/dl	10	g/l
Blood urea nitrogen (BUN)	mg/dl	0.357	mmol/l
Creatinine (serum)	mg/dl	88.4	μmol/l
Creatinine clearance	ml/min	0.01667	ml/s
Hemoglobin	g/dl	10	g/l
Phosphate (serum)	mg/dl	0.323	mmol/l
PTH (parathyroid hormone, serum)	pg/ml	0.106	pmol/l
Urea (plasma)	mg/dl	0.167	mmol/l
Uric acid	mg/dl	59.485	μmol/l
Vitamin D, 25-hydroxyvitamin D	ng/ml	2.496	nmol/l

Note: Metric unit × conversion factor = SI unit.

HbA_{1c} CONVERSION CHART

DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
5.0	31	6.0	42	**7.0**	**53**	8.0	64	9.0	75
5.1	32	6.1	43	7.1	54	8.1	65	9.1	76
5.2	33	6.2	44	7.2	55	8.2	66	9.2	77
5.3	34	6.3	45	7.3	56	8.3	67	9.3	78
5.4	36	6.4	46	7.4	57	8.4	68	9.4	79
5.5	37	**6.5**	**48**	**7.5**	**58**	8.5	69	9.5	80
5.6	38	6.6	49	7.6	60	8.6	70	9.6	81
5.7	39	6.7	50	7.7	61	8.7	72	9.7	83
5.8	40	6.8	51	7.8	62	8.8	73	9.8	84
5.9	41	6.9	52	7.9	63	8.9	74	9.9	85

DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
10.0	86	11.0	97	12.0	108	13.0	119	14.0	130
10.1	87	11.1	98	12.1	109	13.1	120	14.1	131
10.2	88	11.2	99	12.2	110	13.2	121	14.2	132
10.3	89	11.3	100	12.3	111	13.3	122	14.3	133
10.4	90	11.4	101	12.4	112	13.4	123	14.4	134
10.5	91	11.5	102	12.5	113	13.5	124	14.5	135
10.6	92	11.6	103	12.6	114	13.6	125	14.6	136
10.7	93	11.7	104	12.7	115	13.7	126	14.7	137
10.8	95	11.8	105	12.8	116	13.8	127	14.8	138
10.9	96	11.9	107	12.9	117	13.9	128	14.9	139

IFCC-HbA_{1c} (mmol/mol) = [DCCT-HbA_{1c} (%) − 2.15] × 10.929

Abbreviations: DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine.

Source: Diabetes UK, www.diabetes.org.uk.

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Abbreviations and Acronyms

4C	Cardiovascular Comorbidity in Children with CKD
AASK	African American Study of Kidney Disease and Hypertension
ABPM	Ambulatory blood pressure monitoring
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE-I	Angiotensin-converting enzyme inhibitor
ACR	Albumin-to-creatinine ratio
ACS	Acute coronary syndrome
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AER	Albumin excretion rate
AGREE	Appraisal of Guidelines for Research and Evaluation
AKD	Acute kidney disease
AKDN	Alberta Kidney Disease Network
AKI	Acute kidney injury
ANP	Atrial natriuretic peptide
APPROACH	Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease
AusDiab	Australian Diabetes, Obesity and Lifestyle study
ARB	Angiotensin-receptor blocker
BMD	Bone mineral density
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CAPRICORN	Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction
CGA	Cause, GFR and Albuminuria categories
CHARM	Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity
CHF	Congestive heart failure
CHS	Cardiovascular Health Study
CI	Confidence interval
CIBIS II	Cardiac Insufficiency Bisoprolol Study II
CKD	Chronic kidney disease
CKD-EPI	CKD Epidemiology Collaboration
CKD-MBD	Chronic Kidney Disease-Mineral and Bone Disorder
CKiD	Chronic Kidney Disease in Children
COGS	Conference on Guideline Standardization
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival
COX-2	Cyclooxygenase-2
Cr-EDTA	Chromium-ethylenediamine tetraacetic acid
CREATE	Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta Trial
CREDO	Clopidogrel for Reduction of Events During Observation
CrCl	Creatinine clearance
CRIC	Chronic Renal Insufficiency Cohort
CRP	C-reactive protein
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
CVD	Cardiovascular disease
DCCT/EDIC	Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications
DIG	Digitalis Intervention Group
DPI	Dietary protein intake
DXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiography
eGFR	Estimated GFR
EMU	Early morning urine
ERT	Evidence review team
ESA	Erythropoiesis-stimulating agent
ESCAPE	Effect of Strict Blood Pressure Control and ACE-Inhibition on Progression of Chronic Renal Failure in Pediatric Patients
ESRD	End-Stage Renal Disease
ESUR	European Society of Urogenital Radiology
FGF-23	Fibroblast growth factor-23
GBCA	Gadolinium-based contrast agent
GFR	Glomerular filtration rate
GN	Glomerulonephritis
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hb	Hemoglobin
HbA_{1c}	Hemoglobin A1c
HBV	Hepatitis B virus
HDL-C	High-density lipoprotein cholesterol
HOPE	Heart Outcomes Prevention Evaluation
HOT	Hypertension Optimal Treatment
HR	Hazard ratio
HR-pQCT	High-resolution peripheral quantitative computed tomography
HUNT 2	Nord-Trøndelag Health Study (1995-1997)
ICD	International Classification of Diseases
ICU	Intensive-care unit
IDF	International Diabetes Federation
IDMS	Isotope-dilution mass spectrometry
IQR	Interquartile range
IRMM	Institute for Reference Materials and Measurements
ItalKid	Italian Pediatric Registry of Chronic Renal Failure
JCTLM	Joint Committee for Traceability in Laboratory Medicine
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL-C	Low-density lipoprotein cholesterol
LIFE	Losartan Intervention For Endpoint Reduction in Hypertension
LPD	Low-protein diet
LVH	Left ventricular hypertrophy
MAP	Mean arterial pressure
MDRD	Modification of Diet in Renal Disease
MESA	Multi-Ethnic Study of Atherosclerosis

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MI	Myocardial infarction
MRI	Magnetic resonance imaging
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies
NCEP III	Third Report of the National Cholesterol Education Program
NECOSAD	Netherlands Cooperative Study on the Adequacy of Dialysis Study Group
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NKDEP	National Kidney Disease Education Program
NKF	National Kidney Foundation
NSAID	Nonsteroidal anti-inflammatory drug
NSF	Nephrogenic systemic fibrosis
NT-proBNP	N-terminal pro-BNP
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint trial
OR	Odds ratio
PAD	Peripheral arterial disease
PCR	Protein-to-creatinine ratio
PER	Protein excretion rate
PICARD	Program to Improve Care in Acute Renal Disease
PICODD	Population, Intervention or Predictor, Comparator, Outcome, study Design, and Duration of follow-up
PREVEND	Prevention of Renal and Vascular Endstage Disease
PTH	Parathyroid hormone
QOL	Quality of life
RAAS	Renin-angiotensin-aldosterone system
RBC	Red blood cell
RCT	Randomized controlled trial
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
RR	Relative risk
RRT	Renal replacement therapy
SCORE	Systematic COronary Risk Evaluation
SCr	Serum creatinine
SCysC	Serum cystatin C
SD	Standard deviation
SEEK	Study for the Evaluation of Early Kidney disease
SHARP	Study of Heart and Renal Protection
SPECT	Single photon emission computed tomography
SUA	Serum uric acid
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
UKPDS	United Kingdom Prospective Diabetes Study
USA-PRC	USA–People's Republic of China Collaborative Study of Cardiovascular and Cardiopulmonary Epidemiology
USRDS	US Renal Data System
VADT	Veterans Affairs Diabetes Trial
Val-HeFT	Valsartan Heart Failure Trial
VLPD	Very low-protein diet
WBC	White blood cell
WHO	World Health Organization

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Notice

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SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon systematic literature searches last conducted in June 2011, supplemented with additional evidence through November 2012. It is designed to provide information and assist decision making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

SECTION II: DISCLOSURE

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Foreword

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It is our hope that this document will serve several useful purposes. Our primary goal is to improve patient care. We hope to accomplish this, in the short term, by helping clinicians know and better understand the evidence (or lack of evidence) that determines current practice. By providing comprehensive evidence-based recommendations, this guideline will also help define areas where evidence is lacking and research is needed. Helping to define a research agenda is an often neglected, but very important, function of clinical practice guideline development.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rate the quality of evidence and the strength of recommendations. In all, there were 12 (17.1%) recommendations in this guideline for which the overall quality of evidence was graded 'A,' whereas 36 (51.4%) were graded 'B,' 17 (24.3%) were graded 'C,' and 5 (7.1%) were graded 'D.' Although there are reasons other than quality of evidence to make a grade 1 or 2 recommendation, in general, there is a correlation between the quality of overall evidence and the strength of the recommendation. Thus, there were 43 (62.3%) recommendations graded '1' and 26 (37.7%) graded '2.' There were 9 (13.0%) recommendations graded '1A,' 23 (33.3%) were '1B,' 10 (14.5%) were '1C,' and 1 (1.4%) was '1D.' There were 2 (2.9%) recommendations graded '2A,' 13 (18.8%) were '2B,' 7 (10.1%) were '2C,' and 4 (5.8%) were '2D.' There were 41 (37.3%) statements that were not graded.

Some argue that recommendations should not be made when evidence is weak. However, clinicians still need to make decisions in their daily practice, and they often ask, "What do the experts do in this setting?" We opted to give guidance, rather than remain silent. These recommendations are often rated with a low strength of recommendation and a low quality of evidence, or were not graded. It is important for the users of this guideline to be cognizant of this (see Notice). In every case these recommendations are meant to be a place for clinicians to start, not stop, their inquiries into specific management questions pertinent to the patients they see in daily practice.

We wish to thank the Work Group Co-Chairs, Drs. Adeera Levin and Paul Stevens, along with all of the Work Group members who volunteered countless hours of their time developing this guideline. We also thank the Evidence Review Team members and staff of the National Kidney Foundation who made this project possible. Finally, we owe a special debt of gratitude to the many KDIGO Board members and individuals who volunteered time reviewing the guideline, and making very helpful suggestions.

Bertram L Kasiske, MD
KDIGO Co-Chair

David C Wheeler, MD, FRCP
KDIGO Co-Chair

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Work Group Membership

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WORK GROUP CO-CHAIRS

Adeera Levin, MD, FRCPC
University of British Columbia
Vancouver, Canada

Paul E Stevens, MB, FRCP
East Kent Hospitals University
NHS Foundation Trust
Canterbury, United Kingdom

WORK GROUP

Rudy W Bilous, MD
Newcastle University and James Cook University Hospital
Middlesbrough, United Kingdom

Josef Coresh, MD, PhD, MHS
Johns Hopkins University
Baltimore, USA

Angel LM de Francisco, MD, PhD
Hospital Universitario Valdecilla
Santander, Spain

Paul E de Jong, MD, PhD
University Medical Center Groningen
Groningen, The Netherlands

Kathryn E Griffith, BM, BS, MSc, MRCP, MRCGP
University Health Centre, York University
York, United Kingdom

Brenda R Hemmelgarn, MD, PhD, FRCP(C)
University of Calgary
Alberta, Canada

Kunitoshi Iseki, MD
University Hospital of the Ryukyus
Nishihara, Okinawa, Japan

Edmund J Lamb, PhD, FRCPath
East Kent Hospitals University
NHS Foundation Trust
Canterbury, United Kingdom

Andrew S Levey, MD
Tufts Medical Center
Boston, USA

Miguel C Riella, MD, PhD, FACP
Evangelic University Hospital
Curitiba, Brazil

Michael G Shlipak, MD, MPH
VA Medical Center, UCSF
San Francisco, USA

Haiyan Wang, MD
Peking University First Hospital
Beijing, China

Colin T White, MD, FRCPC
University of British Columbia
Vancouver, Canada

Christopher G Winearls, MB, DPhil, FRCP
Oxford Radcliffe Hospitals NHS Trust
Oxford, United Kingdom

EVIDENCE REVIEW TEAM

Tufts Center for Kidney Disease Guideline Development and Implementation

Tufts Medical Center, Boston, MA, USA:

Katrin Uhlig, MD, MS, Project Director; Director, Guideline Development
Dana Miskulin, MD, MS, Staff Nephrologist
Amy Earley, BS, Project Coordinator
Shana Haynes, MS, DHSc, Research Assistant
Jenny Lamont, MS, Project Manager

In addition, support and supervision were provided by:

Ethan M Balk, MD, MPH; Program Director, Evidence Based Medicine

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Abstract

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The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (CKD) serves to update the 2002 KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification following a decade of focused research and clinical practice in CKD. The document aims to provide state-of-the-art guidance on the evaluation, management and treatment for all patients with CKD. Specifically, the guideline retains the definition of CKD but presents an enhanced classification framework for CKD; elaborates on the identification and prognosis of CKD; discusses the management of progression and complications of CKD; and expands on the continuum of CKD care: timing of specialist referral, ongoing management of people with progressive CKD, timing of the initiation of dialysis, and finally the implementation of a treatment program which includes comprehensive conservative management. The development of the guideline followed an explicit process of evidence review and appraisal. Treatment approaches are addressed in each chapter and guideline recommendations are based on systematic reviews of relevant trials. Practical comments or statements which serve as educational purposes are ungraded, but included as important information for the readership. Appraisal of the quality of the evidence and the strength of recommendations followed the GRADE approach. Ongoing areas of controversies, limitations of the evidence, and international relevance are discussed and additional suggestions are provided for future research.

Keywords: Albuminuria; Chronic kidney disease; Classification; Clinical practice guideline; Evidence-based recommendation; GFR; Glomerular filtration rate; KDIGO; Proteinuria; Systematic review

CITATION

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Summary of Recommendation Statements

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Chapter 1: Definition and classification of CKD

1.1: DEFINITION OF CKD

1.1.1: CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. (*Not Graded*)

Criteria for CKD (either of the following present for >3 months)

Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2 (GFR categories G3a–G5)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

1.2: STAGING OF CKD

1.2.1: We recommend that CKD is classified based on cause, GFR category, and albuminuria category (CGA). (*1B*)

1.2.2: Assign cause of CKD based on presence or absence of systemic disease and the location within the kidney of observed or presumed pathologic-anatomic findings. (*Not Graded*)

1.2.3: Assign GFR categories as follows (*Not Graded*):

GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

1.2.4: Assign albuminuria* categories as follows (*Not Graded*):
***note that where albuminuria measurement is not available, urine reagent strip results can be substituted (Table 7)**

Albuminuria categories in CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

Abbreviations: AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR >2220 mg/g; >220 mg/mmol]).

1.3: PREDICTING PROGNOSIS OF CKD

1.3.1: In predicting risk for outcome of CKD, identify the following variables: 1) cause of CKD; 2) GFR category; 3) albuminuria category; 4) other risk factors and comorbid conditions. (*Not Graded*)

1.3.2: In people with CKD, use estimated risk of concurrent complications and future outcomes to guide decisions for testing and treatment for CKD complications. (*Not Graded*)

1.3.3: In populations with CKD, group GFR and albuminuria categories with similar relative risk for CKD outcomes into risk categories. (*Not Graded*)

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

1.4: EVALUATION OF CKD

1.4.1: Evaluation of chronicity

1.4.1.1: In people with GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) or markers of kidney damage, review past history and previous measurements to determine duration of kidney disease. (*Not Graded*)

- **If duration is >3 months, CKD is confirmed. Follow recommendations for CKD.**
- **If duration is not >3 months or unclear, CKD is not confirmed. Patients may have CKD or acute kidney diseases (including AKI) or both and tests should be repeated accordingly.**

1.4.2: Evaluation of cause

1.4.2.1: Evaluate the clinical context, including personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and pathologic diagnosis to determine the causes of kidney disease. (*Not Graded*)

1.4.3: Evaluation of GFR

1.4.3.1: We recommend using serum creatinine and a GFR estimating equation for initial assessment. (*1A*)

1.4.3.2: We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. (*2B*)

1.4.3.3: We recommend that clinicians (*1B*):

- **use a GFR estimating equation to derive GFR from serum creatinine ($eGFR_{creat}$) rather than relying on the serum creatinine concentration alone.**
- **understand clinical settings in which $eGFR_{creat}$ is less accurate.**

1.4.3.4: We recommend that clinical laboratories should (*1B*):

- **measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology.**
- **report $eGFR_{creat}$ in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting $eGFR_{creat}$.**

- **report $eGFR_{creat}$ in adults using the 2009 CKD-EPI creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation.**

When reporting serum creatinine:

- **We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed as standard international units (μmol/l) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dl).**

When reporting $eGFR_{creat}$:

- **We recommend that $eGFR_{creat}$ should be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m^2 in adults using the units ml/min/1.73 m^2.**
- **We recommend $eGFR_{creat}$ levels less than 60 ml/min/1.73 m^2 should be reported as "decreased."**

1.4.3.5: We suggest measuring cystatin C in adults with $eGFR_{creat}$ 45–59 ml/min/1.73 m^2 who do not have markers of kidney damage if confirmation of CKD is required. (*2C*)

- **If $eGFR_{cys}$/$eGFR_{creat\text{-}cys}$ is also <60 ml/min/1.73 m^2, the diagnosis of CKD is confirmed.**
- **If $eGFR_{cys}$/$eGFR_{creat\text{-}cys}$ is ≥ 60 ml/min/1.73 m^2, the diagnosis of CKD is not confirmed.**

1.4.3.6: If cystatin C is measured, we suggest that health professionals (*2C*):

- **use a GFR estimating equation to derive GFR from serum cystatin C rather than relying on the serum cystatin C concentration alone.**
- **understand clinical settings in which $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$ are less accurate.**

1.4.3.7: We recommend that clinical laboratories that measure cystatin C should (*1B*):

- **measure serum cystatin C using an assay with calibration traceable to the international standard reference material.**
- **report eGFR from serum cystatin C in addition to the serum cystatin C concentration in adults and specify the equation used whenever reporting $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$.**
- **report $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$ in adults using the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C equations, respectively, or alternative cystatin C-based GFR estimating equations if they have been shown to improve accuracy of GFR estimates compared to the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C equations.**

When reporting serum cystatin C:

- **We recommend reporting serum cystatin C concentration rounded to the nearest 100th of a whole number when expressed as conventional units (mg/l).**

When reporting $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$:

- **We recommend that $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$ be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m^2 in adults using the units ml/min/1.73 m^2.**
- **We recommend $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$ levels less than 60 ml/min/1.73 m^2 should be reported as "decreased."**

1.4.3.8: We suggest measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact on treatment decisions. (*2B*)

1.4.4: Evaluation of albuminuria

1.4.4.1: We suggest using the following measurements for initial testing of proteinuria (in descending order of preference, in all cases an early morning urine sample is preferred) (*2B*):

1) urine albumin-to-creatinine ratio (ACR);
2) urine protein-to-creatinine ratio (PCR);
3) reagent strip urinalysis for total protein with automated reading;
4) reagent strip urinalysis for total protein with manual reading.

1.4.4.2: We recommend that clinical laboratories report ACR and PCR in untimed urine samples in addition to albumin concentration or proteinuria concentrations rather than the concentrations alone. (*1B*)

1.4.4.2.1: The term microalbuminuria should no longer be used by laboratories. (*Not Graded*)

1.4.4.3: Clinicians need to understand settings that may affect interpretation of measurements of albuminuria and order confirmatory tests as indicated (*Not Graded*):
- Confirm reagent strip positive albuminuria and proteinuria by quantitative laboratory measurement and express as a ratio to creatinine wherever possible.
- Confirm ACR $\geq$ 30 mg/g ($\geq$ 3 mg/mmol) on a random untimed urine with a subsequent early morning urine sample.
- If a more accurate estimate of albuminuria or total proteinuria is required, measure albumin excretion rate or total protein excretion rate in a timed urine sample.

1.4.4.4: If significant non-albumin proteinuria is suspected, use assays for specific urine proteins (e.g., α_1-microglobulin, monoclonal heavy or light chains, [known in some countries as "Bence Jones" proteins]). (*Not Graded*)

Chapter 2: Definition, identification, and prediction of CKD progression

2.1: DEFINITION AND IDENTIFICATION OF CKD PROGRESSION

2.1.1: Assess GFR and albuminuria at least annually in people with CKD. Assess GFR and albuminuria more often for individuals at higher risk of progression, and/or where measurement will impact therapeutic decisions (see figure below). (*Not Graded*)

2.1.2: Recognize that small fluctuations in GFR are common and are not necessarily indicative of progression. (*Not Graded*)

2.1.3: Define CKD progression based on one of more of the following (*Not Graded*):
- Decline in GFR category ($\geq$ 90 [G1], 60–89 [G2], 45–59 [G3a], 30–44 [G3b], 15–29 [G4], $<$ 15 [G5] ml/min/1.73 m^2). A certain drop in eGFR is defined as a drop in GFR category accompanied by a 25% or greater drop in eGFR from baseline.
- Rapid progression is defined as a sustained decline in eGFR of more than 5 ml/min/1.73 m^2/yr.
- The confidence in assessing progression is increased with increasing number of serum creatinine measurements and duration of follow-up.

2.1.4: In people with CKD progression, as defined in Recommendation 2.1.3, review current management, examine for reversible causes of progression, and consider referral to a specialist. (*Not Graded*)

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
GFR categories (ml/min/1.73 m^2) Description and range	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year).

2.2: PREDICTORS OF PROGRESSION

2.2.1: Identify factors associated with CKD progression to inform prognosis. These include cause of CKD, level of GFR, level of albuminuria, age, sex, race/ethnicity, elevated BP, hyperglycemia, dyslipidemia, smoking, obesity, history of cardiovascular disease, ongoing exposure to nephrotoxic agents, and others. (*Not Graded*)

Chapter 3: Management of progression and complications of CKD

3.1: PREVENTION OF CKD PROGRESSION

BP and RAAS interruption

3.1.1: Individualize BP targets and agents according to age, coexistent cardiovascular disease and other comorbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes), and tolerance of treatment as described in the KDIGO 2012 Blood Pressure Guideline. (*Not Graded*)

3.1.2: Inquire about postural dizziness and check for postural hypotension regularly when treating CKD patients with BP-lowering drugs. (*Not Graded*)

3.1.3: Tailor BP treatment regimens in elderly patients with CKD by carefully considering age, comorbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to BP treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *(Not Graded)*

3.1.4: We recommend that in both diabetic and non-diabetic adults with CKD and urine albumin excretion <30 mg/24 hours (or equivalent*) whose office BP is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic. *(1B)*

3.1.5: We suggest that in both diabetic and non-diabetic adults with CKD and with urine albumin excretion of ≥ 30 mg/24 hours (or equivalent*) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤ 130 mm Hg systolic and ≤ 80 mm Hg diastolic. *(2D)*

3.1.6: We suggest that an ARB or ACE-I be used in diabetic adults with CKD and urine albumin excretion 30–300 mg/24 hours (or equivalent*). (*2D*)

3.1.7: We recommend that an ARB or ACE-I be used in both diabetic and non-diabetic adults with CKD and urine albumin excretion >300 mg/24 hours (or equivalent*). (*1B*)

3.1.8: There is insufficient evidence to recommend combining an ACE-I with ARBs to prevent progression of CKD. (*Not Graded*)

3.1.9: We recommend that in children with CKD, BP-lowering treatment is started when BP is consistently above the 90th percentile for age, sex, and height. (*1C*)

3.1.10: We suggest that in children with CKD (particularly those with proteinuria), BP is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. (*2D*)

3.1.11: We suggest that an ARB or ACE-I be used in children with CKD in whom treatment with BP-lowering drugs is indicated, irrespective of the level of proteinuria. (*2D*)

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin-to-creatinine ratio, protein-to-creatinine ratio, and protein reagent strip results— are given in Table 7, Chapter 1.

CKD and risk of AKI

3.1.12: We recommend that all people with CKD are considered to be at increased risk of AKI. (*1A*)

3.1.12.1: In people with CKD, the recommendations detailed in the KDIGO AKI Guideline should be followed for management of those at risk of AKI during intercurrent illness, or when undergoing investigation and procedures that are likely to increase the risk of AKI. (*Not Graded*)

Protein intake

3.1.13: We suggest lowering protein intake to 0.8 g/kg/day in adults with diabetes (*2C*) or without diabetes (*2B*) and GFR <30 ml/min/ 1.73 m^2 (GFR categories G4-G5), with appropriate education.

3.1.14: We suggest avoiding high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression. (*2C*)

Glycemic control

3.1.15: We recommend a target hemoglobin A_{1c} (HbA_{1c}) of ~7.0% (53 mmol/mol) to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease. (*1A*)

3.1.16: We recommend not treating to an HbA_{1c} target of <7.0% (<53 mmol/mol) in patients at risk of hypoglycemia. (*1B*)

3.1.17: We suggest that target HbA_{1c} be extended above 7.0% (53 mmol/mol) in individuals with comorbidities or limited life expectancy and risk of hypoglycemia. (*2C*)

3.1.18: In people with CKD and diabetes, glycemic control should be part of a multifactorial intervention strategy addressing blood pressure control and cardiovascular risk, promoting the use of angiotensin-converting enzyme inhibition or angiotensin receptor blockade, statins, and antiplatelet therapy where clinically indicated. (*Not Graded*)

Salt intake

3.1.19: We recommend lowering salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) in adults, unless contraindicated (see rationale). (*1C*)

3.1.19.1: We recommend restriction of sodium intake for children with CKD who have hypertension (systolic and/or diastolic blood pressure >95th percentile) or prehypertension (systolic and/or diastolic blood pressure >90th percentile and <95th percentile), following the age-based Recommended Daily Intake. (*1C*)

3.1.19.2: We recommend supplemental free water and sodium supplements for children with CKD and polyuria to avoid chronic intravascular depletion and to promote optimal growth. (*1C*)

Hyperuricemia

3.1.20: There is insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD. (*Not Graded*)

Lifestyle

3.1.21: We recommend that people with CKD be encouraged to undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 minutes 5 times per week), achieve a healthy weight (BMI 20 to 25, according to country specific demographics), and stop smoking. (*1D*)

Additional dietary advice

3.1.22: We recommend that individuals with CKD receive expert dietary advice and information in the context of an education program, tailored to severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake where indicated. (*1B*)

3.2: COMPLICATIONS ASSOCIATED WITH LOSS OF KIDNEY FUNCTION

Definition and identification of anemia in CKD

3.2.1: Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl (<130 g/l) in males and <12.0 g/dl (<120 g/l) in females. (*Not Graded*)

3.2.2: Diagnose anemia in children with CKD if Hb concentration is <11.0 g/dl (<110 g/l) in children 0.5–5 years, <11.5 g/dl (115 g/l) in children 5–12 years, and <12.0 g/dl (120 g/l) in children 12-15 years. (*Not Graded*)

Evaluation of anemia in people with CKD

3.2.3: To identify anemia in people with CKD measure Hb concentration (*Not Graded*):

- **when clinically indicated in people with GFR ≥60 ml/min/1.73 m^2 (GFR categories G1-G2);**
- **at least annually in people with GFR 30–59 ml/min/1.73 m^2 (GFR categories G3a-G3b);**
- **at least twice per year in people with GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5).**

3.3: CKD METABOLIC BONE DISEASE INCLUDING LABORATORY ABNORMALITIES

3.3.1: We recommend measuring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity at least once in adults with GFR <45 ml/min/1.73 m^2 (GFR categories G3b-G5) in order to determine baseline values and inform prediction equations if used. (*1C*)

3.3.2: We suggest not to perform bone mineral density testing routinely in those with eGFR <45 ml/min/1.73 m^2 (GFR categories G3b-G5), as information may be misleading or unhelpful. (*2B*)

3.3.3: In people with GFR <45 ml/min/1.73 m^2 (GFR categories G3b-G5), we suggest maintaining serum phosphate concentrations in the normal range according to local laboratory reference values. (*2C*)

3.3.4: In people with GFR <45 ml/min/1.73 m^2 (GFR categories G3b-G5) the optimal PTH level is not known. We suggest that people with levels of intact PTH above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency. (*2C*)

Vitamin D supplementation and bisphosphonates in people with CKD

3.3.5: We suggest not to routinely prescribe vitamin D supplements or vitamin D analogs, in the absence of suspected or documented deficiency, to suppress elevated PTH concentrations in people with CKD not on dialysis. (*2B*)

3.3.6: We suggest not to prescribe bisphosphonate treatment in people with GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5) without a strong clinical rationale. (*2B*)

3.4: ACIDOSIS

3.4.1: We suggest that in people with CKD and serum bicarbonate concentrations <22 mmol/l treatment with oral bicarbonate supplementation be given to maintain serum bicarbonate within the normal range, unless contraindicated. (*2B*)

Chapter 4: Other complications of CKD: CVD, medication dosage, patient safety, infections, hospitalizations, and caveats for investigating complications of CKD

4.1:CKD AND CVD

4.1.1: We recommend that all people with CKD be considered at increased risk for cardiovascular disease. (*1A*)

4.1.2: We recommend that the level of care for ischemic heart disease offered to people with CKD should not be prejudiced by their CKD. (*1A*)

4.1.3: We suggest that adults with CKD at risk for atherosclerotic events be offered treatment with antiplatelet agents unless there is an increased bleeding risk that needs to be balanced against the possible cardiovascular benefits. (*2B*)

4.1.4: We suggest that the level of care for heart failure offered to people with CKD should be the same as is offered to those without CKD. (*2A*)

4.1.5: In people with CKD and heart failure, any escalation in therapy and/or clinical deterioration should prompt monitoring of eGFR and serum potassium concentration. (*Not Graded*)

4.2: CAVEATS WHEN INTERPRETING TESTS FOR CVD IN PEOPLE WITH CKD

BNP/N-terminal-proBNP (NT-proBNP)

4.2.1: In people with GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5), we recommend that serum concentrations of BNP/NT-proBNP be interpreted with caution and in relation to GFR with respect to diagnosis of heart failure and assessment of volume status. (*1B*)

Troponins

4.2.2: In people with GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5), we recommend that serum concentrations of troponin be interpreted with caution with respect to diagnosis of acute coronary syndrome. (*1B*)

Non-invasive testing

4.2.3: We recommend that people with CKD presenting with chest pain should be investigated for underlying cardiac disease and other disorders according to the same local practice for people without CKD (and subsequent treatment should be initiated similarly). (*1B*)

4.2.4: We suggest that clinicians are familiar with the limitations of non-invasive cardiac tests (e.g., exercise electrocardiography [ECG], nuclear imaging, echocardiography, etc.) in adults with CKD and interpret the results accordingly. (*2B*)

4.3: CKD AND PERIPHERAL ARTERIAL DISEASE

4.3.1: We recommend that adults with CKD be regularly examined for signs of peripheral arterial disease and be considered for usual approaches to therapy. (*1B*)

4.3.2: We suggest that adults with CKD and diabetes are offered regular podiatric assessment. (*2A*)

4.4: MEDICATION MANAGEMENT AND PATIENT SAFETY IN CKD

4.4.1: We recommend that prescribers should take GFR into account when drug dosing. (*1A*)

4.4.2: Where precision is required for dosing (due to narrow therapeutic or toxic range) and/or estimates may be unreliable (e.g., due to low muscle mass), we recommend methods based upon cystatin C or direct measurement of GFR. (*1C*)

4.4.3: We recommend temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI. These agents include, but are not limited to: RAAS blockers (including ACE-Is, ARBs, aldosterone inhibitors, direct renin inhibitors), diuretics, NSAIDs, metformin, lithium, and digoxin. (*1C*)

4.4.4: We recommend that adults with CKD seek medical or pharmacist advice before using over-the-counter medicines or nutritional protein supplements. (*1B*)

4.4.5: We recommend not using herbal remedies in people with CKD. (*1B*)

4.4.6: We recommend that metformin be continued in people with GFR ≥ 45 ml/min/1.73 m^2 (GFR categories G1-G3a); its use should be reviewed in those with GFR 30–44 ml/min/1.73 m^2 (GFR category G3b); and it should be discontinued in people with GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5). (*1C*)

4.4.7: We recommend that all people taking potentially nephrotoxic agents such as lithium and calcineurin inhibitors should have their GFR, electrolytes and drug levels regularly monitored. (*1A*)

4.4.8: People with CKD should not be denied therapies for other conditions such as cancer but there should be appropriate dose adjustment of cytotoxic drugs according to knowledge of GFR. (*Not Graded*)

4.5: IMAGING STUDIES

4.5.1: Balance the risk of acute impairment in kidney function due to contrast agent use against the diagnostic value and therapeutic implications of the investigation. (*Not Graded*)

Radiocontrast

4.5.2: We recommend that all people with GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) undergoing elective investigation involving the intravascular administration of iodinated radiocontrast media should be managed according to the *KDIGO Clinical Practice Guideline for AKI* including:

- **Avoidance of high osmolar agents (*1B*);**
- **Use of lowest possible radiocontrast dose (*Not Graded*);**
- **Withdrawal of potentially nephrotoxic agents before and after the procedure (*1C*);**
- **Adequate hydration with saline before, during, and after the procedure (*1A*);**
- **Measurement of GFR 48–96 hours after the procedure (*1C*).**

Gadolinium-based contrast media

4.5.3: We recommend not using gadolinium-containing contrast media in people with GFR <15 ml/min/1.73 m^2 (GFR category G5) unless there is no alternative appropriate test. (*1B*)

4.5.4: We suggest that people with a GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5) who require gadolinium-containing contrast media are preferentially offered a macrocyclic chelate preparation. (*2B*)

Bowel preparation

4.5.5: We recommend not to use oral phosphate-containing bowel preparations in people with a GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) or in those known to be at risk of phosphate nephropathy. (*1A*)

4.6: CKD AND RISKS FOR INFECTIONS, AKI, HOSPITALIZATIONS, AND MORTALITY

CKD and risk of infections

4.6.1: We recommend that all adults with CKD are offered annual vaccination with influenza vaccine, unless contraindicated. (*1B*)

4.6.2: We recommend that all adults with eGFR <30 ml/min/1.73 m^2 (GFR categories G4-G5) and those at high risk of pneumococcal infection (e.g., nephrotic syndrome, diabetes, or those receiving immunosuppression) receive vaccination with polyvalent pneumococcal vaccine unless contraindicated. (*1B*)

4.6.3: We recommend that all adults with CKD who have received pneumococcal vaccination are offered revaccination within 5 years. (*1B*)

4.6.4: We recommend that all adults who are at high risk of progression of CKD and have GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5) be immunized against hepatitis B and the response confirmed by appropriate serological testing. (*1B*)

4.6.5: Consideration of live vaccine should include an appreciation of the patient's immune status and should be in line with recommendations from official or governmental bodies. (*Not Graded*)

4.6.6: Pediatric immunization schedules should be followed according to official international and regional recommedations for children with CKD. (*Not Graded*)

CKD and risk of AKI

4.6.7: We recommend that all people with CKD are considered to be at increased risk of AKI. (*1A*)

4.6.7.1: In people with CKD, the recommendations detailed in the KDIGO AKI Guideline should be followed for management of those at risk of AKI during intercurrent illness, or when undergoing investigation and procedures that are likely to increase the risk of AKI. (*Not Graded*)

CKD and risk of hospitalization and mortality

4.6.8: CKD disease management programs should be developed in order to optimize the community management of people with CKD and reduce the risk of hospital admission. (*Not Graded*)

4.6.9: Interventions to reduce hospitalization and mortality for people with CKD should pay close attention to the management of associated comorbid conditions and cardiovascular disease in particular. (*Not Graded*)

Chapter 5: Referral to specialists and models of care

5.1: REFERRAL TO SPECIALIST SERVICES

5.1.1: We recommend referral to specialist kidney care services for people with CKD in the following circumstances (*1B*):

- **AKI or abrupt sustained fall in GFR;**
- **GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5)*;**
- **a consistent finding of significant albuminuria (ACR ≥ 300 mg/g [≥ 30 mg/mmol] or AER ≥ 300 mg/24 hours, approximately equivalent to PCR ≥ 500 mg/g [≥ 50 mg/mmol] or PER ≥ 500 mg/24 hours);**
- **progression of CKD (see Recommendation 2.1.3 for definition);**
- **urinary red cell casts, RBC >20 per high power field sustained and not readily explained;**
- **CKD and hypertension refractory to treatment with 4 or more antihypertensive agents;**
- **persistent abnormalities of serum potassium;**
- **recurrent or extensive nephrolithiasis;**
- **hereditary kidney disease.**

5.1.2: We recommend timely referral for planning renal replacement therapy (RRT) in people with progressive CKD in whom the risk of kidney failure within 1 year is 10–20% or higher†, as determined by validated risk prediction tools. *(1B)*

*If this is a stable isolated finding, formal referral (i.e., formal consultation and ongoing care management) may not be necessary and advice from specialist services may be all that is required to facilitate best care for the patients. This will be health-care system dependent.
†The aim is to avoid late referral, defined here as referral to specialist services less than 1 year before start of RRT.

GFR categories (ml/min/ 1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90		Monitor	Refer*
	G2	Mildly decreased	60–89		Monitor	Refer*
	G3a	Mildly to moderately decreased	45–59	Monitor	Monitor	Refer
	G3b	Moderately to severely decreased	30–44	Monitor	Monitor	Refer
	G4	Severely decreased	15–29	Refer*	Refer*	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

Referral decision making by GFR and albuminuria. *Referring clinicians may wish to discuss with their nephrology service depending on local arrangements regarding monitoring or referring.

5.2: CARE OF THE PATIENT WITH PROGRESSIVE CKD

5.2.1: We suggest that people with progressive CKD should be managed in a multidisciplinary care setting. (*2B*)

5.2.2: The multidisciplinary team should include or have access to dietary counseling, education and counseling about different RRT modalities, transplant options, vascular access surgery, and ethical, psychological, and social care. (*Not Graded*)

5.3: TIMING THE INITIATION OF RRT

5.3.1: We suggest that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment. This often but not invariably occurs in the GFR range between 5 and 10 ml/min/1.73 m^2. (*2B*)

5.3.2: Living donor preemptive renal transplantation in adults should be considered when the GFR is <20 ml/min/ 1.73 m^2, and there is evidence of progressive and irreversible CKD over the preceding 6–12 months. (*Not Graded*)

5.4: STRUCTURE AND PROCESS OF COMPREHENSIVE CONSERVATIVE MANAGEMENT

5.4.1: Conservative management should be an option in people who choose not to pursue RRT and this should be supported by a comprehensive management program. (*Not Graded*)

5.4.2: All CKD programs and care providers should be able to deliver advance care planning for people with a recognized need for end-of-life care, including those people undergoing conservative kidney care. (*Not Graded*)

5.4.3: Coordinated end-of-life care should be available to people and families through either primary care or specialist care as local circumstances dictate. (*Not Graded*)

5.4.4: The comprehensive conservative management program should include protocols for symptom and pain management, psychological care, spiritual care, and culturally sensitive care for the dying patient and their family (whether at home, in a hospice or a hospital setting), followed by the provision of culturally appropriate bereavement support. (*Not Graded*)

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Introduction: The case for updating and context

Kidney International Supplements (2013) **3,** 15–18; doi:10.1038/kisup.2012.63

Justification for updating the guideline for CKD Definition, Evaluation, Classification, and Stratification from an international perspective

In 2002, the US-based Kidney Disease Outcomes Quality Initiative (KDOQI) group published a guideline on definition, classification and evaluation of chronic kidney disease (CKD). The guideline proposed uniform definitions of CKD together with a staging system[1] and described issues related to measurement of kidney function that had not previously been identified by the clinical community. This publication revolutionized the concept and management of CKD, generating substantial research and controversy, stimulating discussion, and influencing public policy and laboratory practice. The research generated has led to new insights which require contextualizing in the current era, providing the evidence drivers for updating guidance for defining, diagnosing, staging and managing CKD, and promoting improved care of those with early CKD. Successive international controversies conferences, under the direction of Kidney Disease: Improving Global Outcomes (KDIGO), have shaped the scope of this international update through**:**

1. Facilitating global implementation of the definition and classification of CKD, identifying areas of uncertainty, and developing a collaborative research agenda to improve the evidence base and facilitate implementation (November 2004).
2. Evaluating the definition and classification of CKD from a global public health perspective (October 2006).
3. Reviewing the definition and classification of CKD based on data on patient prognosis derived from a unique research collaboration on prognosis (October 2009).

Given the *international* interest in understanding and improving the outcomes of people living with kidney disease and the tremendous amount of data generated since 2002, a need was identified to review, revise, and update the original 2002 KDOQI guideline.

There has been a wealth of published data highlighting the risk of adverse consequences and outcomes in people with albumin excretion rate (AER) >30 mg/24 hours and/or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 (GFR categories G3a-G5), irrespective of the etiology or duration of reduced kidney function. Description of the relationship between GFR, albuminuria and prognosis has significantly improved the understanding of CKD in multiple populations.[2–5] Internationally, the widespread use of albumin-to-creatinine ratio (ACR) and reagent strip urine testing to detect elevated albuminuria together with reporting of estimated GFR (eGFR) has led to easier identification of people with CKD. However elevated albuminuria or reduced GFR alone are not necessarily indicators of need for specialist referral. Clinicians and medical systems are still adjusting to the improved "identification" of CKD and guidance about appropriate stratification of risk and modified action plans for different subgroups of individuals regarding further evaluation, referral, or treatment is needed.

The goal of this guideline is to clarify the definition and classification system of CKD, and to develop appropriate guidance as to the management and care of people with CKD. In addition, we present a framework which should foster an extended collaborative research agenda over the next decade and inform guidelines in the future.

Kidney disease is an important problem worldwide

Kidney disease is defined as an abnormality of kidney structure or function with implications for the health of an individual, which can occur abruptly, and either resolve or become chronic. CKD is a general term for heterogeneous disorders affecting kidney structure and function with variable clinical presentation, in part related to cause, severity and the rate of progression. The concept of CKD evolved after the recognition of the contribution of disordered kidney structure and function on the health of individuals across a wide range of severity.[1] The utility of the concept is that recognition of CKD will have implications for the individual and their care. Kidney failure is traditionally considered as the most serious outcome of CKD. Symptoms are usually due to complications of decreased kidney function and when severe, they can be treated only by dialysis or transplantation. Earlier stages of kidney disease are often asymptomatic, are detected during the evaluation of comorbid conditions, and may be reversible. Rapidly progressive diseases may lead to kidney failure within months but most diseases evolve over decades, and some patients do not progress during many years of follow-up.

Figure 1 shows a conceptual model for the development, progression, and complications of CKD.[1,6] The model includes antecedents associated with increased risk for development of CKD, stages of disease, and complications including death. Risks for development of CKD may be categorized either as susceptibility to kidney disease due to sociodemographic and genetic factors or exposure to factors that can initiate kidney disease. Abnormalities in kidney structure (damage) usually precede abnormalities in function. Outcomes of CKD may be progression, as shown by the horizontal arrows, and complications, as shown by the diagonal arrows, or both.

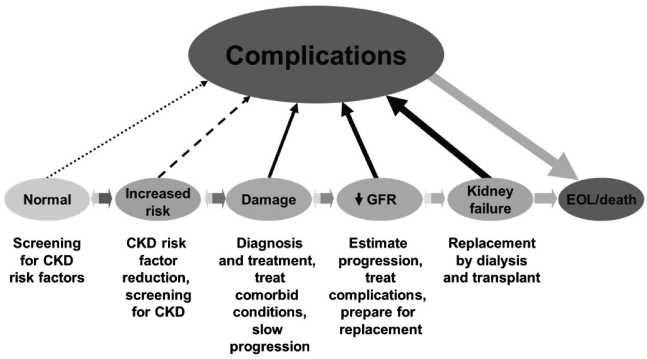


Figure 1 | Conceptual model of CKD. Continuum of development, progression, and complications of CKD and strategies to improve outcomes. Horizontal arrows between circles represent development, progression, and remission of CKD. Left-pointing horizontal arrowheads signify that remission is less frequent than progression. Diagonal arrows represent occurrence of complications of CKD, including drug toxicity, endocrine and metabolic complications, cardiovascular disease, and others such as infection, cognitive impairment, and frailty. Complications might also arise from adverse effects of interventions to prevent or treat the disease. CKD, chronic kidney disease; EOL, end-of-life care and/or conservative management; GFR, glomerular filtration rate. Adapted from Levey AS, Stevens LA, Coresh J.[6] Conceptual model of CKD: applications and implications. Am J Kidney Dis. 2009; 53:S4-16 with permission from the National Kidney Foundation; accessed http://download.journals.elsevierhealth.com/pdfs/journals/0272-6386/PIIS02726386080 17186.pdf

Although the need for treatment of chronic kidney failure with dialysis and/or kidney transplantation arises in only 1% of people with CKD, it remains the most expensive of chronic diseases and reduces lifespan significantly. The costs of dialysis and transplantation consume disproportionate amounts within the health-care budgets in all jurisdictions (5% of annual budgets consumed by less than 1% of the population). Failure to recognize CKD results in neglect of its consequences and complications, and late referral of people with advanced CKD resulting in worse renal replacement therapy (RRT) outcomes. In addition, there is a growing body of evidence that indicates people with CKD are at increased risk of acute kidney injury (AKI), which is also associated with poor outcomes and may accelerate progression of CKD. Therefore, identification of people at earlier time points in the trajectory of CKD, with appropriate management and earlier referral of those who would benefit from specialist kidney services, should lead to both economic and clinical benefits.

In those countries where access to dialysis and transplantation services may be limited or unavailable, the final consequence of progressive CKD is death. In all locations, irrespective of availability of dialysis and transplantation, early identification of CKD therefore assumes great importance, as delay or prevention of progression has the potential to prolong health and save lives for much lower cost than RRT. Although etiologies vary in frequency or absolute numbers in different countries, the proportion of people with important antecedents to CKD, such as diabetes, is growing alarmingly worldwide in both developed and developing countries.

Complications of CKD affect all organ systems. Kidney failure leads to the commonly recognized symptoms of uremia. Less severe CKD has been recognized as an independent risk factor for cardiovascular disease (CVD) and other common conditions affecting the elderly, such as infection and impairments in physical function and cognition. In addition, CKD is associated with increased risk from adverse effects of drugs, intravascular radiocontrast administration, surgery and other invasive procedures. Altogether, these complications are associated with higher morbidity, mortality and cost. If CKD is detected early, the associated complications and the progression to kidney failure can be delayed or even prevented through appropriate interventions. Regular testing of high-risk groups (i.e., people with diabetes, hypertension, CVD, structural renal tract disease, multisystem diseases with potential kidney involvement such as systemic lupus erythematosus, family history of kidney failure, hereditary kidney disease, the elderly, those receiving potential nephrotoxic drugs or those opportunistically found to have hematuria or proteinuria) can give an early indication of kidney damage, thus permitting the introduction of available interventions at an early stage, and the testing of novel interventions with potential added value.

Factors associated with progression of CKD and with increased cardiovascular risk are overlapping to a large extent. Thus targeting of those risk factors that are modifiable may both reduce CVD in people with CKD and reduce progression of CKD to end-stage renal disease (ESRD). There is strong evidence that blockade of the renin-angiotensin-aldosterone system (RAAS) is a blood pressure (BP) lowering strategy which is more effective in reducing risk of kidney and cardiovascular disease in the presence of albuminuria.

The development of guidance for health-care providers will provide opportunities to improve the care of people with kidney disease. We hope that this publication serves to stimulate strategic research initiatives from basic, translational, clinical and health outcome perspectives.

General summary for the reader: what you will and will not find in this guideline

1. The guideline will offer best practice and evidence-based advice on the evaluation and approach to management of CKD.
   a. The target population for the guideline is all people identified with CKD who are not on RRT (i.e., not on dialysis or have not received a kidney transplant).
   b. The target population includes adults and children. The guideline will cover the spectrum of individuals with CKD, from children to the elderly who form important subgroups, underscoring current issues at the extremes of age with respect to the evidence base, especially in relation to implementation and management issues. Where the guideline does not apply to

children, statements to that effect will be made. It is beyond the scope of this guideline to address all issues related to children with CKD, given the heterogeneous nature of this group of individuals who range from newborn to post-adolescents, with specific physiological differences within each of those groups. Specific evidence and rationale will be articulated as appropriate in each section.

c. The target condition is CKD of any or unknown etiology. Identifying the cause of the CKD is strongly encouraged, both because treatment may need to be adjusted according to etiology and because it influences the prognosis and relative importance of risk factors associated with CKD. A comprehensive list of possible etiologies is not practical and guidance on detailed work-up for specific causes of CKD is beyond the scope of this document (readers will be referred to other pertinent sources). We will describe how knowledge of the etiology of CKD in an individual may be important in prognostication and management.

d. The target audience of the guideline includes nephrologists, primary care physicians, non-nephrology specialists (e.g., cardiologists, diabetologists, etc), clinical chemists and other practitioners caring for adults and children with CKD. The guideline is also expected to be suitable for use in public policy and other health-care arenas.

e. As a global guideline it is written for use in different health-care settings, but unavoidably its full implementation relies on health-care resources that are not universally available. We recognize this overtly in some of the discussion sections within the guideline.

f. The target health-care settings include primary, secondary, and tertiary care.

2. The guideline will provide information, advice, and education to support self-management for people with CKD and aid caregivers with the diagnosis and management of CKD. To avoid redundancy and potential for becoming outdated, the reader is asked to refer to existing KDIGO guidance on anemia, metabolic bone disease, BP, AKI, hepatitis C, lipid management, glomerulonephritis (GN) and other pertinent guidelines.
3. The guideline will provide a blueprint for an approach to CKD care in an international context. While the guideline will be sensitive to issues related to ethnicity and also geographical considerations, it is expected that subsequent regional adaptation will be required for specific health-care settings or contexts.
4. Research recommendations in general are described to inform a framework for ongoing research agendas in the international community. We have attempted to identify important study questions in need of answers. Through identification of gaps in knowledge, the reader will be better able to define methodologies, definitions of populations, and outcome measures of relevance to study designs in the future.

Topics that will not be covered

This document is not intended to provide enough detail to replace training and education in nephrology, nor is it intended to serve as a textbook of medicine or nephrology.

Thus, there are some specific topics that will not be covered. Specifically we will not discuss:

1. Evaluation and management of people receiving RRT (management of kidney failure by dialysis or kidney transplantation).
2. Specific approaches to the diagnosis of people with AKI and other acute kidney diseases. This topic has been extensively reviewed in *KDIGO Clinical Practice Guideline for Acute Kidney Injury.*[7]
3. Diagnostic work-up or treatment of specific causes of CKD, including GN.[8]
4. Management of pregnancy in women with CKD or of pregnant women who develop kidney disease.
5. Detailed management of endocrine and metabolic complications of CKD. These are reviewed extensively by recent KDIGO guidelines on CKD-MBD,[9] management of BP[10] and anemia[11] in CKD.
6. Detailed management of CVD and CVD risk factors in CKD. This is reviewed in a recent KDIGO publication.[12]
7. Drug dosing in CKD. This topic has been addressed in a recent KDIGO publication.[13]
8. Details of resource implications and barriers to implementation are beyond the scope of this guideline. By virtue of its being international, the variability in these aspects by country, region, and even jurisdiction is vast. We look to the individual commentaries from around the world to inform those aspects more fully.

Brief overview on methodology

The Work Group included an international group of kidney specialists, primary care physicians, diabetologists, epidemiologists, clinical chemists, administrators, and a professional Evidence Review Team (ERT) who provided support and guidance to the group. Details of the methods used by the ERT are described in *Methods for Guideline Development*, along with the systematic searches for areas identified by Work Group members and performed by the ERT.

The recommendations and statements created herein will serve to direct both care and research in the next decade. Importantly, we expect the renewed classification system and risk stratification concepts to direct research and enrollment into trials which address test therapies to improve patient outcomes.

Statement grading and wording. The methods for formulating recommendations were based on modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, and have used the words

Table 1 | KDIGO nomenclature and description for grading recommendations

	Implications		
Grade*	Patients	Clinicians	Policy
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category "Not Graded" was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

'recommend' when the balance of evidence would support the notion that the majority of patients would benefit from the implementation of this recommendation. The words 'suggest' are used when the balance of evidence would support the notion that some patients would benefit from the implementation of the recommendation, but that individual patient, physician and health-care system considerations would be necessary to adopt the practice. There are also ungraded statements many of which are often key practice points or educational issues (Table 1). The Work Group had struggled whether to organize them differently or move them to the rationale section. Ultimately they remain here in the guideline statement format so that they are not overlooked by those wishing to understand the condition better.

A significant proportion of statements in this guideline are ungraded because the grading system is most appropriate for statements of intervention. The international system, GRADE, allows for such statements which guide thoughts and attitude, and not specific actions. In the descriptive statements identifying, classifying, and defining the condition of CKD, grading is not possible. Since few studies have compared different methods of evaluation or care models, those statements too are difficult to grade. Thus, grading of specific statements is reserved for interventions or alternative diagnostic test strategies for which there is a substantial body of evidence.

Consideration of health benefits, side effects, and risks. These have been considered when formulating the recommendations but given the paucity of data in many of the areas reviewed, this has been less consistent than the Work Group would have liked. We see this as an area of research and future study that will inform future updates.

Review process. As with all KDIGO guidelines a two step process was used. This included a review by the Board of Directors, with feedback to the Work Group Chairs followed by revisions to the document. The public review, consisting of interested stakeholders from international communities, organizations and individuals, was then undertaken. The draft document was sent to a total of 2320 external reviewers, with 293 responses received and tabulated. The feedback was carefully reviewed and where appropriate, suggested changes were incorporated into the final document. In the interest of transparency, the Work Group prepared individual responses to each reviewer comment and these will be posted on the KDIGO website.

Planned update. At the current time there is no official plan to update the guideline in its entirety. Given the breadth and depth of the current undertaking and with knowledge of new studies and applications of some of these recommendations, the Work Group recommends that individual sections of this guideline be updated every 3-5 years as new evidence becomes available. We believe that this will be more practical for the readership.

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Chapter 1: Definition and classification of CKD

Kidney International Supplements (2013) **3,** 19–62; doi:10.1038/kisup.2012.64

1.1: DEFINITION OF CKD

1.1.1: CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health (Table 2). (*Not Graded*)

RATIONALE

The definition of CKD remains intact, but we have clarified the classification and risk stratification as indicated below. The addition of 'with implications for health' is intended to reflect the notion that a variety of abnormalities of kidney structure or function may exist, but not all have implications for health of individuals, and therefore need to be contextualized.

Kidney damage refers to a broad range of abnormalities observed during clinical assessment, which may be insensitive and non-specific for the cause of disease but may precede reduction in kidney function (Table 2). Excretory, endocrine and metabolic functions decline together in most chronic kidney diseases. GFR is generally accepted as the best overall index of kidney function. We refer to a GFR <60 ml/min/1.73 m^2 as decreased GFR (Table 2) and a GFR <15 ml/min/1.73 m^2 as kidney failure. AKI may occur in patients with CKD and hasten the progression to kidney failure.[14]

Complications include drug toxicity, metabolic and endocrine complications, increased risk for CVD, and a variety of other recently recognized complications, including infections, frailty, and cognitive impairment.[15–18] Complications may occur at any stage, often leading to death without progression to kidney failure. Complications may also arise from adverse effects of interventions to prevent or treat the disease and associated comorbidity.

Criteria for CKD

Defining terms: The following section aims to define specific terms and concepts so as to ensure clarity among all users. In addition, the rationale for including these terms is included.

Table 3 provides a justification for the criteria for CKD. The criteria for definition of CKD are objective and can be ascertained by means of simple laboratory tests without identification of the cause of disease, thereby enabling detection of CKD by non-nephrologist physicians and other health professionals.

Duration >3 Months

Kidney diseases may be acute or chronic. We explicitly but arbitrarily define duration of >3 months (>90 days) as delineating "chronic" kidney disease. The rationale for defining chronicity is to differentiate CKD from acute kidney diseases (such as acute GN), including AKI, which may require different interventions, and have different etiologies and outcomes.[7] We did not define acute kidney disease (AKD) because there does not appear be an evidence base for a precise definition.

The duration of kidney disease may be documented or inferred based on the clinical context. For example, a patient with decreased kidney function or kidney damage in the midst of an acute illness, without prior documentation of kidney disease, may be inferred to have AKI. Resolution over days to weeks would confirm the diagnosis of AKI. A patient with similar findings in the absence of an acute illness may be inferred to have CKD, and if followed over time would be confirmed to have CKD. In both cases, repeat ascertainment of kidney function and kidney damage is recommended for accurate diagnosis. The timing of the evaluation depends on clinical judgment, with earlier evaluation for the patients suspected of having AKI and later evaluation for the patient suspected of having CKD. For further details on the *Evaluation of CKD*, see Chapter 1.4.

Reversibility. Most kidney diseases do not have symptoms or findings until later in their course and are detected only when they are chronic. Most causes of CKD are irreversible with a life-long course, and treatment aimed at slowing progression to kidney failure. However, chronicity is not synonymous with irreversibility. In some cases, CKD is entirely reversible, either spontaneously or with treatment, and in other cases, treatment can cause partial regression of kidney damage and improvement in function (e.g., immunosuppressive therapies for GN). Even kidney failure may be reversed with transplantation. Because of the long course of most cases of CKD, patients often have one or more episodes of AKI, superimposed upon CKD.

Decreased GFR

The kidney has many functions, including excretory, endocrine and metabolic functions. The GFR is one component of excretory function, but is widely accepted as the best overall index of kidney function because it is generally reduced after widespread structural damage and most other kidney functions decline in parallel with GFR in CKD.

We chose a threshold of GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) for >3 months to indicate CKD. A GFR <60 ml/min/1.73 m^2 is less than half of the normal value in young adult men and women of approximately 125 ml/min/1.73 m^2. Figure 2 shows a compilation of GFR measurements in apparently healthy men and women in the US and Europe by age from more than 40 years ago.[20] The age-associated GFR decline is observed in longitudinal as well as cross

Table 2 | Criteria for CKD (either of the following present for >3 months)

Markers of kidney damage (one or more)	Albuminuria (AER ≥ 30 mg/24 hours; ACR ≥ 30 mg/g [≥ 3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR < 60 ml/min/1.73 m^2 (GFR categories G3a-G5)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

Table 3 | Criteria for definition of CKD[19]

Criteria	Comment
Duration >3 months, based on documentation or inference	Duration is necessary to distinguish chronic from acute kidney diseases ● Clinical evaluation will often enable documentation or inference of duration ● Documentation of duration is usually not declared in epidemiologic studies
GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5)	GFR is the best overall index of kidney function in health and disease ● The normal GFR in young adults is approximately 125 ml/min/1.73 m^2. GFR <15 ml/min/1.73 m^2 (GFR category G5) is defined as kidney failure ● Decreased GFR can be detected by current estimating equations for GFR based on SCr or cystatin C but not by SCr or cystatin C alone ● Decreased eGFR can be confirmed by measured GFR, if required
Kidney damage as defined by structural abnormalities or functional abnormalities other than decreased GFR	Albuminuria as a marker of kidney damage [increased glomerular permeability], urine AER ≥30 mg/24 hours, approximately equivalent to urine ACR ≥ 30 mg/g (≥ 3 mg/mmol)* ● The normal urine ACR in young adults is <10 mg/g (<1 mg/mmol) ● Urine ACR 30-300 mg/g (3–30 mg/mmol; category A2) generally corresponds to "microalbuminuria," now referred to as "moderately increased" ● Urine ACR >300 mg/g (>30 mg/mmol; category A3) generally corresponds to "macroalbuminuria," now termed "severely increased" ● Urine ACR > 2200 mg/g (220 mg/mmol) may be accompanied by signs and symptoms of nephrotic syndrome (e.g., low serum albumin, edema, and high serum cholesterol) ● Threshold value corresponds approximately to urine reagent strip values of trace or +, depending on urine concentration. ● High urine ACR can be confirmed by urine albumin excretion in a timed urine collection expressed as AER Urinary sediment abnormalities as markers of kidney damage ● Isolated non-visible (microscopic) hematuria with abnormal RBC morphology (anisocytosis) in GBM disorders ● RBC casts in proliferative glomerulonephritis ● WBC casts in pyelonephritis or interstitial nephritis ● Oval fat bodies or fatty casts in diseases with proteinuria ● Granular casts and renal tubular epithelial cells in many parenchymal diseases (non-specific) Renal tubular disorders ● Renal tubular acidosis ● Nephrogenic diabetes insipidus ● Renal potassium wasting ● Renal magnesium wasting ● Fanconi syndrome ● Non-albumin proteinuria ● Cystinuria Pathologic abnormalities detected by histology or inferred (examples of causes) ● Glomerular diseases (diabetes, autoimmune diseases, systemic infections, drugs, neoplasia) ● Vascular diseases (atherosclerosis, hypertension, ischemia, vasculitis, thrombotic microangiopathy) ● Tubulointerstitial diseases (urinary tract infections, stones, obstruction, drug toxicity) ● Cystic and congenital diseases

Table 3 | Continued

Criteria	Comment
	Structural abnormalities as markers of kidney damage detected by imaging (ultrasound, computed tomography and magnetic resonance with or without contrast, isotope scans, angiography) ● Polycystic kidneys ● Dysplastic kidneys ● Hydronephrosis due to obstruction ● Cortical scarring due to infarcts, pyelonephritis or associated with vesicoureteral reflux ● Renal masses or enlarged kidneys due to infiltrative diseases ● Renal artery stenosis ● Small and hyperechoic kidneys (common in more severe CKD due to many parenchymal diseases)
	History of kidney transplantation ● Kidney biopsies in most kidney transplant recipients have histopathologic abnormalities even if GFR is >60 ml/min/1.73 m^2 (GFR categories G1-G2) and ACR is <30 mg/g (<3 mg/mmol) ● Kidney transplant recipients have an increased risk for mortality and kidney failure compared to populations without kidney disease ● Kidney transplant recipients routinely receive subspecialty care

Abbreviations: ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; GFR, glomerular filtration rate; RBC, red blood cell; SCr, serum creatinine; WBC, white blood cell.
*For conversion, see Table 7, Chapter 1

sectional studies, but varies substantially among individuals within the population.[21] More recent data in kidney donors confirm these general trends.[22,23] Limited data are available for non-whites in the US and Europe or in other countries, although data suggest that the normal range for measured GFR and the age-associated decline is similar.[24–26]

A GFR <60 ml/min/1.73 m^2 can be detected by routine laboratory testing. Current estimating equations for GFR (eGFR) based on serum creatinine (SCr), but not SCr alone, are sensitive for detecting measured GFR <60 ml/min/1.73 m^2.[27] A decreased eGFR using SCr can be confirmed by GFR estimation using an alternative filtration marker (cystatin C) or GFR measurement, as necessary.

A GFR <60 ml/min/1.73 m^2 is associated with a higher risk of complications of CKD than in subjects with CKD and conserved GFR. The causal mechanisms underlying these associations are not fully understood. We consider three main types of complications, which are of relevance to all patients with CKD and reduced GFR, irrespective of country, age or etiology:

Drug toxicity. Altered pharmacokinetics of drugs excreted by the kidney and an increased risk of drug-interactions are common and require adjustment in the dosage of many drugs (see Chapter 4.4).[13] At lower GFR, altered pharmacokinetics and pharmacodynamics of drugs not excreted by the kidney may also be observed. Errors in drug dosing are common in patients with CKD and may be associated with toxicity to the kidney (resulting in AKI) or systemic toxicity, resulting in threats to patient safety.

Metabolic and endocrine complications. As GFR declines a variety of complications reflecting loss of endocrine or exocrine function of the kidneys develop including anemia, acidosis, malnutrition, bone and mineral disorders (described in Chapters 3 and 4).

Risk of CVD and death. A meta-analysis by the CKD Prognosis Consortium demonstrated associations of eGFR <60 ml/min/1.73 m^2 with subsequent risk of all-cause and cardiovascular mortality, kidney failure, AKI, and CKD progression in the general population and in populations with increased risk for CVD.[3-5] Figure 3 shows the relationship for total and cardiovascular mortality in general population cohorts. The risk for all outcomes was relatively constant between eGFR of 75-105 ml/min/1.73 m^2, with a suggestion of a U-shaped curve for total mortality. The increased relative risk (RR) for all outcomes was significant for eGFR of <60 ml/min/1.73 m^2.

Kidney Damage

Damage to the kidney can be within the parenchyma, large blood vessels or collecting systems, and is most often inferred from markers rather than direct examination of kidney tissue. The markers of kidney damage often provide a clue to the likely site of damage within the kidney and in association with other clinical findings, the cause of kidney disease.

Proteinuria. Proteinuria is a general term for the presence of increased amounts of protein in the urine. Proteinuria may reflect abnormal loss of plasma proteins due to a) increased glomerular permeability to large molecular weight proteins (albuminuria or glomerular proteinuria), b) incomplete tubular reabsorption of normally filtered low-molecular-weight proteins (tubular proteinuria), or c) increased plasma concentration of low-molecular-weight proteins (overproduction proteinuria, such as immunoglobulin light chains). Proteinuria may also reflect abnormal loss of proteins derived from the kidney (renal tubular cell constituents due to tubular damage) and lower urinary tract. Albuminuria, tubular proteinuria and renal tubular cell constituents are pathognomonic of kidney damage. In addition, findings

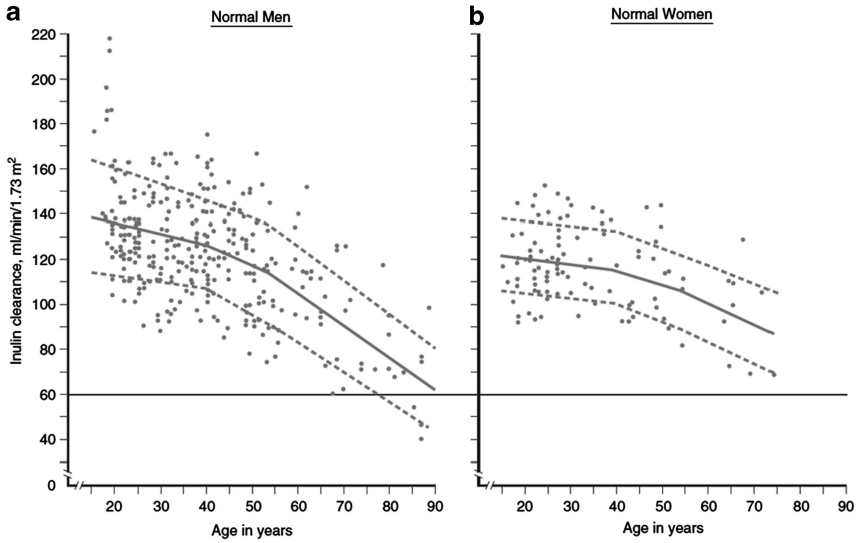


Figure 2 | Normal values for GFR by age. GFR is shown for men (Panel **a**) and women (Panel **b**) of various ages, with the GFR measured as the urinary clearance of inulin. The horizontal line indicates a GFR value of 60 ml/min/1.73 m^2, which is the threshold for the definition of CKD. Solid lines represent the mean value of GFR per decade of age, and dashed lines represent the value 1 SD from the mean value of GFR per decade of age. CKD, chronic kidney disease; GFR, glomerular filtration rate; SD, standard deviation. Adapted with permission from Wesson L.[20] Physiology of the Human Kidney. Grune & Stratton: New York, 1969.

from experimental and clinical studies have suggested an important role for proteinuria in the pathogenesis of disease progression of CKD.[28]

Albuminuria. Albuminuria refers to abnormal loss of albumin in the urine. Albumin is one type of plasma protein found in the urine in normal subjects and in larger quantity in patients with kidney disease.

For a number of reasons, clinical terminology is changing to focus on albuminuria rather than proteinuria: a) albumin is the principal component of urinary protein in most kidney diseases; recent recommendations for measurement of urine proteins emphasize quantification of albuminuria rather than total protein; b) recent epidemiologic data from studies around the world demonstrate a strong graded relationship of the quantity of urine albumin with both kidney and CVD risk; and c) later recommendations in these guidelines classify kidney disease by level of albuminuria. In this guideline, we will refer to proteinuria when discussing general concepts and will refer either to total protein, albumin or other specific proteins when discussing measurements, patterns, and interpretation of proteinuria.

Albuminuria is a common but not uniform finding in CKD. It is the earliest marker of glomerular diseases, including diabetic glomerulosclerosis, where it generally appears before the reduction in GFR. It is a marker of hypertensive nephrosclerosis but may not appear until after the reduction in GFR. It is often associated with underlying hypertension, obesity, and vascular disease, where the underlying renal pathology is not known.

Normative values for albuminuria and proteinuria are generally expressed as the urinary loss rate. The urinary loss rate of albumin and protein has commonly been referred to as AER and protein excretion rate (PER), respectively, although in the strict physiological sense they are not excreted. The terms AER and PER will be retained herein.

We chose a threshold for urinary AER of $\geq$30 mg/24 hours sustained for $>$3 months to indicate CKD. This value is considered to be approximately equivalent to an ACR in a random untimed urine sample of $\geq$30 mg/g or $\geq$3 mg/mmol. The rationale for this threshold is as follows:

- An AER of $\geq$30 mg/24 hours (ACR $\geq$30 mg/g [$\geq$3 mg/mmol]) is greater than 3 times the normal value in young adult men and women of approximately 10 mg/24 hours (ACR 10 mg/g or 1 mg/mmol).
- An AER of $\geq$30 mg/24 hours (ACR $\geq$30 mg/g [$\geq$3 mg/mmol]) may sometimes be detectable as 'trace' using a urine reagent strip, depending on urine concentration, but this is not a consistent finding until AER exceeds approximately 300 mg/24 hours (ACR $\geq$300 mg/g [$\geq$30 mg/mmol]). As described later, trace or positive reagent strip values/readings can be confirmed by ACR, and an elevated ACR can be confirmed by urine AER in a timed urine collection, as necessary.
- An AER $\geq$30 mg/24 hours (ACR $\geq$30 mg/g [$\geq$3 mg/mmol]) is associated with an increased risk for complications of CKD. A meta-analysis by the CKD Prognosis Consortium demonstrated associations of an ACR $\geq$30 mg/g ($\geq$3 mg/mmol) or reagent strip 1+ protein with subsequent risk of all-cause and cardiovascular mortality, kidney failure, AKI, and CKD progression in the general population and in populations with increased risk for CVD[3-5] (Figure 4).

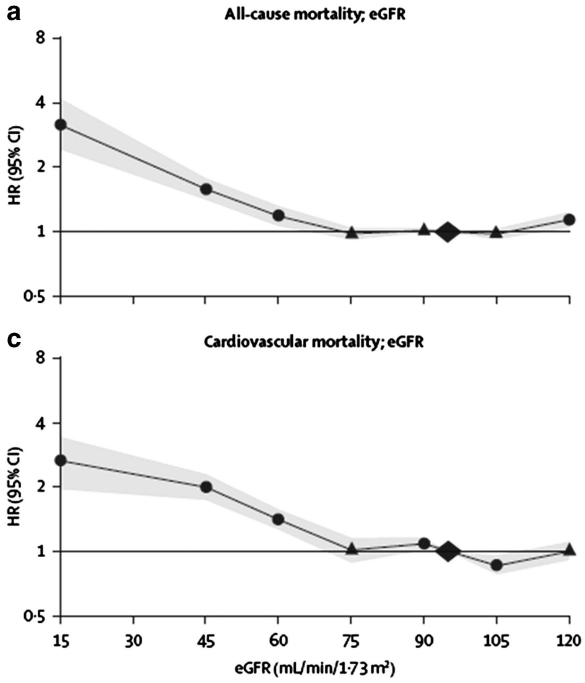


Figure 3 | Relationship of eGFR with mortality. HRs and 95% CIs for all-cause (**a**) and cardiovascular mortality (**c**) according to spline eGFR. HRs and 95% CIs (shaded areas) are adjusted for ACR, age, sex, ethnic origin, history of CVD, systolic BP, diabetes, smoking, and total cholesterol. The reference (diamond) was eGFR 95 ml/min/1.73 m^2 and ACR 5 mg/g (0.6 mg/mmol), respectively. Circles represent statistically significant and triangles represent not significant. ACR, albumin-to-creatinine ratio; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio. Reprinted from The Lancet, vol 375, Matshushita K, van de Velde M, Astor BC, et al.[4] Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis, p. 2073-2081, 2010, with permission from Elsevier; accessed http://download.thelancet.com/pdfs/journals/lancet/PIIS0140673610606745.pdf

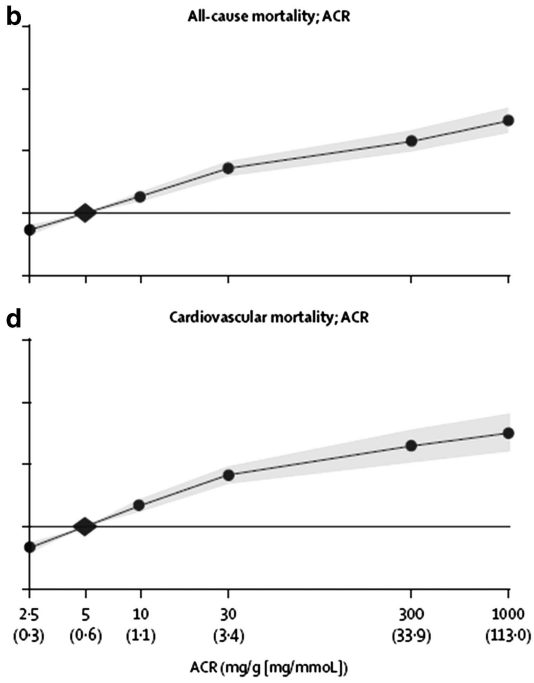


Figure 4 | Relationship of albuminuria with mortality. HRs and 95% CIs for all-cause (**b**) and cardiovascular mortality (**d**) according to ACR. HRs and 95% CIs (shaded areas) are adjusted for age, sex, ethnic origin, history of CVD, systolic BP, diabetes, smoking, and total cholesterol and spline eGFR. The reference (diamond) was ACR 5 mg/g (0.6 mg/mmol) and eGFR 95 ml/min/1.73 m^2, respectively. Circles represent statistically significant and triangles represent not significant. ACR plotted in mg/g. To convert ACR in mg/g to mg/mmol multiply by 0.113. Approximate conversions to mg/mmol are shown in parentheses. ACR, albumin-to-creatinine ratio; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio. Reprinted from The Lancet, vol 375, Matshushita K, van de Velde M, Astor BC, et al.[4] Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis, p. 2073-2081, 2010, with permission from Elsevier; accessed http://download.thelancet.com/pdfs/journals/lancet/PIIS0140673610606745.pdf

Urine sediment abnormalities. Formed elements, such as cells, casts, crystals, and microorganisms may appear in the urine sediment in a variety of disorders of the kidney and urinary tract, but renal tubular cells, red blood cell (RBC) casts, white blood cell (WBC) casts, coarse granular casts, wide casts, and large numbers of dysmorphic RBCs are pathognomonic of kidney damage.

Electrolyte and other abnormalities due to tubular disorders. Abnormalities of electrolytes and other solutes may result from disorders of renal tubular reabsorption and secretion. These syndromes are uncommon but pathognomonic of kidney disease. Often the diseases are genetic without underlying pathologic abnormalities. Other diseases are acquired, due to drugs or toxins, and are usually with prominent tubular pathologic lesions.

Pathologic abnormalities directly observed in kidney tissue obtained by biopsy. Evidence of abnormalities of renal parenchyma in kidney biopsies irrespective of eGFR or other markers of kidney damage must be acknowledged as an important parameter in defining kidney damage. The pathologic classification of diseases of the renal parenchyma reflects the localization of the disease to glomeruli, vessels, tubules and interstitium, or cysts. Renal biopsies are performed in the minority of CKD patients.

Imaging abnormalities. Imaging techniques allow the diagnosis of diseases of the renal structure, vessels and/or collecting systems. Thus, patients with significant structural abnormalities are considered to have CKD if the abnormality persists for greater than 3 months (note that this does not include simple cysts and clinical context is required for action).

History of kidney transplantation. Kidney transplant recipients are defined as having CKD, irrespective of the level of GFR or presence of markers of kidney damage. The rationale

for this designation is that biopsies in kidney transplant recipients reveal pathologic abnormalities even in patients without decreased GFR or albuminuria. Kidney transplant recipients have an increased risk of mortality and kidney outcomes compared to the general population and they require specialized medical management.[29]

Implications for Health

CKD is associated with a wide range of complications leading to adverse health outcomes. For some complications, the causal pathway between kidney disease and adverse outcomes is well-known. For these complications, there are clinical practice guidelines for testing and treatment for modifiable factors to prevent adverse outcomes. Since 2002 a large number of epidemiologic studies have linked decreased GFR and albuminuria to the risk of adverse health outcomes not previously identified as CKD complications. The exploration of the mechanisms for the relationships of CKD with these complications is a rapidly growing topic for basic and clinical research. Because of the high prevalence, adverse outcomes, and high cost of CKD, especially kidney failure, some countries have developed public health programs for early identification and treatment of CKD and its complications. The effectiveness of these programs is being evaluated.

Implications for Clinical Practice and Public Policy

CKD was first defined in the 2002 KDOQI Guidelines and endorsed at subsequent KDIGO Controversies Conferences with minor modifications.[30,31] The definition of CKD proposed here is intended for use in clinical practice, research and public health, and has not changed. Thus, the updated version does not change any of the initiatives that have been commenced with respect to public policy. We recognize the variation around the world regarding measurement of urine albumin versus total protein in clinical practice, and we anticipate variation in implementation of the guideline until more widespread dissemination of the guideline has occurred. For additional discussion about methods for ascertainment of urine albumin versus total protein, see Recommendation 1.4.4 (Evaluation of albuminuria). The implications of highlighting the importance of albuminuria for general practitioners in evaluation and prognostication may help with identification and care planning. Nonetheless, a number of concerns about the definition remain, which are clarified below.[30,32–36]

Areas of Controversy, Confusion, or Non-consensus and Clarification of Issues and Key Points

General concerns:

a) The use of single thresholds without consideration of patient specific factors

The use of single thresholds to define decreased GFR and increased AER, without consideration for cause of disease, age, sex, race-ethnicity and clinical context is consistent with the use of single thresholds for disease markers to define other chronic non-communicable diseases, such as hypertension, diabetes, and hypercholesterolemia, that primarily affect the elderly and are associated with an increased risk for cardiovascular mortality. Biologic variability and error in ascertainment of GFR and AER can lead to misclassification and false negative and false positive diagnosis. Furthermore, these single thresholds appear to differentiate groups of individuals and outcomes, irrespective of specific patient characteristics in a multitude of studies. However, they correspond to thresholds for RRs for complications, rather than predictions of absolute risk. Furthermore, as with any diagnostic tests, findings must be interpreted with considerations of likelihood of disease based on the clinical context but this should not negate the application of a standard definition for CKD.

Specific concerns:

b) Relationship of CKD criteria to aging

Epidemiologic studies show an increased prevalence of decreased eGFR and increased ACR in older subjects. There has been vigorous debate as to whether decreased GFR or increased ACR in older people represent a disease or "normal aging." Numerous studies show pathologic abnormalities associated with aging, including glomerular sclerosis, tubular atrophy and vascular sclerosis. The cause for this association is not clear but has been hypothesized to reflect disparate processes, such as vascular disease or senescence.[37–39] Irrespective of cause, there appears to be increased risk associated with decreased eGFR or increased ACR in older people, and for this reason, we consider all individuals with persistently decreased GFR or increased albuminuria to have CKD. Comparison of the magnitude of risk to younger individuals is complicated. As with other CVD risk factors, absolute risk appears to be higher in older than in younger individuals, but RR appears to be lower.[3-5] Note is also made that healthy older individuals do not necessarily have decreased GFR, so that while one may expect some decline, levels below 60 ml/min/1.73 m^2 in individuals without comorbidity is the exception.[20]

c) Isolated decreased GFR without markers of kidney damage

A variety of clinical circumstances are associated with GFR <60 ml/min/1.73 m^2 for >3 months in the absence of known structural alterations. Below are examples of these conditions and the rationale for considering them as CKD:

- ***Heart failure, cirrhosis of the liver, and hypothyroidism***. Decreased GFR complicates the management of the primary disease and patients with these disorders with decreased GFR have a worse prognosis than those without decreased GFR. In addition, renal biopsy in these patients may reveal renal parenchymal lesions.
- ***Kidney donors***. The usual level of GFR in kidney donors after transplantation is approximately 70% of the pre-donation level, in the range of 60-90 ml/min/1.73 m^2 in most donors. However, a minority of donors have GFR <60 ml/min/1.73 m^2. The prognosis of these donors

compared to those with higher GFR has not been carefully studied. However, as with decreased GFR due to recognized kidney diseases, donors with decreased GFR require closer follow-up for adjustment of drug doses.

- ***Malnutrition***. The level of GFR is affected by habitual protein intake.[40] Healthy adults with lower protein intake may have lower mean GFR, but usually do not have GFR <60 ml/min/1.73 m^2. Older studies of patients with protein-calorie malnutrition and more recent studies of subjects with anorexia nervosa have documented reduced measured GFR that can improve following restoration of nutritional status. However, renal biopsies may reveal structural abnormalities in these conditions and decreased GFR can complicate their management.

d) Isolated albuminuria without decreased GFR

As described later, transient ACR ≥ 30 mg/g (≥ 3 mg/mmol) can occur in disorders other than CKD. Remission of albuminuria within 3 months in association with recovery from these disorders is not defined as CKD. Patients with persistent albuminuria would be considered to have CKD. Below are examples of these conditions and the rationale for considering them as CKD:

- ***Obesity and metabolic syndrome.*** Albuminuria can be associated with obesity and metabolic syndrome, and can remit during weight loss. The mechanism of albuminuria in these conditions is not known but renal biopsies may reveal prominent vascular lesions. Patients with obesity and metabolic syndrome are at increased risk for development of diabetes and hypertension. The risk of persistent albuminuria in this condition has not been carefully studied.
- ***Orthostatic (postural) proteinuria.***[41] Albuminuria may rarely be observed in the upright but not recumbent posture in patients with the syndrome of postural proteinuria. This condition is not associated with an increased risk of long-term adverse outcomes but a thorough evaluation is required to exclude other causes of CKD. Exclusion is generally possible by studying a first pass early morning urine (EMU) after overnight recumbency: total protein loss of >1000 mg/24 hours is unlikely to be explained by orthostatic proteinuria.

e) Remission of decreased GFR or markers of kidney damage

If decreased GFR and markers of kidney damage resolve while on treatment, the patient would be considered to have treated CKD, consistent with nomenclature for treated hypertension, treated diabetes, or treated hypercholesterolemia if blood pressure, blood glucose and blood cholesterol are within normal range while on medications. If resolution of decreased GFR and markers of kidney damage is sustained after withdrawal of treatment, the patient would be considered to have a history of CKD.

f) Kidney disease in the absence of decreased GFR and markers of kidney damage

A GFR ≥ 60 ml/min/1.73 m^2 may reflect a decline from a higher value, and an AER of <30 mg/24 hours (ACR <30 mg/g or <3 mg/mmol) may reflect a rise from a lower value. Both findings may be associated with a pathologic process, even in the absence of other markers of kidney damage. Although such patients do not fulfill the criteria for CKD, a clinician's high index of suspicion may warrant additional diagnostic testing or close follow-up to detect the onset of CKD.

Pediatric Considerations

In general the definition of CKD in adults applies to children (birth-18 years) with the following exceptions or allowances:

- the criteria for duration >3 months does not apply to newborns or infants ≤ 3 months of age.
- the criteria of a GFR <60 ml/min/1.73 m^2 does not apply to children <2 years of age in whom an age appropriate value should be applied.
- a urinary total protein or albumin excretion rate above the normal value for age may be substituted for albuminuria ≥ 30 mg/24 hours.
- all electrolyte abnormalities are to be defined in light of age normative values.

Developmental renal abnormalities account for as many as 30-50% of the children with CKD or ESRD.[42] As such many infants while born with normal SCr for age will in fact meet the definition of CKD based on structural abnormalities despite the appearance of a normal GFR and may be classified as such within the first few days of life.

Normal GFR in newborns is less than 60 ml/min/1.73 m^2, and it is not until approximately 2 years of age that one expects to see body surface area (BSA) adjusted GFR values comparable to those seen in the adult.[43,44] The expected increases in GFR that occur in the first months of life are due to increases in mean arterial pressure (MAP), decrease in renal vascular resistance, and redistribution of intrarenal blood flows to the superficial cortical nephrons in the newborn and increases in glomerular size and capillary permeability in the infant.[45–48] As such direct application of the GFR threshold values in the current CKD definition would not be appropriate in children less than 2 years of age as their normative maximal values would be below those of the adult or older child; hence most neonates and infants would be classified *a priori* at a decreased GFR based not on a reduction in GFR from a higher value, but rather failure of maturity of the kidney.

Numerous references exist for fetal,[49] neonatal term,[44,48] pre-term,[46,50,51] infant, child and adolescent GFR values[43,44] and the reader is strongly encouraged to use such references when comparison to a normative range is required for approximating the reduction in renal clearance of the individual child. It should be noted that across these ages the method of GFR measurement has often varied with the

majority of such measurements in the neonate (term or preterm) or infant being derived from urinary collections and creatinine clearance (CrCl) measurements, whereas the older children and adolescents are often investigated with exogenous markers including inulin, radionuclides, and other markers such as iohexol or iothalamate.

The most comprehensive list of GFR based on the gold standard of inulin clearance and stratified by age for both term and preterm babies and children up to the age of young adults can be found in Schwartz and Furth's review on GFR measurements and estimation in pediatric CKD.[52]

Similarly, age relevant normative values should be utilized when interpreting urinary protein (albumin) excretions as well as other important urinary and serum laboratory values. Such values may be found in a number of pediatric nephrology texts. For neonates and infants this includes Waters[53] and for post-neonate to young adults, more comprehensive values can be found in Langlois.[54]

1.2 STAGING OF CKD

1.2.1: We recommend that CKD is classified based on cause, GFR category, and albuminuria category (CGA). (*1B*)

RATIONALE

This statement is worded in this way because a classification encompassing cause and severity, as expressed by the level of GFR and the level of albuminuria, links to risks of adverse outcomes including mortality and kidney outcomes. These factors will therefore guide management of CKD and this recommended classification is consistent with other classification systems of disease which are based on the general domains of cause, duration and severity which provide a guide to prognosis. We included only kidney measures as factors in the classification of kidney disease, although we acknowledge that factors other than kidney measures, such as level of BP, also affect prognosis in CKD.

This recommended staging with inclusion of two additional domains represents a revision of the previous CKD guidelines, which included staging only by level of GFR. Cause of disease is included because of its fundamental importance in predicting the outcome of CKD and choice of cause-specific treatments. With inclusion of cause of kidney disease in the classification, we considered that it was no longer necessary to retain the use of the letter "T" to refer to kidney transplant recipients. Albuminuria is included as an additional expression of severity of disease not only because it is a marker of the severity of injury but also because albuminuria itself strongly associates with progression of kidney disease. Numerous studies have identified the adverse prognostic implication of albuminuria irrespective of level of kidney function.

We propose that this classification of CKD by Cause, GFR and Albuminuria, respectively be referred to as CGA staging. It can be used to inform the need for specialist referral, general medical management, and indications for investigation and therapeutic interventions. It will also be a tool for the study of the epidemiology, natural history, and prognosis of CKD.

Pediatric Considerations

The principles inherent in this guideline are fully applicable to children.

While large scale trials in children relating cause, GFR and albuminuria or proteinuria are rare, the principles of a multimodal classification in these three spheres should apply to children.

To date the only large scale trial utilizing a validated exogenously measured GFR (iohexol) and urinary protein excretion in a well-described cohort of children with renal disease is the Chronic Kidney Disease in Children (CKiD) trial.[55] They have enrolled over 600 children aged 1-16 years and have described GFR and urinary proteinuria related outcomes in the areas of neurodevelopment, cognition, behavior, cardiovascular health and risk, and somatic growth. They have also collected samples for ongoing and future genetic study. While these data are sparse in relation to overall adult numbers, this represents one of the largest pediatric nephrology trials. The use of true measured GFR, the quality and completeness of the data, and the long term longitudinal follow-up will form the basis for the best evidence-based outcomes in children with CKD for the foreseeable future. A recent review article by Copelovitch et al.[56] summarizes the major findings of the trial up to the present time.

1.2.2: Assign cause of CKD based on presence or absence of systemic disease and the location within the kidney of observed or presumed pathologic-anatomic findings. (*Not Graded*)

RATIONALE

This statement has been included so as to ensure that clinicians are alerted to the fact that CKD is not a diagnosis in and of itself, and that the assignment of cause is important for prognostication and treatment.

The cause of CKD has been traditionally assigned based on presence or absence of underlying systemic diseases and location of known or presumed pathologic-anatomic abnormalities. The distinction between systemic diseases affecting the kidney and primary kidney diseases is based on the origin and locus of the disease process. In primary kidney disease the process arises and is confined to the kidney whereas in systemic diseases the kidney is only one victim of a specific process, for example diabetes mellitus. Certain genetic diseases cross this boundary by affecting different tissues, e.g., adult polycystic kidney disease. The location of pathologic-anatomic findings is based on the magnitude of proteinuria, findings from the urine sediment examination, imaging, and renal pathology.

Table 4 | Classification* of CKD based on presence or absence of systemic disease and location within the kidney of pathologic-anatomic findings

	Examples of systemic diseases affecting the kidney	Examples of primary kidney diseases (absence of systemic diseases affecting the kidney)
Glomerular diseases	Diabetes, systemic autoimmune diseases, systemic infections, drugs, neoplasia (including amyloidosis)	Diffuse, focal or crescentic proliferative GN; focal and segmental glomerulosclerosis, membranous nephropathy, minimal change disease
Tubulointerstitial diseases	Systemic infections, autoimmune, sarcoidosis, drugs, urate, environmental toxins (lead, aristolochic acid), neoplasia (myeloma)	Urinary-tract infections, stones, obstruction
Vascular diseases	Atherosclerosis, hypertension, ischemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, systemic sclerosis	ANCA-associated renal limited vasculitis, fibromuscular dysplasia
Cystic and congenital diseases	Polycystic kidney disease, Alport syndrome, Fabry disease	Renal dysplasia, medullary cystic disease, podocytopathies

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; CKD, chronic kidney disease, GN, glomerulonephritis
Genetic diseases are not considered separately because some diseases in each category are now recognized as having genetic determinants.
*Note that there are many different ways in which to classify CKD. This method of separating systemic diseases and primary kidney diseases is only one, proposed by the Work Group, to aid in the conceptual approach.

Table 4 represents an example of a classification of causes of kidney diseases based on these two domains.

There is wide geographic variation in the cause of kidney disease. In developed countries, hypertension and diabetes are the most frequent causes of CKD, especially in the elderly. In populations with a high prevalence of diabetes and hypertension, it can be difficult to distinguish CKD due to hypertension and diabetes from CKD due to other disorders. In other countries, other causes of CKD may be as frequent as hypertension and diabetes (e.g., glomerular disease in East Asia) or coexist with them. Specialized diagnostic testing, such as kidney biopsy or invasive imaging studies are performed only when it is essential to confirm some diagnoses and the benefits justify the risks and cost. It is anticipated that cause of disease will not be known with certainty for many patients with CKD but can be either inferred or not known.

Pediatric Considerations

The principles inherent in this guideline are fully applicable to children.

1.2.3: Assign GFR categories as follows [Table 5] (*Not Graded*):

Table 5 | GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

RATIONALE

The purpose of this statement is to ensure clarity in communication. The terms associated with each of the GFR categories are descriptors which need to be taken in the context of the individual and are all references to normal young adults. Note that mildly decreased kidney function (G2) in the absence of other markers, does not constitute CKD.

The associations of lower categories of GFR and risks of metabolic and endocrine complications formed the basis of the previous stratification into 5 stages. This current classification further acknowledges the importance of dividing Stage 3 based on data supporting different outcomes and risk profiles into categories G3a and G3b (Figure 5). A number of other concurrent complications are associated with decreased categories of GFR including infection, impaired cognitive and physical function, and threats to patient safety.[57]

Figures 6 and 7 detail the RRs of decreased eGFR and increasing ACR with future complications, including mortality and kidney outcomes.[30] Even for the group with the lowest value of albuminuria, the increased RR for all outcomes is significant for eGFRs below 60 ml/min/1.73 m^2 in the continuous analysis and in the range of 45–59 ml/min/1.73 m^2 for the categorical analysis.

Pediatric Considerations

In children <2 years of age with CKD, the GFR categories as per the adult in Table 5 do not apply; these children should be categorized as having normal, moderately reduced, or severely reduced age-adjusted GFR.

No currently agreed upon set of international normative values or categories exist for GFR in children under the age of 1-2 years. However, the international pediatric nephrology community has embraced the adult CKD staging system as per the 2002 KDOQI guidelines in children over the age of 2 years, as suggested by Hogg et al.[43]

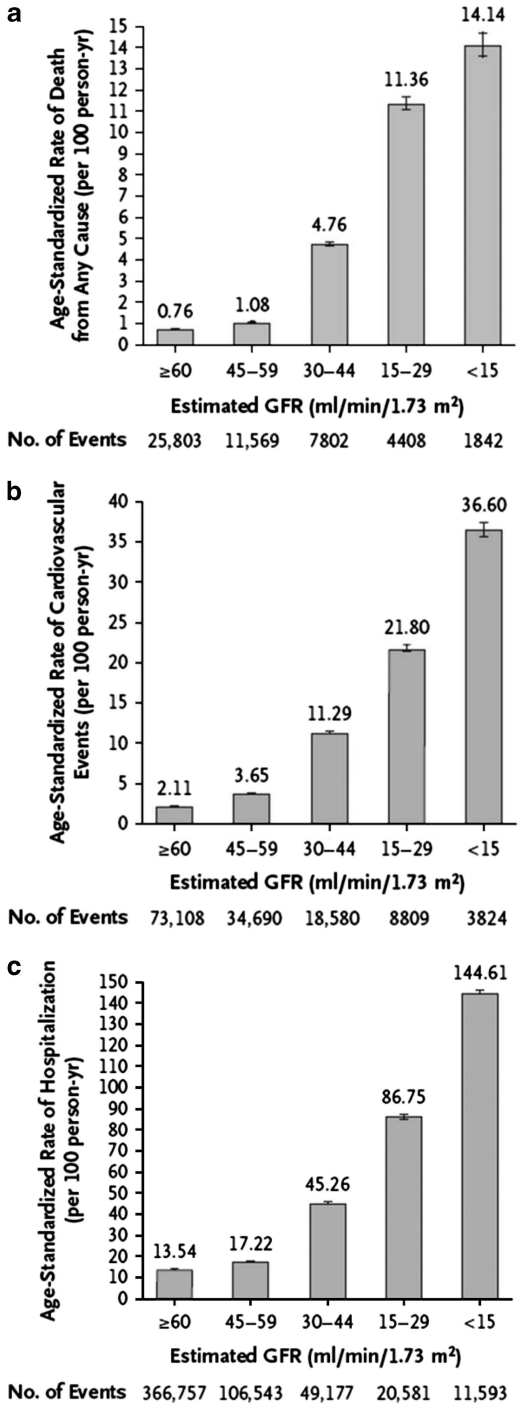


Figure 5 | Age-standardized rates of death from any cause (panel a), cardiovascular events (panel b), and hospitalization (panel c), according to the eGFR among 1,120,295 ambulatory adults. eGFR, estimated glomerular filtration rate. From N Engl J Med, Go AS, Chertow GM, Fan D, et al.[58] Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization, 351: 1296-1305. Copyright © (2004) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; accessed http://www.nejm.org/doi/pdf/10.1056/NEJMoa041031

As indicated in *Pediatric Considerations* for Guideline 1.1, the normative GFR values for children less than 2 years vary quite widely by both age and method of measurement. More importantly these values are expected to increase in a non-linear fashion over the first 2 years of life with significant changes seen in the first few months post-birth and no current evidence of presence of comorbid conditions at any given level of measured or estimated GFR in this population. As such, specific categorization of G1-5 as suggested in this Recommendation would seem not be of value, and might be misleading if applied to a child less than 2 years of age.

With this in mind, it is suggested that based on the chosen method of GFR measurement or comparison for the individual (i.e., CrCl, radioactive or cold exogenous serum markers, or estimating formula), that one should attempt to classify the child under the age of 2 years as having normal, moderate or severe reductions in GFR based on the normative range and standard deviations (SDs) for the method. No evidence exists for this recommendation but recognition that values of GFR more than 1 SD below the mean would seem likely to raise concern of the clinician and foster the need for closer monitoring. For drug dosing adjustments it is suggested that those children with GFRs below the mean by >1 but <2 SD be classified as having a moderate reduction in GFR whereas those more than 2 SD below the mean for the method be classified as having a severe reduction in GFR.

1.2.4: Assign albuminuria* categories as follows [Table 6] (*Not Graded*):
***note that where albuminuria measurement is not available, urine reagent strip results can be substituted (Table 7)**

Table 6 | Albuminuria categories in CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

Abbreviations: AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR >2220 mg/g; >220 mg/mmol]).

RATIONALE

The purpose of this statement is to ensure communication and to reflect that albuminuria category is an important predictor of outcomes. The association of high levels of proteinuria with signs and symptoms of nephrotic syndrome is well known. The detection and evaluation of lesser quantities of proteinuria have gained additional significance as multiple studies have demonstrated its diagnostic, pathogenic, and prognostic importance. There is a continuous risk associated with albuminuria but the use of a simple categorical approach was selected to simplify the concept for

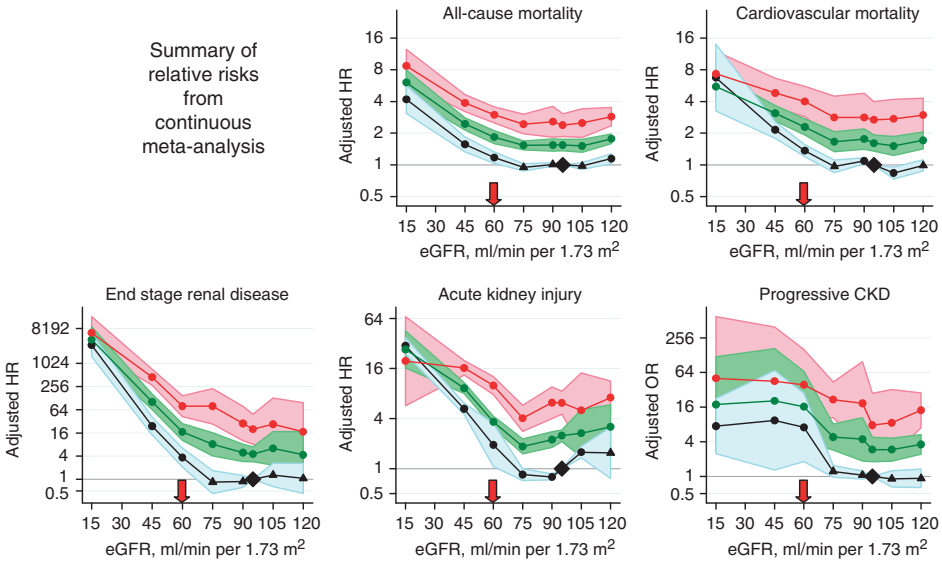


Figure 6 | Summary of continuous meta-analysis (adjusted RRs) for general population cohorts with ACR. Mortality is reported for general population cohorts assessing albuminuria as urine ACR. Kidney outcomes are reported for general population cohorts assessing albuminuria as either urine ACR or reagent strip. eGFR is expressed as a continuous variable. The three lines represent urine ACR of <30, 30-299 and ≥300 mg/g (<3, 3-29, and ≥30 mg/mmol, respectively) or reagent strip negative and trace, 1+ positive, ≥2+ positive. All results are adjusted for covariates and compared to reference point of eGFR of 95 ml/min/1.73 m^2 and ACR of <30 mg/g (<3 mg/mmol) or reagent strip negative (diamond). Each point represents the pooled RR from a meta-analysis. Solid circles indicate statistical significance compared to the reference point ($P < 0.05$); triangles indicate non-significance. Red arrows indicate eGFR of 60 ml/min/1.73 m^2, threshold value of eGFR for the current definition of CKD. ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; OR, odds ratio, RR, relative risk. Reprinted with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17-28[30]; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

clinical practice. Several groups had suggested subdividing one or more GFR categories based on albuminuria category.

For the detection of diabetic nephropathy some guidelines recommend the use of different ACR thresholds for males and females (>25 mg/g [>2.5 mg/mmol] and >35 mg/g [>3.5 mg/mmol], respectively) to take into account variations in creatinine excretion. A single threshold is used in North America (30 mg/g or 3.4 mg/mmol). Earlier KDIGO guidance was reluctant to adopt gender-specific thresholds due to greater complexity, uncertainty about assay precision, and effects of race, ethnicity, diet and measures of body size on creatinine and this stance is maintained here. For simplicity, and to reflect the fact that it is an approximation, 3.4 mg/mmol as the current guideline threshold has been rounded to 3.0 mg/mmol.

There is a graded increase in risk for higher albuminuria categories, at all GFR categories, without any clear threshold value. Even for subjects with GFR >60 ml/min/1.73 m^2, the increased RR is statistically significant for urine ACR ≥30 mg/g (≥3 mg/mmol) for mortality and kidney outcomes (Figures 6 and 7). The predictive ability of albuminuria at all categories of GFR supports the suggestion to add albuminuria categories to all GFR categories. Since the relationship with albuminuria is continuous, the selection of the number of categories and the cutoff values appears arbitrary. The Work Group has recommended the classification of albuminuria into only 3 categories, based on practical considerations, but recognized that further subdivisions within the category of <30 mg/24 hours (ACR<30 mg/g or <3 mg/mmol) may be useful for risk stratification, and that subdivisions within the category of >300 mg/24 hours (ACR>300 mg/g or >30 mg/mmol) may be useful for diagnosis and management. Specifically there is a recognition that nephrotic range proteinuria (AER>2200 mg/24 hours [ACR>2200 mg/g;>220 mg/mmol]; PER>3000 mg/24 hours [>3000 mg/g;>300 mg/mmol]) confers unique additional risks and is usually associated with specific conditions (such as GN). As these are relatively rare in general practices, the simplicity of the AER categorization was preferred. Table 7 shows the approximate relationships of categories of AER to other measures of albuminuria and proteinuria.

Implications for Clinical Practice and Public Policy

Data from around the world suggest that CKD prevalence is between 10-16% but information concerning population prevalence by category of GFR and ACR is scant. Figure 8 shows the proportion of adults in the US by categories of GFR and albuminuria.[19] While CKD is common, few individuals have severely reduced GFR or kidney failure or severely increased albuminuria.

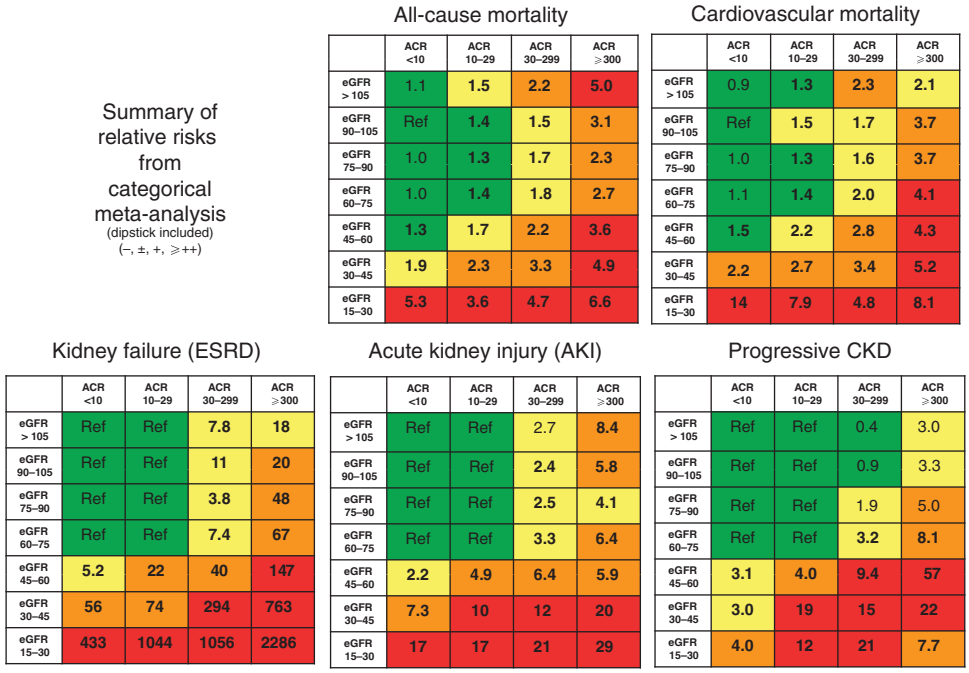


Figure 7 | Summary of categorical meta-analysis (adjusted RRs) for general population cohorts with ACR. Mortality is reported for general population cohorts assessing albuminuria as urine ACR. Kidney outcomes are reported for general population cohorts assessing albuminuria as either urine ACR or reagent strip. eGFR and albuminuria are expressed as categorical variables. All results are adjusted for covariates and compared to the reference cell (Ref). Each cell represents a pooled RR from a meta-analysis; bold numbers indicate statistical significance at $P < 0.05$. Incidence rates per 1000 person-years for the reference cells are 7.0 for all-cause mortality, 4.5 for CVD mortality, 0.04 for kidney failure, 0.98 for AKI, and 2.02 for CKD progression. Colors reflect the ranking of adjusted RR. The point estimates for each cell were ranked from 1 to 28 (the lowest RR having rank number 1, and the highest number 28). The categories with a rank number 1-8 are green, rank numbers 9-14 are yellow, the rank numbers 15-21 are orange and the rank numbers 22-28 are colored red. (For the outcome of CKD progression, two cells with RR < 1.0 are also green, leaving fewer cells as yellow, orange and red). ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RR, relative risk. Reprinted with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, et al.[30] The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17-28; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

The classification of kidney disease by cause, category of GFR and category of albuminuria does not conform to the International Classification of Diseases (ICD) maintained by the World Health Organization (WHO). Currently the WHO is developing an update (ICD 11). It will be important to communicate and coordinate efforts with the kidney disease subgroup for ICD 11. However, the proposed current classification does address the need in clinical practice to acknowledge the multiple dimensions and variables by which individual patients are assessed. Table 8 gives examples of the use of CGA nomenclature.

Definition of GFR categories have been deliberately based upon the concept of "true" GFR, whereas clinical practice and research has predominantly used creatinine-based estimates of GFR. The belief of the Work Group is that the non-GFR determinants of creatinine and the imprecision of creatinine-based GFR estimates have resulted in the absence of strong dose-dependent association of eGFR with clinical outcomes in the GFR range of >60 ml/min/1.73 m^2. The Work Group felt confident that GFR levels of ≥ 90 ml/min/1.73 m^2 portend better prognosis than GFR levels 60-89 ml/min/1.73 m^2, if they could be estimated accurately. Therefore, the GFR categories include separate G1 (≥ 90 ml/min/1.73 m^2) and G2 (60-89 ml/min/1.73 m^2) designations despite limited data from creatinine-based estimates that prognosis differs between these two categories. It is also an acknowledgement that the degree of precision of some of our measurements may not be able to differentiate between these 2 categories reliably. As described later, studies that have used cystatin C have found gradients in prognosis at eGFR levels above 60 ml/min/1.73 m^2, which supports the belief of the committee that separating these 2 GFR categories is appropriate for CKD classification.

Albuminuria categories are "wide" with respect to risk, with significant gradients within each category. The decision to propose only 3 categories is based on the perceived need for simplification in clinical practice. In specialized clinical nephrology centers, A3 (>300 mg/g or >30 mg/mmol) is often more precisely assessed and divided into additional categories. For example, nephrotic range proteinuria is defined as PER >3500 mg/24 hours or PCR (protein-to-creatinine ratio) >3500 mg/g [>350 mg/mmol] which is approximately equivalent to AER >2200 mg/24 hours or ACR >2200 mg/g [220 mg/mmol]. It is clearly recognized

Table 7 | Relationship among categories for albuminuria and proteinuria

	Categories		
Measure	Normal to mildly increased (A1)	Moderately increased (A2)	Severely increased (A3)
AER (mg/24 hours)	<30	30–300	>300
PER (mg/24 hours)	<150	150–500	>500
ACR			
(mg/mmol)	<3	3–30	>30
(mg/g)	<30	30–300	>300
PCR			
(mg/mmol)	<15	15–50	>50
(mg/g)	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

Abbreviations: ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; PCR, protein-to-creatinine ratio; PER, protein excretion rate.
Albuminuria and proteinuria can be measured using excretion rates in timed urine collections, ratio of concentrations to creatinine concentration in spot urine samples, and using reagent strips in spot urine samples. Relationships among measurement methods within a category are not exact. For example, the relationships between AER and ACR and between PER and PCR are based on the assumption that average creatinine excretion rate is approximately 1.0 g/d or 10 mmol/d. The conversions are rounded for pragmatic reasons. (For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.) Creatinine excretion varies with age, sex, race and diet; therefore the relationship among these categories is approximate only. ACR <10 mg/g (<1 mg/mmol) is considered normal; ACR 10–30 mg/g (1-3 mg/mmol) is considered "high normal." ACR >2200 mg/g (>220 mg/mmol) is considered "nephrotic range." The relationship between urine reagent strip results and other measures depends on urine concentration.

Percentage of US Population by eGFR and Albuminuria Category: KDIGO 2012 and NHANES 1999-2006				Persistent albuminuria categories Description and range			
				A1	A2	A3	
				Normal to mildly increased	Moderately increased	Severely increased	
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30mg/mmol	
GFR categories (ml/min/ 1.73m^2) Description and range	G1	Normal or high	≥90	55.6	1.9	0.4	57.9
	G2	Mildly decreased	60-89	32.9	2.2	0.3	35.4
	G3a	Mildly to moderately decreased	45-59	3.6	0.8	0.2	4.6
	G3b	Moderately to severely decreased	30-44	1.0	0.4	0.2	1.6
	G4	Severely decreased	15-29	0.2	0.1	0.1	0.4
	G5	Kidney failure	<15	0.0	0.0	0.1	0.1
				93.2	5.4	1.3	100.0

Figure 8 | Prevalence of CKD in the USA by GFR and albuminuria. Cells show the proportion of adult population in the USA. Data from the NHANES 1999-2006, N = 18,026. GFR is estimated with the CKD-EPI equation and standardized serum creatinine.[19] Albuminuria is determined by one measurement of ACR and persistence is estimated as described elsewhere.[59] Values in cells do not total to values in margins because of rounding. Category of very high albuminuria includes nephrotic range. Green, low risk (if no other markers of kidney disease, no CKD); Yellow, moderately increased risk; Orange, high risk; Red, very high risk. ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease; CKD-EPI, CKD Epidemiology Collaboration; GFR, glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey. Modified with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, et al.[30] The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17-28; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

that these very high levels of proteinuria carry a different risk than lower values within the same category. Further differentiation after quantification and evaluation would inform treatment decisions for an individual patient. These categories serve as an initial assessment and prognostication tool; further classification is appropriate for specific circumstances and is not limited by the initial classification into only 3 categories.

Note that the term 'microalbuminuria' is not used and is discouraged in this classification system. This will require a formal education program and review of existing guidelines in other disciplines so that consistency of terminology and

Table 8 | CGA staging of CKD: examples of nomenclature and comments

Cause	GFR category	Albuminuria category	Criterion for CKD	Comment
Diabetic kidney disease	G5	A3	Decreased GFR, Albuminuria	Most common patient in the low clearance clinic
Idiopathic focal sclerosis	G2	A3	Albuminuria	Common cause of nephrotic syndrome in childhood
Kidney transplant recipient	G2	A1	History of kidney transplantation	Best outcome after kidney transplantation
Polycystic kidney disease	G2	A1	Imaging abnormality	Most common disease caused by a mutation in a single gene
Vesicoureteral reflex	G1	A1	Imaging abnormality	Common condition in children
Distal renal tubular acidosis	G1	A1	Electrolyte abnormalities	Rare genetic disorder
Hypertensive kidney disease	G4	A2	Decreased GFR and albuminuria	Usually due to long-standing poorly controlled hypertension, likely to include patients with genetic predisposition- more common in blacks- who should be referred to nephrologist because of severely decreased GFR
CKD presumed due to diabetes and hypertension	G4	A1	Decreased GFR	Should be referred to nephrologist because of severely decreased GFR
CKD presumed due to diabetes and hypertension	G2	A3	Albuminuria	Should be referred to nephrologist because of albuminuria
CKD presumed due to diabetes and hypertension	G3a	A1	Decreased GFR	Very common, may not require referral to nephrologist
CKD cause unknown	G3a	A1	Decreased GFR	May be the same patient as above

Abbreviations: CGA, Cause, GFR category and albuminuria category; CKD, chronic kidney disease; GFR, glomerular filtration rate.
Note: Patients above the thick horizontal line are likely to be encountered in nephrology practice. Patients below the thick horizontal line are likely to be encountered in primary care practice and in nephrology practice.

understanding of the changes are universal (see Recommendation 1.4.4.2.1).

Pediatric Considerations

This statement would need to be altered for application in pediatric practice in the following way. In children with CKD any expression of abnormal urinary protein excretion, irrespective of the marker:

- must account for variation in that measurement as seen across age, sex, puberty and or body size (height, weight, body mass index [BMI]).
- should account for the possibility of tubular versus glomerular proteinuria dominance dependent on the underlying disease.
- may utilize proteinuria in place of albuminuria.

There is no set standard encompassing all children with respect to the normal range of urinary protein (or albumin) excretion. Values vary across age, sex, race, pubertal status, the presence of obesity (high BMI) and may be modified by exercise, fever, and posture.[60–63]

In general, neonates and young infants/ children are both expected and allowed to have higher urinary losses of both glomerular and tubular proteinuria due to lack of maturation in the proximal tubular reabsorption of proteins. The rough equivalences for ACR and PCR quoted in the pediatric literature are similar, but not identical to those quoted in the adult literature. Normal ranges vary but at least one reference suggests as much as 6-8 $mg/m^2/hr$ or >240 $mg/m^2/day$ of proteinuria as being acceptable at <6 months of age;[64] normal ranges for urinary albumin losses are not known at this age.

The normal range of protein excretion for children 6-24 months of age in a 24-hour urine collection is quoted as being <4 $mg/m^2/hr$ (<150 $mg/m^2/day$), whereas the first morning spot urine protein sample is said to be normal at levels of <500 mg/g creatinine (<50 mg/mmol). In children older than 24 months these values are <4 $mg/m^2/hr$ (<150 $mg/m^2/day$) for the 24-hour collection and PCR <200 mg/g creatinine (<20 mg/mmol) in the first morning urine sample, or a first morning urine ACR <30 mg/g (<3 mg/mmol).[43,65]

At all ages, total urinary protein excretion >40 $mg/m^2/hr$ (>3 grams/1.73 m^2/day) is considered to represent 'nephrotic range' loss of protein, with intermediate values, i.e., 4-40 $mg/m^2/hr$ or its equivalent representing abnormal but 'non-nephrotic' losses.[43,65]

Children older than 24 months of age are expected to achieve normal ('adult') urinary protein values with the caveat of an exaggerated postural loss of glomerular proteins (albumin) as can commonly be seen in the 2-5% of the adolescent population (i.e., orthostatic proteinuria).[62]

Based on National Health and Nutrition Examination Survey III (NHANES III) data from just under 6000 healthy 6-19 year old children using either immunonephelometry or radioimmunoassay, the definition of urinary albumin excretion was determined to be 30-300 mg/24 h collection; 20-200 μg/min in an overnight collection and 30-300 mg/g creatinine (3-30 mg/mmol) in a first morning urine sample.[66]

Of note, to date the majority of studies that have examined the effects of urinary protein losses or therapeutic interventions have concentrated on so-called total protein excretion or random or first morning PCRs. The utility of measuring the albumin only fraction, and in particular

quantitating this at the lower level of detection, i.e., <30 mg/g (<3 mg/mmol) creatinine, is only now being investigated in more detail in large pediatric studies. As such it should be recognized that in children the quantification of total protein, as compared to the albumin only fraction, may be the preferred method for assigning risk as it relates to the presence of urinary protein loss.

In summary, for children older than 2 years of age the assignment of 'proteinuria' categories can be used as per the adult guidelines with the understanding that modification to the upper limit of expected values may be necessary in consideration of the factors outlined above. Although there is a preference for reporting albumin values, currently many clinicians still categorize these children based on total protein and in the child <2 years of age or the adolescent with demonstrable orthostatic proteinuria, the current albuminuria categories are unlikely to apply.

1.3: PREDICTING PROGNOSIS OF CKD

1.3.1: In predicting risk for outcome of CKD, identify the following variables: 1) cause of CKD; 2) GFR category; 3) albuminuria category; 4) other risk factors and comorbid conditions. (*Not Graded*)

1.3.2: In people with CKD, use estimated risk of concurrent complications and future outcomes to guide decisions for testing and treatment for CKD complications (Figure 9). (*Not Graded*)

1.3.3: In populations with CKD, group GFR and albuminuria categories with similar relative risk for CKD outcomes into risk categories (Figure 9). (*Not Graded*)

RATIONALE

These statements are worded in this way because for all CKD complications, prognosis will vary depending on: 1) cause; 2) GFR; 3) degree of albuminuria; and 4) other comorbid conditions. The relative strength of each of these factors will vary for each complication or outcome of interest. Risk for kidney disease end points, such as kidney failure and AKI, is predominately driven by an individual patient's clinical diagnosis, GFR, and the degree of albuminuria or other markers of kidney damage and injury. For CVD, risk will be determined by history of CVD and traditional and non-traditional CVD risk factors. For other conditions, the risk will be determined by risk factors specific for those conditions. For all conditions, the cause of CKD, GFR category, and albuminuria category will still have important influence as "risk multipliers," but will have smaller overall influence on disease prediction than risk factors specific for the condition. All these conditions have an impact on life expectancy and quality of life (QOL) and contribute substantially to predicting the prognosis of CKD. CKD is associated with numerous complications directly or indirectly related to the cause of CKD, decreased GFR, or albuminuria (Table 9).

The risk associations of GFR and albuminuria categories appear to be largely independent of one another. Therefore, neither the category of GFR nor the category of albuminuria alone can fully capture prognosis for a patient with CKD. The magnitude and gradients of risk across categories of GFR and albuminuria will likely differ for each specific adverse event. This heterogeneity across the GFR and ACR grids in RRs for different outcomes makes it impractical to have a simple hierarchical staging of prognosis across all cells. Thus, the staging using CGA should be descriptive, but encompassing the ordered categories of GFR and ACR (Figure 9).

The CGA staging system proposed in this guideline provides a framework for future recommendations on CKD clinical management. At present, much of the evidence on clinical decision making in CKD is based solely on GFR. This recommendation serves to highlight the multidimensional

Table 9 | Prognosis of CKD: Relationship of outcomes and strength of relationship to Cause (C), GFR (G), Albuminuria (A) and other measures*[67,68]

	Kidney measures			
Outcomes	Cause	GFR	Albuminuria	Other measures
Kidney outcomes				
GFR decline	+++	+	+++	High BP, male sex, black race, younger age
Albuminuria rise	+++	+	+++	High BP, diabetes
AKI	+	+++	+	Older age
Chronic kidney failure (GFR <15 ml/min/1.73 m^2; category G5)	+++	+++	+	Younger age
Complications (current and future)				
Drug toxicity	+	+++	+	Drug exposure, liver disease
Endocrine and metabolic	+	+++	+	Various
CVD and mortality	++	+++	+++	Older age, history of CVD, CVD risk factors
Others (infection, cognitive impairment, frailty, etc)	++	++	++	Older age, comorbid conditions

Abbreviations: AKI, acute kidney injury; BP, blood pressure; CVD, cardiovascular disease; GFR, glomerular filtration rate.
Plus signs indicate the strength of the risk relationship between the CKD characteristic and the outcome: +, somewhat associated; ++, moderately associated; +++, strongly associated.
*Note that the + designations refer to strength of relationship not strength of evidence to support, and are based on consensus overview by the Work Group members. Adapted with permission from Uhlig K, Levey AS.[68] Developing guidelines for chronic kidney disease: we should include all of the outcomes. Ann Intern Med 2012; 156(8): 599-601.

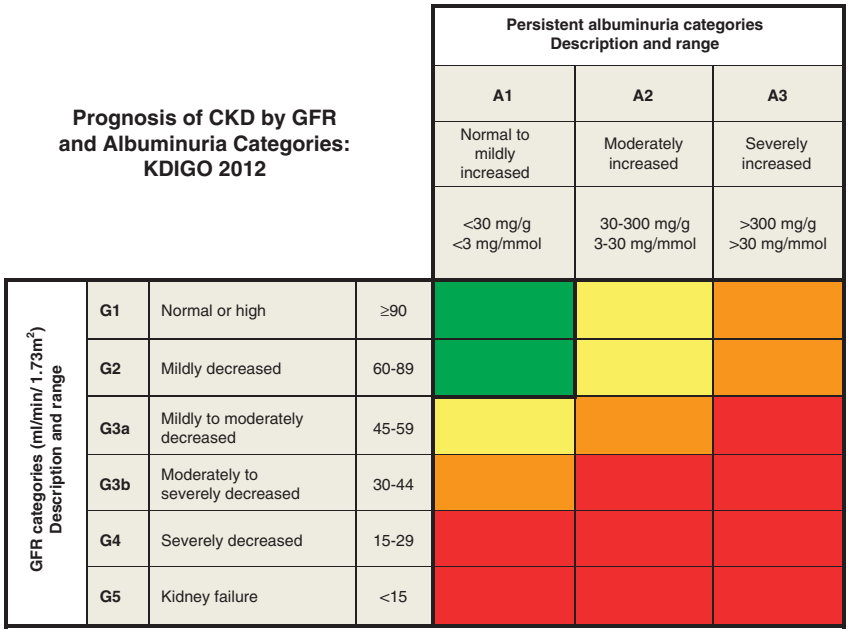


Figure 9 | Prognosis of CKD by GFR and albuminuria category. Green, low risk (if no other markers of kidney disease, no CKD); Yellow, moderately increased risk; Orange, high risk; Red, very high risk. CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes. Modified with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, et al.[30] The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17-28; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

aspect of CKD so as to ensure appropriate consideration of the complexity of the condition.

Evidence Base

The evidence base from which these statements are derived includes large observational cohort studies from diverse populations. For some outcomes, including mortality, CVD, and kidney disease progression, meta-analyses have summarized the risk associations. For outcomes that occur predominately in older adults (e.g., dementia, fracture), the evidence is largely limited to cohorts of older people.

Extensive work by the CKD Prognosis Consortium has defined the RRs across GFR and albuminuria categories for several important outcomes, including all-cause mortality, CVD, and kidney failure (Figures 6 and 7). Risk increases incrementally in both directions - down the GFR categories and across the albuminuria categories. Levels of risk can be identified and grouped into categories, but they may differ somewhat for each outcome. Additional research is needed to map these GFR and albuminuria categories and cause of kidney disease to other important outcomes of CKD (Table 9).

International Relevance

The above statements appear to be robust when applied in North America, Europe and Asia.[30] Thus, it appears for all methods used to determine GFR and to detect albuminuria, the use of the 3 parameters (cause, category of GFR and category of albuminuria) influences prognosis irrespective of ethnicity or country of origin.

Implications for Clinical Practice and Public Policy

Providers must incorporate cause of kidney disease, GFR category and albuminuria category in order to better develop an accurate assessment of an individual's prognosis related to CKD. Many providers who are not nephrologists will need guidance in the local methods for requesting and interpreting a urine albumin assessment and an eGFR. Use of risk scores which are being developed and refined is advised.

Public policy and estimates of total burden of illness in a community need to take into account the incidence and prevalence of specific conditions (such as diabetes and congestive heart failure). In addition, knowledge of distribution of levels of eGFR and ACR may be valuable for resource planning. Community or health-system based interventions to reduce the incidence of kidney failure in populations should be targeted and prioritized based on these 3 criteria.

The primary impact on clinical practice will relate to kidney-specific complications of CKD and referral patterns to help prevent and manage them. Decisions related to screening and monitoring CKD disorders will be informed and guided by the CGA system. At present, this evidence for issues such as management of anemia, CKD bone and mineral disorders, and acid-base disorders has not been organized and presented in this way.

Decisions on screening and referral strategies have major impact on the costs and quality of health-care. The value of

this revised system of classification is that it will allow the evaluation of different referral patterns and the impact of treatment strategies in those with diverse CGA assignment. In this way, we will develop additional evidence which will inform practice patterns. These will necessarily be developed locally and reflect the values and economic realities of each health-care system.

Areas of Controversy, Confusion, or Non-consensus and Clarification of Issues and Key points

Current clinical practice has not overtly incorporated these 3 variables into all decision making activities. The utility of the system will need to be vetted by those referring and those to whom patients are referred. The overt description of the 3 dimensions of diagnosis and staging of kidney disease which include the cause, the category of GFR and the category of albuminuria, should help to inform referral and treatment patterns of large groups of individuals. Risk calculators for specific events are under development.

- The CGA classification system will be useful for quantifying risk for specific outcomes of CKD but its utility has not been fully assessed in clinical practice and research studies.
- Additional evidence is required before decisions on screening, monitoring, and referral patterns can be fully informed.

Pediatric Considerations

For Recommendation 1.3.1 the rationale and principles behind this statement would apply to pediatrics though the data are not available.

Unlike in adults, the knowledge of risk of progression or outcomes of CKD is less robust in children, with the majority of such information gleaned from either registry datasets or longitudinal trials. In a 2008 report of a select group of patients enrolled by various North American pediatric nephrology centers in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry, 46% of nearly 7100 cases had reached a final 'end point' with 86% progressing to ESRD over their time in the registry.[69] Data from the prospective registry and population-based Italian Pediatric Registry of Chronic Renal Failure (ItalKid) study demonstrated a risk of progression to ESRD of ~68% by age 20 years.[70]

Cause of CKD. Specific information related to rate of progression for all pediatric causes of CKD is not easily available. However data from the prospective longitudinal CKiD trial has demonstrated a more rapid decline in renal function in children whose underlying cause of CKD is classified as glomerular with an annualized rate of change in iohexol GFR of −10.5% as compared to those with a non-glomerular cause in whom the annualized rate of change is only −3.9%.[71] In terms of absolute rates of change in measured iohexol GFR this translated, in a separate analysis from the same dataset, into a median change of GFR of −4.3 ml/min/1.73 m^2 versus −1.5 ml/min/1.73 m^2 in the glomerular versus non-glomerular groups, respectively.[72] This paper also provides the only current individual disease-specific estimate of annual decline in a pediatric population. Table 10 illustrates that the median values for annualized change in GFR for various diagnosis categories.

Similarly, a randomized controlled trial (RCT) from Europe[73] examining the effects of diet on rate of progression demonstrated a statistically significant difference in CrCl between their glomerular and non-glomerular cohorts at 2 years of follow-up; with the mean decline [SD] in the glomerular group being −10.7 [11.3] versus −8.4 [13.5] ml/min/1.73 m^2 in the non-glomerular patients ($P = 0.048$).

GFR category. It is also well recognized that there is an inverse relationship between the rates of progression of kidney disease to the level of kidney function present at that presentation with more rapid decline seen in patients with lower initial levels of GFR. Staples et al.[74] in their retrospective review of the NAPRTCS CKD database involving nearly 4200 children registered with GFR categories G2-G4 (GFR 15-89 ml/min/1.73m^2) demonstrated significantly higher rates of progression, defined by progression to GFR category G5 (GFR <15 ml/min/1.73m^2) or initiation of dialysis or transplant, for children in GFR categories G3a-G4 (GFR 15–59 ml/min/1.73m^2) as compared to those with CKD and GFR category G2 (GFR 60–89 ml/min/1.73m^2) at time of enrollment: hazard ratio (HR) of GFR categories 3a and 3b (GFR 30–59 ml/min/1.73m^2) (GFR category 2 (GFR 60–89 ml/min/1.73m^2) = 1.00 as referent): 2.00; 95% confidence interval (CI) 1.64-2.42; $P<0.0001$ and HR of GFR category 4 (GFR 15–29 ml/min/1.73m^2): 6.68; 95% CI 5.46-8.18; $P<0.0001$.

Albuminuria (proteinuria). Several studies have also demonstrated the effect of proteinuria on rate of progression of CKD in children. Using registry data, and in non-glomerular conditions the ItalKids trial[75] demonstrated a significantly slower decline in CrCl in patients with baseline PCRs of <200 mg/g (20 mg/mmol) and 200–900 mg/g (20–90 mg/mmol) when compared to those patients with a PCR of >900 mg/g (>90 mg/mmol); slope +0.16 ± 3.64 and

Table 10 | Annual percentage change in GFR across diagnosis categories

Disease	Annualized percentage change [number of patients]
Focal and segmental glomerulosclerosis	-13.3% [N=34]
Hemolytic uremic syndrome	-1.3% [N=27]
Other glomerular	-15.5% [N=51]
Obstructive uropathy	-4.6% [N=109]
Aplastic/hypoplastic/dysplastic kidneys	-3.3% [N=96]
Reflux nephropathy	-3.8% [N=82]
Autosomal recessive polycystic kidney disease	-4.4% [N=18]
Other non-glomerular	-2.5% [N=119]

Abbreviation: GFR, glomerular filtration rate.
Data from Furth et al.[72]

-0.54 ± 3.67 versus -3.61 ± 5.47 ($P < 0.0001$). This translated to higher rates of kidney survival over 5 years in the lower proteinuria groups, 96.7% and 94.1% versus 44.9%, ($P < 0.01$). Multivariate analysis confirmed that the baseline PCR correlated with a more rapid decline in CrCl for any given level of baseline function.

In a prospective multicenter randomized trial of protein intake on rates of progression in children aged 2-18 years of age, Wingen et al. employed the Schwartz equation to estimate CrCl and demonstrated that baseline proteinuria in multivariate analysis was the most important independent predictor of change in CrCl. The authors reported a partial R^2 of 0.259 at 2 years follow-up and similar results were found after the study was extended for a third year.[73] Life-table analysis in this study also suggested a cutoff value of 50 mg/kg/day of proteinuria as a strong predictor of time to a decline in CrCl > 10 ml/min/1.73 m^2 and found a risk ratio of 4.01 (95% CI 2.23–7.25; $P < 0.001$).

Finally Wong et al.[76] used cross sectional data from the prospective longitudinal CKiD trial to demonstrate that even after controlling for age, race, BMI, cause of CKD and use of RAAS antagonists they could expect an average decline in measured GFR of 10% for every increase in urinary PCR of 14% (95% CI 10-18%).

Other risk factors and comorbid conditions. Many other risk factors and comorbid conditions have also been associated with greater risk of progression of CKD in adults but only a few of these have been convincingly proven in children due to lack of pediatric prospective trials.

Hypertension is by far the best studied of these risk factors in children, with clear evidence from multiple sources to document the value of aggressive BP control on slowing the rate of progression of CKD. Wingen et al.[73] demonstrated the importance of systolic BP in rate of progression in both univariate and multivariate models. In this study Cox proportional hazards analysis demonstrated a systolic BP > 120 mm Hg was an independent risk for decline in CrCl by > 10 ml/min/1.73 m^2; risk ratio was 3.1 (95% CI 1.74-5.53; $P < 0.001$).

The most important prospective pediatric BP trial to date, the Effect of Strict Blood Pressure Control and ACE-Inhibition on Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) study, used ambulatory BP monitoring (ABPM) and a fixed dose of ramipril plus additional antihypertensive agents that do not target the RAAS to assess (as primary outcomes) the time to decline of 50% in GFR or development of ESRD. Their results demonstrated a 35% reduction in the risk of achieving the primary end point in the more intensely treated BP: HR 0.65; 95% CI 0.44-0.94; $P = 0.02$. Further sub-analysis as reported in the KDIGO BP Guideline[10] demonstrated that kidney survival was 66.1% at 5 year follow-up in patients with systolic BP $< 90^{th}$ percentile for age whereas it was 41% in the patients who did not achieve this level of reduction ($P = 0.0002$); similar numbers were seen if diastolic BP was the metric considered.

The issue of puberty and its effect on rate of progression has recently been addressed by the ItalKids investigators.[77] While the methodology of their analysis is less than ideal as they did not determine actual Tanner stages in the majority of their cohort and used estimated rather than measured GFR, they do appear to demonstrate a decrease in kidney survival probability beginning around 10.9 years in girls and 11.6 years in boys with CKD. Of note, the rate of decline in kidney survival, using these age points as 'inflection' or break points, is dramatically increased in both sexes based on their evidence provided in graphical form, although more precise analyses are not possible from the data provided.

As in adults, other factors for consideration and value in monitoring in children with respect to risk of progression include obesity, metabolic acidosis, anemia, calcium-phosphate metabolism, chronic inflammation, diabetes, hyperuricemia, dyslipidemia, and smoking.

The most comprehensive review of many of these factors in children comes from a retrospective study of the NAPRTCS CKD database. Staples et al.[74] demonstrated that in a multivariate analysis of nearly 4200 children registered with CKD and GFR categories G2-G4 (GFR 15–89 ml/min/1.73m^2), the following factors were significantly associated with the risk of CKD progression (defined by progression to GFR category G5 (GFR < 15 ml/min/1.73m^2) or initiation of dialysis or transplant): age; primary disease; GFR category; registration year; hypertension; corrected calcium, phosphorus, albumin, and hematocrit; and as proxies, the use of medications for anemia and short stature. The ability of this paper to prove causation or value in treating any of these conditions in hopes of delaying CKD progression is limited by its retrospective nature, and the fact that data were accrued from a voluntary registry.

There is optimism that prospective data from current large pediatric trials such as CKiD[55] and the European Cardiovascular Comorbidity in Children with CKD (4C) trial[78] will lead to a better understanding of how risk factors may be influencing the rate of progression of CKD in children.

For Recommendation 1.3.2 the rationale and principles behind this statement would apply to pediatrics, though the data are not available. Insufficient evidence currently exists with respect to the predictive value of prevalent risk factors to guide future decisions for testing or treatment for CKD complications in an individual child.

It is hoped that well powered, prospective trials with adequate follow-up, such as the CKiD[55] and European 4C[78] trials, will gather sufficient numbers of patients, comorbidities, and outcomes to allow for predictive models to be built in pediatric CKD that incorporate traditional and non-traditional cardiac risk factors including dyslipidemia and hypertension, proteinuria (albuminuria), specific disease-related issues (e.g., diabetes, tubulopathy), prematurity, and birth weight.

For Recommendation 1.3.3 the rationale and principles behind this statement would apply to pediatrics, though the data are not available. Current evidence and a paucity of

numbers do not allow for the statistically relevant categorization of RR for CKD outcomes based solely on GFR and albuminuria or proteinuria. Again both the CKiD[55] and European 4C[78] trials may be able to address these shortcomings.

1.4: EVALUATION OF CKD

1.4.1: Evaluation of chronicity

1.4.1.1: In people with GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) or markers of kidney damage, review past history and previous measurements to determine duration of kidney disease. (Not Graded)

- **If duration is >3 months, CKD is confirmed. Follow recommendations for CKD.**
- **If duration is not >3 months or unclear, CKD is not confirmed. Patients may have CKD or acute kidney diseases (including AKI) or both and tests should be repeated accordingly.**

RATIONALE

When evidence of CKD is first ascertained, proof of chronicity can be obtained or confirmed by:

(i) review of past measurements of GFR;
(ii) review of past measurements of albuminuria or proteinuria and urine examinations;
(iii) imaging findings such as reduced kidney size and reduction in cortical thickness;
(iv) pathological findings such as fibrosis and atrophy;
(v) medical history especially duration of disorders known to cause CKD;
(vi) repeat measurements within and beyond the 3 month point.

Chronicity should not be assumed as AKI can present with similar abnormalities.

Pediatric Considerations

See Pediatric Considerations for next section.

1.4.2: Evaluation of cause

1.4.2.1: Evaluate the clinical context, including personal and family history, social and environmental factors, medications, physical examination, laboratory measures, imaging, and pathologic diagnosis to determine the causes of kidney disease. (*Not Graded*)

RATIONALE

Once the presence of CKD is proven it is essential to establish a cause for this which will inform specific management and modify risk projections. The diagnosis will be reached by standard clinical method (i.e., history examination) and special investigation, based on knowledge of the common causes of CKD and their manifestations. Not all evaluations are required in all patients, and will be directed by clinical context, and resource availability. For most patients the following evaluations are indicated:

- Reagent strip urinalysis to detect hematuria or pyuria. If positive, use urine microscopy to detect RBC casts or WBC casts.
- Ultrasound to assess kidney structure (i.e., kidney shape, size, symmetry and evidence of obstruction) as clinically indicated.
- Serum and urine electrolytes to assess renal tubular disorders, as clinically indicated.

Many individuals found to have CKD will not have a primary kidney disease but kidney damage caused by diabetes mellitus, vascular disease, and hypertension. The issue for the clinician will be to decide whether the presence of these is a sufficient explanation and if not, to investigate further. The prevalence of other conditions will vary depending on region, age, and other factors.

It is beyond the scope of this guideline to describe how specific diagnoses are reached but non-nephrologists in the first instance should review the family history, medications, symptoms and signs for manifestations of systemic diseases. Urinalysis should be performed, along with imaging of the kidneys if obstruction of the urinary tract or polycystic kidney disease is considered.

Pediatric Considerations

For Recommendations 1.4.1.1 and 1.4.2.1, the statements would need to be altered for application in pediatric practice in the following way.

In any child with GFR <60 ml/min/1.73 m^2 (or more than 1 SD below expected for their age and sex) or with markers of kidney damage, a complete review of their past history and previous measurement or estimate of renal function and full consideration of the clinical context, including prenatal history, drug exposures of fetus or mother, genetic conditions, coincident organ abnormalities, physical examination, fetal and post-natal laboratory measures including amniotic fluid, pre- and post-natal imaging and pathologic diagnosis including those of the fetus and placenta should be used to determine the cause(s) of kidney disease.

As noted in *Pediatric Considerations* for Recommendation 1.1.1, developmental renal abnormalities account for as many as 30-50% of the children with CKD.[42] A careful review of all fetal or maternal exposures, genetic risks factors, and any relevant information on the intrauterine environment during gestation are all relevant to the determination of the presence of CKD either prior to or present immediately at the time of delivery. An infant may be born with CKD, leading to

immediate classification within the CGA framework – up to and including that of dialysis dependency.

1.4.3 Evaluation of GFR

This section describes the various methods by which GFR can be estimated. We describe laboratory techniques that satisfy the requirements for robust result reporting and we compare the accuracy of available equations for the purpose of reporting eGFR using a single equation where applicable. We emphasize equations based on standardized measurements of SCr, but also consider newly developed equations based on standardized measurements of serum cystatin C (SCysC) because they are being introduced into clinical practice. We encourage practitioners to have a clear understanding of the value and limitations of both filtration markers, the importance of standardization of assays for both, and to understand that when an accurate assessment of kidney function is required, direct measurement should be undertaken.

1.4.3.1: We recommend using serum creatinine and a GFR estimating equation for initial assessment. (*1A*)

1.4.3.2: We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. (*2B*)

RATIONALE

These statements specifically address the need to ensure that estimating equations are put into routine clinical practice, and that clinicians understand the utility of further evaluation with additional methods if required.

GFR is measured by the clearance of an exogenous or endogenous filtration marker.[27] All clearance methods are complex so in clinical practice, GFR is estimated from the serum concentration of the endogenous filtration marker creatinine. Cystatin C is an alternative endogenous filtration marker; other filtration markers are also under evaluation. The principles of GFR estimation are discussed in the rationale for recommendations regarding the use of creatinine as a filtration marker but the concepts apply to GFR estimation from all endogenous filtration markers. Specific comments about GFR estimation using cystatin C are presented separately.

For most clinical circumstances, estimating GFR from SCr is appropriate for diagnosis, staging, and tracking the progression of CKD. However, like all diagnostic tests, interpretation is influenced by varying test characteristics in selected clinical circumstances and the prior probability of disease. In particular, an isolated decreased eGFR in otherwise healthy individuals is more likely to be false positive than in individuals with risk factors for kidney disease or markers of kidney damage. Confirmation of decreased eGFR by measurement of an alternative endogenous filtration marker (cystatin C) or a clearance measurement is warranted in specific circumstances when GFR estimates based on SCr are thought to be inaccurate and when decisions depend on more accurate knowledge of GFR, such as confirming a diagnosis of CKD, determining eligibility for kidney donation, or adjusting dosage of toxic drugs that are excreted by the kidneys.[79] The choice of confirmatory test depends on the clinical circumstance and the availability of methods where the patient is treated.

Pediatric Considerations

For Recommendation 1.4.3.1, the statements would need to be altered for application in pediatric practice in the following way. The use of SCr and a recently derived pediatric specific GFR estimating equation, which incorporates a height term,[80] is preferred over the use of SCr alone in the initial assessment of pediatric renal function.

For Recommendation 1.4.3.2, this guideline is fully applicable in pediatrics.

1.4.3.3: We recommend that clinicians (*1B*):

- **use a GFR estimating equation to derive GFR from serum creatinine ($eGFR_{creat}$) rather than relying on the serum creatinine concentration alone.**
- **understand clinical settings in which $eGFR_{creat}$ is less accurate.**

RATIONALE

Estimating GFR from the SCr concentration alone requires implicit judgments that are difficult in routine clinical care, including reciprocal transformation, consideration of the non-GFR determinants, and conversion to the GFR scale. Using GFR estimating equations provides a more direct assessment of GFR than SCr alone. The SCr concentration is influenced by GFR and other physiological processes, collectively termed "non-GFR determinants," including creatinine generation by muscle and dietary intake, tubular creatinine secretion by organic anion transporters, and extrarenal creatinine elimination by the gastrointestinal tract (Figure 10).

GFR estimating equations are developed using regression to relate the measured GFR to steady state SCr concentration and a combination of demographic and clinical variables as surrogates of the non-GFR determinants of SCr. By definition, GFR estimates using SCr concentration are more accurate in estimating measured GFR than the SCr concentration alone in the study population in which they were developed. Sources of error in GFR estimation from SCr concentration include non-steady state conditions, non-GFR determinants of SCr, measurement error at higher GFR, and interferences with the creatinine assays (Table 11). GFR estimates are less precise at higher GFR levels than at lower levels.

The clinician should remain aware of caveats for any estimating equation which may influence the accuracy in a given individual patient.

Because of the physiologic and statistical considerations in developing GFR estimating equations, GFR estimates are less precise at higher GFR levels than at lower levels. In principle, equations based on multiple endogenous filtration markers can overcome some of the imprecision of GFR estimates at higher levels, due to cancellation of errors from non-correlated non-GFR determinants.

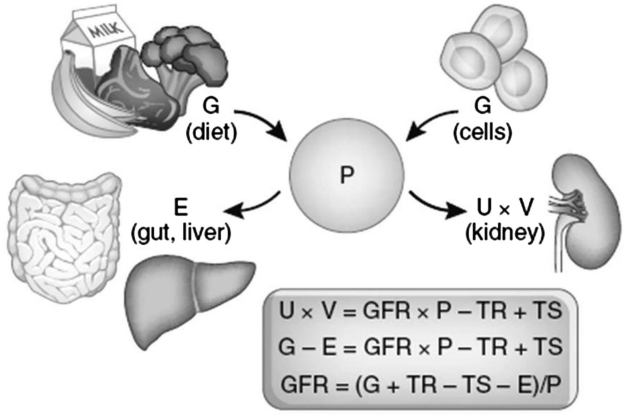


Figure 10 | Determinants of the serum level of endogenous filtration markers. The plasma level (P) of an endogenous filtration marker is determined by its generation (G) from cells and diet, extrarenal elimination (E) by gut and liver, and urinary excretion (UV) by the kidney. Urinary excretion is the sum of filtered load (GFR X P), tubular secretion (TS), and reabsorption (TR). In the steady state, urinary excretion equals generation and extrarenal elimination. By substitution and rearrangement, GFR can be expressed as the ratio of the non-GFR determinants (G, TS, TR, and E) to the plasma level. GFR, glomerular filtration rate. Reprinted with permission of American Society of Nephrology, Measured GFR as a confirmatory test for estimated GFR, Stevens LA, Levey AS.[79] J Am Soc Nephrol 20: 2305-2313, 2009; permission conveyed through Copyright Clearance Center, Inc.; accessed http://jasn.asnjournals.org/content/20/11/2305.full.pdf

Pediatric Considerations

This guideline is fully applicable in pediatrics.

1.4.3.4: We recommend that clinical laboratories should (*1B*):

- **measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology.**
- **report $eGFR_{creat}$ in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting $eGFR_{creat}$.**
- **report $eGFR_{creat}$ in adults using the 2009 CKD-EPI creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation.**

When reporting serum creatinine:

- **We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed as standard international units (μmol/l) and rounded to the nearest 100^{th} of a whole number when expressed as conventional units (mg/dl).**

Table 11 | Sources of error in GFR estimating using creatinine

Source of error	Example
Non-steady state	• AKI
Non-GFR determinants of SCr that differ from study populations in which equations were developed	

Factors affecting creatinine generation	• Race/ethnicity other than US and European black and white
	• Extremes of muscle mass
	• Extremes of body size
	• Diet and nutritional status
	  ◦ high protein diet
	  ◦ creatine supplements
	• Muscle wasting diseases
	• Ingestion of cooked meat

Factors affecting tubular secretion of creatinine	• Decrease by drug-induced inhibition
	  ◦ trimethoprim
	  ◦ cimetidine
	  ◦ fenofibrate

Factors affecting extra-renal elimination of creatinine	• Dialysis • Decrease by inhibition of gut creatininase by antibiotics • Increased by large volume losses of extracellular fluid
Higher GFR	Higher biological variability in non-GFR determinants relative to GFR • Higher measurement error in SCr and GFR
Interference with creatinine assay	• Spectral interferences (e.g., bilirubin, some drugs) • Chemical interferences (e.g., glucose, ketones, bilirubin, some drugs)

Abbreviations: AKI, acute kidney injury; GFR, glomerular filtration rate; SCr, serum creatinine.

When reporting $eGFR_{creat}$:

- **We recommend that $eGFR_{creat}$ should be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m^2 in adults using the units ml/min/1.73 m^2.**
- **We recommend $eGFR_{creat}$ levels less than 60 ml/min/1.73 m^2 should be reported as "decreased."**

RATIONALE

The statement is worded this way to acknowledge that calibration of assays is essential to interpretation of kidney function measures. This recommendation is directed to laboratories with the intent to clarify the details of such calibration and the use of specific equations so as to facilitate international standardization.[81]

There are numerous assay methods for creatinine for use in clinical laboratories. Variation in assigned values for SCr concentration among methods is greater at low concentrations, corresponding to high levels of GFR. Variation in assays at low SCr concentrations contributes to imprecision of GFR estimates at high GFR levels.

Currently available assays fall into two broad categories, the alkaline picrate (Jaffe) assay and enzymatic assays. In general, enzymatic assays are less biased compared to a standardized reference material and less susceptible to interferences. All assays are available on a number of platforms.

We recommend that laboratories use assays that are traceable to pure creatinine standards via a valid calibration hierarchy and that are specific and minimally-biased compared with isotope-dilution mass spectrometry (IDMS) reference method results. Results should be traceable to reference materials and methods listed on the Joint Committee for Traceability in Laboratory Medicine (JCTLM) database. Ideally laboratories should move to enzymatic assays for creatinine measurement: as a minimum, the use of traditional kinetic or end point Jaffe assays should cease and be replaced with IDMS aligned Jaffe methods.

Clinical laboratory information systems generally have access to patient age and sex and thus can report eGFR based on SCr age and sex, thus providing the clinician with the test result in units which are recommended for interpretation. Estimated GFR is now reported together with SCr when creatinine is ordered in more than 75% of clinical laboratories in the US.[82] In the UK, 93% of NHS laboratories report eGFR with SCr,[83] as is the case in Australia, Canada, and many European countries.

Selection of a single equation for use, where applicable, would facilitate communication among providers, patients, researchers and public health officials. Criteria for selection should be based on accuracy compared to measured GFR and usefulness in clinical care and public health.

The interpretation of measured and eGFR is based on comparison to normative values, which are adjusted for BSA because of the physiologic matching of GFR to kidney size, which is in turn related to BSA. The value of 1.73 m^2 reflects the average value of BSA of 25-year old men and women in the USA in 1927.[84] While it is known that modern populations may have different normal values for BSA, the 1.73 m^2 value will be maintained for normalization purposes.

Drug dosing should be based on GFR which is not adjusted for BSA. The effect of drug dosing based on GFR adjusted for BSA compared to GFR unadjusted for BSA has not been studied rigorously and more precise recommendations are not available.

Flagging decreased values for eGFR can alert clinicians to the possibility of AKD or CKD, and may indicate the need for additional investigations or treatments, including adjustment of doses of drugs that are excreted by the kidney. However, values for GFR between 60 and 89 ml/min/1.73 m^2 are mildly decreased compared to the usual values in young healthy people. Thus it is important that clinicians appreciate that eGFR values that are not flagged because they are >60 ml/min/1.73 m^2 are not necessarily normal.

Evidence Base

Numerous equations have been developed to estimate GFR or CrCl in adults. In general, GFR estimating equations using creatinine include age, sex, race, and body size as surrogates for creatinine generation by muscle. For our review of GFR estimating equations, we only considered equations that were developing using assays that were traceable to reference methods and study populations in which SCr concentration was measured using traceable assays (Supplemental Table 1).[85]

Based on published data, only the Modification of Diet in Renal Disease (MDRD) Study equation, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and modifications of these equations were developed using creatinine assays traceable to the international reference material for creatinine (Table 12).[86,87] The Cockcroft and Gault formula and others were developed before standardization of creatinine assays but cannot be re-expressed for use with standardized creatinine assays (Supplemental Table 2).

The MDRD Study equation was developed in 1999 and is currently recommended for eGFR reporting in adults by the National Kidney Disease Education Program (NKDEP) and by the Department of Health in the UK. It uses standardized SCr, age, sex, and race (black versus white and other) to estimate GFR adjusted for BSA (ml/min/1.73 m^2).[86,94] Because of imprecision at higher GFR, NKDEP recommends that eGFR ≥ 60 ml/min/1.73 m^2 computed using the MDRD Study equation not be reported as a numeric value. For a similar reason, the UK Department of Health recommends not reporting eGFR >90 ml/min/1.73 m^2 using the MDRD Study equation as a numeric value.

The CKD-EPI equation was developed in 2009 and uses the same four variables as the MDRD Study equation.[87] The CKD-EPI equation had less bias than the MDRD Study equation, especially at GFR ≥ 60 ml/min/1.73 m^2, a small

Table 12 | Equations based on serum creatinine assays in adults that are traceable to the standard reference material

Study	Equation name	Equation	Development and internal validation population, *N*	GFR measurement method	SCr assay method
North America, Europe, and Australia					
Levey et al.[86]	MDRD equation	$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times 1.212$ (if black)	1628 patients enrolled in the MDRD Study (mean age, 50.6 y)	^{125}I-Iothalamate (urine); GFR measured in ml/min per 1.73 m^2; mean GFR, 39.8 ml/min per 1.73 m^2 (SD, 21.2)	Samples from MDRD Study were assayed from 1988 to 1994 with the Beckman Synchron CX3 kinetic Jaffe assay (Global Medical Instrumentation, Inc., Ramsey, Minnesota). Samples were reassayed in 2004 with the same instrument. The Beckman assay (Global Medical Instrumentation, Inc., Ramsey, Minnesota) was calibrated to the Roche enzymatic assay (Roche Diagnostics, Basel, Switzerland), which is traceable to an IDMS assay at NIST.
	MDRD equation without ethnicity factor*	$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female)			
Levey et al.[87]	CKD-EPI equation	$141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ (if female) $\times 1.159$ (if black), where κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.	8254 participants from 6 research studies and 4 clinical populations (mean age, 47 y)	^{125}I-Iothalamate (urine); GFR measured in ml/min per 1.73 m^2; mean GFR, 68 ml/min per 1.73 m^2 (SD, 40)	SCr values were recalibrated to standardized SCr measurements at the Cleveland Clinic by using a Roche enzymatic assay (Roche–Hitachi P-Module instrument with Roche Creatininase Plus assay, Hoffman-La Roche, Basel, Switzerland).
Outside of North America, Europe, and Australia					
Horio et al.[88]	MDRD equation with Japanese coefficient	$0.808 \times 175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female)	413 Japanese patients in 80 medical centers (mean age, 51.4 y)	Inulin (urine) GFR measured in ml/min per 1.73 m^2 (ND for development or internal validation set)	SCr levels were measured by using a Hitachi enzymatic creatinine assay and the values obtained were compared with those of the Cleveland Clinic.
Imai et al.[89]	Japanese-modified MDRD equation	$0.741 \times 175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female)	248 inpatients with CKD for estimating and determining the coefficient of the MDRD Study equation for Japanese patients (mean age, 50.1 y)	Inulin (urine) GFR measured in ml/min per 1.73 m^2 (ND for development or internal validation set)	SCr levels were assayed by both enzymatic and noncompensated kinetic Jaffe methods for the 116 patients in the inulin clinical study and by an enzymatic method for the 132 inpatients at Tokyo Women's Medical University between 2003 and 2004 and the 168 patients with CKD at the University of Tsukuba Hospital from 1988 to 1994. The SCr levels of the samples from the 101 patients from Tokyo Women's Medical University between 2001 and 2002 were measured by a noncompensated kinetic Jaffe method. SCr levels used in the inulin clinical trial were simultaneously measured by both the noncompensated kinetic Jaffe method and enzymatic method at the International Organization for Standardization–approved central laboratory. SCr values from the noncompensated Jaffe method were 0.207 higher than those from the enzymatic method throughout the measured range, based on calibrated standards which were indirectly calibrated with IDMS.

Table 12 | Continued

Study	Equation name	Equation	Development and internal validation population, *N*	GFR measurement method	SCr assay method
Praditpornsilpa et al.[90]	MDRD equation with Thai coefficient	$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.129 (if Thai)	250 cases of Thai patients with CKD patients who were in stable condition (mean age, 59.5 y)	^{99m}Tc-DTPA (plasma); GFR measured in ml/min per 1.73 m^2 (ND for development or internal validation set)	Fasting SCr levels measured by using a Roche enzymatic assay (Roche Diagnostics, Indianapolis, IN) and values adjusted by using IDMS reference SCr (SRM 967) from NIST. SCr levels also measured by a Roche kinetic Jaffe assay Roche (Roche Diagnostics, Indianapolis, IN) without adjustments to IDMS reference. SCr levels obtained from enzymatic and Jaffe assays were used in each estimated GFR equation accordingly.
Horio et al.[88]	CKD-EPI equation with Japanese coefficient	$0.813 \times 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ (if female) $\times$ 1.159 (if black), where κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.	413 Japanese patients in 80 medical centers (mean age, 51.4 y)	Inulin (urine) GFR measured in ml/min per 1.73 m^2 (ND for development or internal validation set)	SCr levels measured by Hitachi enzymatic assay and values obtained compared with those of the Cleveland Clinic.
Matsuo et al.[91]	JSN-CKDI equation (equation 2)	$171 \times SCr^{-1.004} \times age^{-0.287} \times 0.782$ (if female)	413 Japanese patients in 80 medical centers; data collected from 1 December 2006 to 20 April 2007 (mean age, 51.4 y)	Inulin (urine) Mean GFR, 59.1 ml/min per 1.73 m^2 (SD, 35.4)	SCr levels measured by Hitachi enzymatic assay (Hitachi, Tokyo, Japan) and values obtained compared with those of the Cleveland Clinic.
	3-variable Japanese equation (equation 4)	$194 \times SCr^{-1.094} \times age^{-0.287} \times 0.739$ (if female)			
Levey et al.[92]	Original MDRD equation, calibrated to the Cleveland Clinic creatinine measurements (study equation 2)†	$186 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female)	1628 patients whose GFR was measured as part of the MDRD Study (mean age, 50.6 y)	^{125}I-Iothalamate (urine) GFR measured in ml/min per 1.73 m^2; mean GFR, 39.8 ml/min per 1.73 m^2 (SD, 21.2)	Serum and urine creatinine levels measured by using kinetic Jaffe assay.
Ma et al.[93]	Original MDRD equation, calibrated to Cleveland Clinic creatinine measurements, with Chinese coefficient (study equation 4)†	$186 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.227 (if Chinese), with SCr calibrated to the Cleveland Clinic	454 patients from 9 renal institutes of university hospitals located in 9 geographic regions of China (mean age, 49.9 y)	^{99m}Tc-DTPA (plasma) GFR measured in ml/min per 1.73 m^2 (ND for development or internal validation set)	SCr levels measured by using Hitachi kinetic Jaffe assay and values calibrated to the Cleveland Clinic Laboratory.
	Chinese equation (study equation 6)‡	$206 \times SCr^{-1.234} \times age^{-0.227} \times 0.803$ (if female), with SCr calibrated to the Cleveland Clinic			
Praditpornsilpa et al.[90]	Thai estimated GFR equation	$375.5 \times SCr^{-0.848} \times age^{-0.364} \times 0.712$ (if female); $r^2 = 0.869$	250 Thai patients with CKD who were in stable condition (mean age, 59.5 y)	^{99m}Tc-DTPA (plasma) GFR measured in ml/min per 1.73 m^2 (ND for development or internal validation set)	Fasting SCr levels measured by using a Roche enzymatic assay (Roche Diagnostics, Indianapolis, IN) and values adjusted by using IDMS reference SCr (SRM 967) from NIST. SCr also measured by a Roche kinetic Jaffe assay (Roche Diagnostics, Indianapolis, IN) without adjustments to IDMS reference. SCr levels obtained from enzymatic and Jaffe assays used in each estimated GFR equation accordingly.

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; IDMS, isotope-dilution mass spectrometry; JSN-CKDI, Japanese Society of Nephrology-Chronic Kidney Disease Initiatives; MDRD, Modification of Diet in Renal Disease; ND, not documented; NIST, National Institute of Standards and Technology; SCr, serum creatinine; SRM, standard reference material; Tc-DTPA, technetium-diethylenetriamine pentaacetic acid.

*African American coefficient of the MDRD Study equation.

†Derived by using the original MDRD equation (with the 186 coefficient). For use with an SCr traceable to the SRM, the 186 coefficient should be replaced with the 175 coefficient from the reexpressed MDRD equation.

‡Derived by using the original MDRD equation (with the 186 coefficient). For use with an SCr traceable to the SRM, the SCr should be replaced by SCr $\times$ 0.95, which represents the calibration factor relating the SCr assay in the Cleveland Clinic laboratory to the standardized SCr assay.

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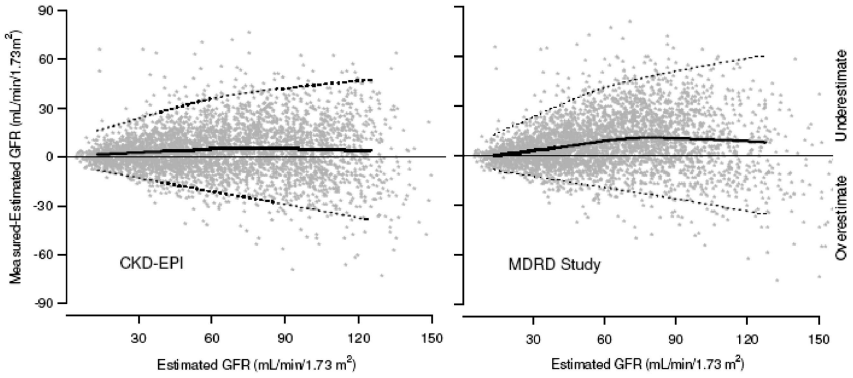


Figure 11 | Performance of the CKD-EPI and MDRD Study equations in estimating measured GFR in the external validation data set. Both panels show the difference between measured and estimated versus estimated GFR. A smoothed regression line is shown with the 95% CI (computed by using the lowest smoothing function in R), using quantile regression, excluding the lowest and highest 2.5% of estimated GFR. To convert GFR from ml/min per 1.73 m^2 to ml/s per m^2, multiply by 0.0167. CKI-EPD, Chronic Kidney Disease Epidemiology Collaboration; CI, confidence interval; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease. Reprinted with permission from Levey AS, Stevens LA, Schmid CH, et al.[87] A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150(9): 604-612.

improvement in precision, and greater accuracy (Figure 11). Most but not all studies from North America, Europe and Australia show that the CKD-EPI equation is more accurate than the MDRD Study equation, especially at higher GFR (Table 13),[85] which enables reporting of numeric values across the range of GFR. At this time, large commercial clinical laboratories in the US have changed from using the MDRD Study equation to the CKD-EPI equation for eGFR reporting.

Lesser bias of the CKD-EPI equation compared to the MDRD Study equation reflects higher eGFR throughout most of the range for age and creatinine, especially in younger individuals, women and whites. Higher eGFR results in lower prevalence estimates for CKD in these groups (Figure 12), with more accurate risk relationships of lower eGFR and adverse outcomes (Figure 13).[107]

To account for possible differences in muscle mass and diet according to race, ethnicity and geographic region, the MDRD Study and CKD-EPI equations have been modified for use in other racial and ethnic groups and in other countries. In some, but not all studies, these modifications are associated with increased accuracy (Table 14), and should be used in preference to unmodified equations. Where tested, the CKD-EPI equation and its modifications were generally more accurate than the MDRD Study and its modifications. In the absence of specific modifications for race, ethnicity, or regional difference, it is reasonable to use the CKD-EPI equation for GFR estimation. Reliance upon SCr alone is not an appropriate alternative since the uncertainty about the effect of non-GFR determinants affects interpretation of SCr as much as it affects interpretation of eGFR. More widespread testing of GFR estimating equations is necessary to resolve uncertainties about the need for racial, ethnic, and geographic modifications.[108]

Pediatric Considerations

This recommendation would need to be altered for application in pediatric practice in the following way.

- Creatinine measurements in all infants and children should be derived from methods that minimize confounders and are calibrated against an international standard.
- $eGFR_{creat}$ may only be reported when the height of the child is known by the laboratory.
- If reporting $eGFR_{creat}$ laboratories should utilize the most current and accurate pediatric derived equations based on the demographic and laboratory markers available.

In infants or small children the level of creatinine when measured is often below that of the normal 'bottom range' of the adult assay. As such laboratories measuring creatinine in infants or small children must ensure their lower calibration samples include the lowest end of the expected range of values for the group of interest.

As the majority and the most accurate of the published pediatric $eGFR_{creat}$ formulas require height, standard laboratory reporting of $eGFR_{creat}$ is neither practical nor recommended in children. In a pediatric CKD population, and using the plasma disappearance of iohexol as the gold standard measure of GFR, Schwartz et al. derived a number of novel GFR prediction equations.[80] Their analysis demonstrated the importance of the height/SCr variable in the population as it provided the best correlation with the iohexol GFR ($R^2 = 65\%$). The simplest of such formula, using only height and SCr and a constant of either 41.3 or 0.413 depending on whether height was expressed as meters or centimeters respectively, provided 79% of estimated GFRs within 30% of the iohexol values and 37% of estimated GFRs within 10% of the iohexol values.

Table 13 | Performance comparison of creatinine-based GFR estimating equations in North America, Europe, and Australia

				Measured GFR		GFR estimation		Results		
Study	Country	Population	Patients, *N*	Reference standard	Value (SD), *ml/min per 1.73* m^2	SCr calibration and assay	Equation	Bias (95% CI), *ml/min per 1.73* m^2*	Precision (95% CI)†	P_{30} (95% CI), %‡
Murata et al.[95]	United States	Adults who underwent an outpatient iothalamate clearance at the Mayo Clinic in Rochester, Minnesota (women, 45%; African American, 2%; mean age, 56 y; donor or potential donor, 13%; KTR, 26%)	5238	^{125}I-Iothalamate (urine)	55.9 (29.7)	Roche Jaffe assay (Roche P- or D-Modular or Roche Cobas C501 with Roche Creatininase Plus assay; Roche Diagnostics, Indianapolis, IN) with demonstrated IDMS alignment	MDRD CKD-EPI	−4.1 −0.7	ND	77.6 78.4
Levey et al.[87]	United States	External validation set comprising 16 studies (women, 45%; white or other, 87%; black, 10%; Hispanic, 2%; Asian, 2%; mean age, 50 y; diabetes, 28%; donor, 16%; KTRs, 29%)	3896	^{125}I-Iothalamate (urine) and others	68 (36)	Roche enzymatic assay (Roche–Hitachi P-Module instrument with Roche Creatininase Plus assay, Hoffman-La Roche, Basel, Switzerland) recalibrated to standardized SCr at the Cleveland Clinic	MDRD CKD-EPI	−5.5 (−5.0 to −5.9) −2.5 (−2.1 to −2.9)	0.274 (0.265 to 0.283)§ 0.250 (0.241 to 0.259)§	80.6 (79.5 to 82.0) 84.1 (83.0 to 85.3)
Lane et al.[96]	United States	Patients before and after nephrectomy for causes other than donation at the Cleveland Clinic (women, 93%; white, 91%; black, 7%; median age, 58 y)	425	^{125}I-Iothalamate (urine)	50 (IQR, 29 to 69)	Measured at the Cleveland Clinic; assay standardized against NIST	MDRD CKD-EPI	−1.0 −1.7	15.0‖ 13.8‖	75 80
Michels et al.[97]	The Netherlands	Potential kidney donors and adults who underwent GFR measurement for clinical reasons at the Academic Medical Center in Amsterdam (women, 56%; black, 12%; mean age, 44 y)	271	^{125}I-Iothalamate (urine)	78.2 ml/min (33.4)	Hitachi enzymatic assay (Hitachi H911; Boehringer Mannheim, Mannheim, Germany) validated against IDMS	MDRD CKD-EPI	14.6 ml/min 12.3 ml/min	19.9¶ 12.1¶	81.2 84.5
Tent et al.[98]	The Netherlands	Living kidney donors who donated from 1996–2007 (women, 57%; white, 100%; mean age, 50 y)	253 before donation	^{125}I-Iothalamate (urine)	115 ml/min (20)	Roche enzymatic assay or Jaffe assay on MEGA analyzer (Merck KGaA, Darmstadt, Germany); both methods calibrated to reference standard at the Cleveland Clinic	MDRD CKD-EPI	−22 ml/min (20 to 25) −14 ml/min (11 to 16)	20 (14 to 26)‖ 18 (14 to 22)‖	73 (68 to 79) 89 (85 to 93)
			253 after donation		73 ml/min (13)		MDRD CKD-EPI	−15 ml/min (14 to 16) −11 ml/min (9 to 11)	12 (9 to 15)‖ 12 (10 to 16)‖	71 (65 to 76) 89 (85 to 93)
Kukla et al.[99]	United States	KTRs receiving immunosuppression (women, 40%; white, 86%; mean age, 49 y; receiving trimethoprim, 100%)	107 on steroid-free immunosuppression early posttransplantation	^{125}I-Iothalamate (urine)	55.5 (17.0)	Measured by using a Jaffe CXR Synchron method and, later, an IDMS-traceable assay; Jaffe assay-based SCr converted to IDMS-traceable values	MDRD CKD-EPI	8.23 13.30	17.9§ 21.1§	71.7 58.5
			81 on steroid-free immunosuppression at 1 y		56.8 (17.7)		MDRD CKD-EPI	2.40 6.91	15.8§ 17.3§	75.0 66.7
White et al.[100]	Canada	Stable KTRs (women, 36%; white, 92%; receiving trimethoprim, 19%)	207	^{99m}Tc-DTPA (plasma)	58 (22)	For the reexpressed MDRD Study and CKD-EPI equations, SCr adjusted to IDMS standard	MDRD CKD-EPI	−7.4 −5.2	14.4‖ 15.7‖	79 (73 to 84) 84 (78 to 88)
Pöge et al.[101]	Germany	Patients with stable renal function after transplantation (women, 40%; white, 99%; mean age, 49 y)	170	^{99m}Tc-DTPA (plasma)	39.6 (IQR, 11.8 to 82.9)	Jaffe assay on Dimension RxLTM analyzer (Dade Behring, Marburg, Germany); assay adjusted for calibration with the IDMS method	MDRD CKD-EPI	4.49 8.07	10.0¶ 10.9¶	71.8 64.1
Jones and Imam[102] and Jones[103]	Australia	Australian patients referred for routine GFR measurements (women, 43%; mean age, 61 y)	169	^{99m}Tc-DTPA (plasma)	75 (IQR, 5 to 150)	Roche Jaffe assay (Roche, Australia) with demonstrated IDMS alignment	MDRD CKD-EPI	−3** −1.5**	ND	81 86

Table 13 Continued

Study	Country	Population	Patients, *N*	Measured GFR: Reference standard	Measured GFR: Value (SD), *ml/min per 1.73* m^2	GFR estimation: SCr calibration and assay	GFR estimation: Equation	Results: Bias (95% CI), *ml/min per 1.73* m^2*	Results: Precision (95% CI)†	Results: P_{30} (95% CI), %‡
Cirillo et al.[104]	Italy	White adults with and without kidney disease (with kidney disease, 49%; women, 41%; mean age, 47 y; diabetic nephropathy, 26 cases; glomerulonephritis, 40 cases; PKD, 15 cases)	356	Inulin (plasma)	71.5 (36.3)	Kinetic Jaffe assay (Bayer Express Plus; Siemens, Munich, Germany) standardized to NIST	MDRD CKD-EPI	−5.2 −0.9	14.9¶ 13.2¶	87.4 88.2
Eriksen et al.[105]	Norway	Patients participating in the 6th Tromsø population survey who had no previous myocardial infarction, angina, stroke, diabetes, or renal disease (women, 51%; mean age, 57 y)	1621	Iohexol (plasma)	91.7 (14.4)	Hitachi enzymatic method (CREA Plus; Roche Diagnostics, Mannheim, Germany) standardized against IDMS	MDRD CKD-EPI	1.3 (0.4 to 2.1) 2.9 (2.2 to 3.5)	18.2 (17.2 to 19.5)‖ 15.4 (14.5 to 16.3)‖	93 (91 to 94) 95 (94 to 96)
Redal-Baigorri et al.[106]	Denmark	Patients with cancer who were referred for determination of GFR before chemotherapy (women, 57%; mean age, 62 y)	185	^{51}Cr-EDTA (plasma)	85.1 (20.3)	Jaffe (Abbott Architect C systems 8000, reagent 7D64; Abbott Park, Illinois) method standardized to IDMS	MDRD CKD-EPI	0.81 (IQR −1.56 to 3.19) 1.16 IQR (−0.76 to 3.09)	16.49¶ 13.37¶	88.6 89.7

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CI, confidence interval; Cr-EDTA, chromium-ethylenediamine tetraacetic acid; GFR, glomerular filtration rate; IDMS, isotope-dilution mass spectrometry; IQR, interquartile range; KTR, kidney transplant recipient; MDRD, Modification of Diet in Renal Disease; ND, not documented; NIST, National Institute of Standards and Technology; P_{30}, percentage of estimated GFR values within 30% of measured GFR; PKD, polycystic kidney disease; SCr, serum creatinine; Tc-DTPA, technetium-diethylenetriamine pentaacetic acid.

*Computed as estimated GFR minus measured GFR. Positive numbers indicate overestimation and negative numbers indicate underestimation of measured GFR. Smaller absolute values indicate lesser bias.

†Lower values indicate greater precision.

‡Higher values indicate greater accuracy. Among the 3 studies[99,101,104] that reported alternative measures of accuracy, results were consistent with P_{30} in all. In addition to P_{30}, three references[99,101,104] reported P_{10}; Cirillo et al.[104] also reported P_{20}.

§Evaluated as the root mean squared error for the regression of estimated GFR on measured GFR.

‖Evaluated as the IQR for the differences between estimated and measured GFR.

¶Evaluated as the SD of the differences between estimated and measured GFR.

**Converted to raw scale by multiplying percentage of bias by measured GFR.

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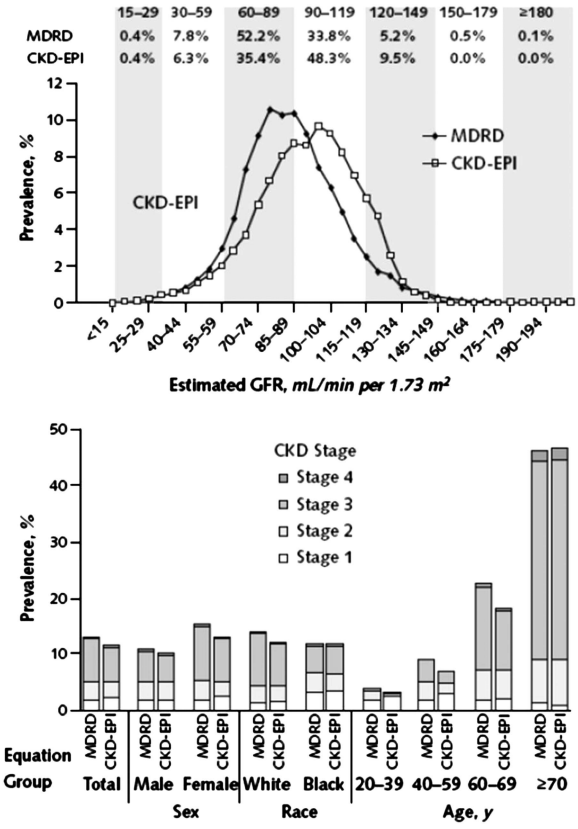


Figure 12 | Comparison of distribution of GFR and CKD prevalence by age (NHANES 1999-2004). GFR was categorized on the basis of the classification system established by the NKF-KDOQI. Top. Distribution of estimated GFR, by 4-ml/min per 1.73 m^2 categories. Values are plotted at the midpoint. Bottom. Prevalence of CKD, by age. CKD, chronic kidney disease; GFR, glomerular filtration rate; NKF-KDOQI, National Kidney Foundation-Kidney Disease Outcomes Quality Initiative; NHANES, National Health and Nutrition Examination Survey. Reprinted with permission from Levey AS, Stevens LA, Schmid CH, et al.[87] A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150(9): 604-612.

Any $eGFR_{creat}$ formula used in children will preferably be validated at the appropriate age and level of renal function, and the laboratory methods used locally will be calibrated or comparable to those used in the process of developing the formula being applied. Currently the most robust pediatric eGFR formulas, derived using iohexol disappearance and creatinine measurements which were measured centrally and calibrated and traceable to international standards come from the CKiDs study.[80]

The two most common creatinine-based formulas recommended for use in clinical practice include:

Updated "Bedside" Schwartz equation:

eGFR (ml/min/1.73 m^2) = 41.3 × (height/SCr), where height is in meters and SCr is in mg/dl.

"1B" Equation (include blood urea nitrogen [BUN] not cystatin C):

eGFR (ml/min/1.73 m^2) = $40.7 \times (\text{height/SCr})^{0.64} \times (30/\text{BUN})^{0.202}$, where height is in meters, SCr and BUN are in mg/dl.

The additional recommendation for laboratory reporting of SCr is fully applicable in pediatrics.

When the individual clinician has information regarding current and accurate height and applies the appropriate pediatric formula, the recommendation to report an individual child's $eGFR_{creat}$ value of less than 60 ml/min/1.73 m^2 as "decreased," would be applicable in children over the age of 2 years.

1.4.3.5: We suggest measuring cystatin C in adults with $eGFR_{creat}$ 45-59 ml/min/1.73m^2 who do not have markers of kidney damage if confirmation of CKD is required. (*2C*)

- **If $eGFR_{cys}$/$eGFR_{creat\text{-}cys}$ is also <60 ml/min/1.73 m^2, the diagnosis of CKD is confirmed.**
- **If $eGFR_{cys}$/$eGFR_{creat\text{-}cys}$ is ≥ 60 ml/min/1.73 m^2, the diagnosis of CKD is not confirmed.**

RATIONALE

A major foundation of this guideline is that CKD classification and staging should be influenced primarily by clinical prognosis. As will be reviewed in the sections below, abundant evidence has shown that GFR estimates based on cystatin C are more powerful predictors of clinical outcomes than creatinine-based eGFR. These findings have been strongest for mortality and CVD events, and the prognostic advantage of cystatin C is most apparent among individuals with GFR >45 ml/min/1.73 m^2. In addition, new findings show that using cystatin C in addition to SCr can lead to improved accuracy of GFR estimation, including CKD classification. In the opinion of the Work Group, these considerations warrant new recommendations for GFR estimation using cystatin C.

Evidence Base

Evidence supports the use of cystatin C-based eGFR within the population of persons diagnosed with CKD based on an $eGFR_{creat}$ 45-59 ml/min/1.73 m^2 (G3a) but without albuminuria (A1) or other manifestations of kidney damage. This group represents 3.6% of the US population and 41% of people in the US estimated to have CKD based on $eGFR_{creat}$ and urine ACR alone (Figure 8), and there has been substantial controversy over whether or not these persons have CKD. Data described below indicate that use of cystatin C to estimate GFR in this population leads to more accurate estimation of GFR and prediction of risk for future adverse events.

In several studies, $eGFR_{cys}$ has been measured in populations with and without $eGFR_{creat}$ <60 ml/min/1.73 m^2, and participants were separated into those with and without $eGFR_{cys}$ <60 ml/min/1.73 m^2 (Figure 14). Those with both $eGFR_{creat}$ and $eGFR_{cys}$ <60 ml/min/1.73 m^2, about two-thirds of those with $eGFR_{creat}$ <60 ml/min/1.73 m^2, had

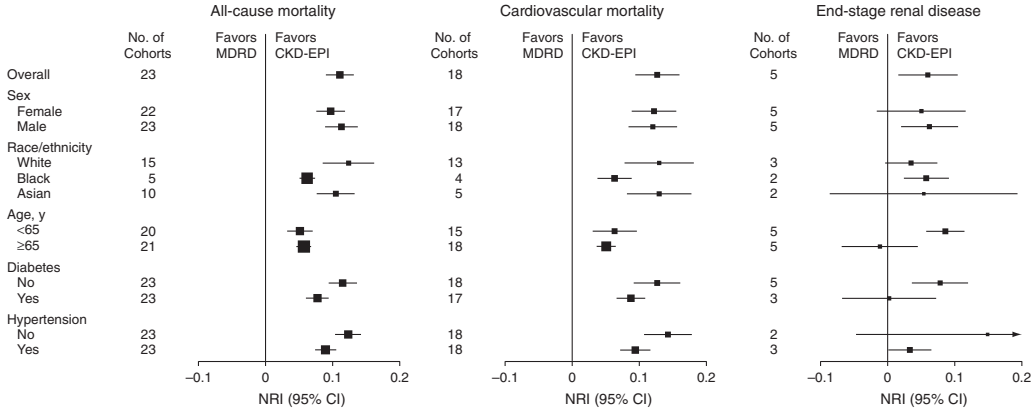


Figure 13 | Meta-analysis of NRI for all-cause mortality, CVD mortality, and ESRD. NRI summarizes the risk of clinical outcomes among participants who are reclassified from one estimated GFR category using the MDRD Study equation to another estimated GFR category using the CKD-EPI equation compared with those who are not reclassified. NRI greater than zero favors the CKD-EPI equation. NRI less than zero favors the MDRD Study equation. The sizes of the data markers are proportional to the inverse of the variance of the NRIs. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NRI, net reclassification improvements. Reprinted with permission from Matsushita K, Mahmoodi BK, Woodward M, et al.[107] Comparison of risk prediction using the CKD-EPI equation and the MDRD Study equation for estimated glomerular filtration rate. JAMA 2012; 307(18): 1941-1951. Copyright © (2012) American Medical Association. All rights reserved.

markedly elevated risks for death, CVD, and ESRD end points compared with persons with $eGFR_{creat} > 60$ ml/min/1.73 m^2. The Work Group therefore considers this group to have "confirmed CKD." In contrast, about one-third of those with $eGFR_{creat} < 60$ ml/min/1.73 m^2 had $eGFR_{cys} > 60$ ml/min/1.73 m^2 and this group were similar in risk for adverse outcomes as persons with $eGFR_{creat} > 60$ ml/min/1.73 m^2.

New data from CKD-EPI also showed improved accuracy in GFR estimation using both creatinine and cystatin C ($eGFR_{creat-cys}$) compared to either marker alone. In the subgroup with $eGFR_{creat}$ 45-59 ml/min/1.73 m^2, the combined equation correctly reclassified 16.8% of those with eGFR 45-59 ml/min/1.73 m^2 to measured GFR ≥ 60 ml/min/1.73 m^2.[113]

The consensus of the Work Group was therefore that the large group of persons with $eGFR_{creat}$ 45-59 ml/min/1.73 m^2 without markers of kidney damage, but with $eGFR_{cys}$/$eGFR_{creat-cys}$ ≥ 60 ml/min/1.73 m^2 could be considered not to have CKD. The removal of the diagnosis and label of CKD may be reassuring to patients and may help clinicians to focus their efforts on higher risk CKD patients.

The guideline statement suggesting the use of $eGFR_{cys}$/$eGFR_{creat-cys}$ requires several important qualifiers. First, clinicians may not want or need to confirm the diagnosis of CKD in patients with $eGFR_{creat}$ 45-59 ml/min/1.73 m^2 without markers of kidney damage, either because the likelihood of CKD is high because of the presence of risk factors for CKD or presence of complications of CKD. Second, cystatin C is not universally available, so it may not be practical for a clinician to request a cystatin C blood test. Third, in certain clinical settings, the cost of measuring cystatin C (US $1–5) may be prohibitive. For all these reasons, the guideline statement 1.4.3.5 is stated as a suggestion.

In addition to the population described above, $eGFR_{cys}$ may be useful as a confirmatory test in situations where either the $eGFR_{creat}$ may be inaccurate or biased, or when the clinical scenario warrants a secondary test (Recommendation 1.4.3.2). In these clinical situations, a clearance measurement using an exogenous filtration marker may be optimal when it is available. The measurement of $eGFR_{cys}$/$eGFR_{creat-cys}$ would be a relatively low-cost, feasible alternative when GFR measurement is not practical. The Work Group believed that measured urinary CrCl was an inferior confirmatory test relative to either GFR measurement or GFR estimation using both creatinine and cystatin C.

If cystatin C testing is desired, it is very important that clinicians understand principles of GFR estimation using cystatin C. As with creatinine, GFR should be estimated from cystatin C and an appropriate equation should be chosen for the specific clinical population (Recommendation 1.4.3.6), and an assay be chosen for measurement that is traceable to the international standard reference material (Recommendation 1.4.3.7).

Pediatric Considerations

The utility of this specific statement to pediatrics is unclear as the vast majority of children with significant reductions in GFR, e.g., below 60 ml/min/1.73 m^2, have either structural abnormalities or findings of renal damage as evidenced by urinary or serum abnormalities. It is very unlikely that isolated reduction in GFR would occur as in older adults. As such, the confirmation of CKD will be made on criteria beyond that of GFR alone.

1.4.3.6: If cystatin C is measured, we suggest that health professionals (*2C*):

- **use a GFR estimating equation to derive GFR from serum cystatin C rather than relying on the serum cystatin C concentration alone.**
- **understand clinical settings in which $eGFR_{cys}$ and $eGFR_{creat-cys}$ are less accurate.**

Table 14. Performance comparison of creatinine-based GFR estimating equations outside of North America, Europe, and Australia

				Measured GFR		GFR estimation		Results		
Study	Country	Population	Patients, *N*	Reference standard	Value (SD), *ml/min per 1.73* m^2	SCr calibration and assay	Equation	Bias (95% CI), *ml/min per 1.73* m^2*	Precision (95% CI)†	P_{30} (95% CI), %‡
Stevens et al.[109]	China, Japan, and South Africa	Populations from 3 studies in China, Japan, and South Africa (women, 48%; Asian, 90%; black, 10%; mean age, 49 y; diabetes, 6%; KTRs, 0%)	99 black patients (South Africa)	^{125}I-Iothalamate (urine) and other filtration markers	61 (32)	Calibrated to standardized SCr measurements by using Roche (Roche-Hitachi P-Module instrument with Roche Creatininase Plus assay; Hoffmann–La Roche, Basel, Switzerland) enzymatic assay at the Cleveland Clinic	CKD-EPI equation with 2-level race or ethnicity coefficient CKD-EPI equation with 4-level race or ethnicity coefficient	12.4 (7.6 to 18.3) 12.5 (7.6 to 18.4)	0.326 (0.292 to 0.361)‖ 0.327 (0.292 to 0.362)‖	55.6 (46.5 to 64.6) 55.6 (46.5 to 64.6)
			248 Asian patients (Japan)		55 (35)		CKD-EPI equation with 2-level race or ethnicity coefficient CKD-EPI equation with 4-level race or ethnicity coefficient	17.8 (14.7 to 20.1) 21.4 (18.2 to 23.3)	0.469 (0.424 to 0.515)‖ 0.507 (0.463 to 0.553)‖	29.4 (23.8 to 35.1) 36.3 (30.6 to 42.3)
			675 Asian patients (China)		53 (31)		CKD-EPI equation with 2-level race or ethnicity coefficient CKD-EPI equation with 4-level race or ethnicity coefficient	−2.7 (−3.7 to −1.9) −1.3 (−2.2 to −0.6)	0.325 (0.302 to 0.348)‖ 0.318 (0.295 to 0.343)‖	73.2 (69.9 to 76.6) 72.1 (68.7 to 75.7)
Matsuo et al.[91]	Japan	Hospitalized Japanese patients; external validation set (women, 42%; mean age, 54 y; diabetes, 44 cases; donors, 10; KTRs, 2; glomerulonephritis, 176 cases; PKD, 0 cases; lupus, 3 cases)	350	Inulin (urine)	57.2 (34.7) (GFR ≥60, 41%; GFR <60, 59%)	Hitachi enzymatic assay (Hitachi, Tokyo, Japan) with excellent agreement against Cleveland Clinic	MDRD Japanese-modified MDRD (equation 1) JSN-CKDI equation (equation 2) MDRD with Japanese coefficient (equation 3) 3-variable Japanese equation (equation 4)	12.0 −5.9 −7.9 −1.3 −2.1	25.2‖ 19.9‖ 20.3‖ 19.4‖ 19.1‖	59 (54 to 64) 72 (67 to 76) 73 (69 to 78) 73 (59 to 78) 75 (70 to 79)
Horio et al.[88]	Japan	Japanese patients (women, 42%; mean age, 54 y; diabetes, 22%; donors, 3%; KTRs, 1%; hypertension, 58%)	350	Inulin (urine)	45 (25)	Enzymatic assay validated by using the calibration panel of the Cleveland Clinic	MDRD with Japanese coefficient CKD-EPI with Japanese coefficient	−1.3 −0.4	19.4‖ 17.8‖	73 (69 to 78) 75 (70 to 79)
Yeo et al.[110]	Korea	Korean KTRs in the early postoperative period (women, 43%; mean age, 42 y; diabetes, 16%)	102	^{51}Cr-EDTA (plasma)	76.8 (17.0)	Rate-blanked, Toshiba-compensated kinetic Jaffe assay (Toshiba Medical Systems Tokyo, Japan) using a Roche calibrator (Roche Diagnostics, Indianapolis, Indiana) traceable to IDMS reference method	MDRD Japanese-modified MDRD	−0.33 17.95	12.57¶ 11.06¶	94.1 68.6
van Deventer et al.[111]	South Africa	Black South African patients (women, 49%; median age, 47 y; diabetes, 25%; donors, 7%; HIV, 20%; hypertension, 36%)	100	^{51}Cr-EDTA (plasma)	61.5 (49.6)	Rate-blanked, Roche-compensated, kinetic Jaffe assay (Roche Modular analyzer; Roche Diagnostics, Indianapolis, Indiana) with calibration traceable to IDMS, compared with Roche enzymatic assay (Creatinine Plus; Roche Diagnostics, Indianapolis, Indiana) at the Cleveland Clinic with values adjusted by regression	MDRD with race or ethnicity factor** MDRD without race or ethnicity factor**	13.1 (5.5 to 18.3) 1.9 (−0.8 to 4.5)	28.5‖ 16.6‖	52 74

Table 14 Continued

Study	Country	Population	Patients, *N*	Measured GFR: Reference standard	Measured GFR: Value (SD), *ml/min per 1.73* m^2	GFR estimation: SCr calibration and assay	GFR estimation: Equation	Results: Bias (95% CI), *ml/min per 1.73* m^2*	Results: Precision (95% CI)†	Results: P_{30} (95% CI), %‡
Teo et al.[112]	Singapore	Outpatients with CKD in the nephrology clinic at National University Hospital, Singapore (women, 48%; Chinese, 41%; Malay, 31%; Indian or other, 28%; median age, 58 y; diabetes, 23%; hypertension, 50%)	232	^{99}Tc-DTPA (plasma)	51.7 (27.5) (GFR ≥60, 69%; GFR <60, 31%)	Siemens enzymatic assay (Siemens Advia 2400; Siemens, Munich, Germany) calibrated with manufacturer-provided materials traceable to standardized creatinine (NIST SRM 967) measured by using IDMS	MDRD	−3.0 (−4.2 to −1.7)	12.2 (10.0 to 14.4)§	79.7 (74.6 to 84.9)
							CKD-EPI	−1.2 (−2.7 to 0.3)	12.1 (9.0 to 15.1)§	82.8 (77.9 to 87.6)
Ma et al.[93]	China	Patients with CKD from 9 renal institutes at university hospitals located in 9 geographic regions of China	230	^{99}Tc-DTPA (plasma)	ND	Hitachi kinetic Jaffe assay with values adjusted by regression analysis to Cleveland Clinic Beckman CX3 assay (Beckman Coulter, Fullerton, California)	Original MDRD equation, calibrated to the Cleveland Clinic creatinine measurements (study equation 2)††	−7.8 (−21.5 to −1.8)	ND	66.1
							Original MDRD equation, calibrated to Cleveland Clinic creatinine measurements, with Chinese coefficient (study equation 4)††	−0.9 (−9.6 to 7.4)	ND	77.8
							Chinese equation (study equation 6)††	−0.8 (−9.7 to 7.4)	ND	79.6
Praditpornsilpa et al.[90]	Thailand	Thai patients with CKD who were in stable condition	100	^{99}Tc-DTPA (plasma)	51.1 (28.4)	Roche enzymatic assay (Roche Diagnostics, Indianapolis, Indiana) with values adjusted to IDMS reference serum SRM 967	MDRD	−11.9	8.8¶	62.7
							CKD-EPI	−10.9	7.8¶	68.0
							MDRD equation with Thai racial factor correction	−10.3	8.5¶	73.3
							Thai estimated GFR equation	−7.2	6.3¶	90.0

CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CI, confidence interval; Cr-EDTA, chromium-ethylenediamine tetraacetic acid; GFR, glomerular filtration rate; IDMS, isotope-dilution mass spectrometry; JSN-CKDI, Japanese Society of Nephrology-Chronic Kidney Disease Initiatives; KTR, kidney transplant recipient; MDRD, Modification of Diet in Renal Disease; ND, not documented; NIST, National Institute of Standards and Technology; P_{30}, percentage of estimated GFR values within 30% of measured GFR; PKD, polycystic kidney disease; SCr, serum creatinine; SRM, standard reference material; Tc-DTPA, technetium-diethylenetriamine pentaacetic acid.

* Computed as estimated GFR minus measured GFR. Positive numbers indicate overestimation and negative numbers indicate underestimation of measured GFR. Smaller absolute values indicate lesser bias.

†Lower values indicate greater precision.

‡Higher values indicate greater accuracy. Among the 5 studies[90,91,93,110,112] that reported alternative measures of accuracy, results were consistent with P_{30} in 3. Of the studies reporting results consistent with P_{30}, Praditpornsilpa et al.[90] reported P_{10} and P_{15}, Yeo et al.[110] reported P_{10}, and Matsuo et al.[91] reported P_{15}. Two studies[93,112] reported inconsistent results between P_{15} and P_{30}.

§Evaluated as the interquartile range for the differences between estimated and measured GFR.

‖Evaluated as the root mean squared error for the regression of estimated GFR on measured GFR.

¶Evaluated as the SD of the differences between estimated and measured GFR.

**African American coefficient of the MDRD Study equation.

††Derived by using the original MDRD equation (with the 186 coefficient). For use with an SCr traceable to the SRM, the 186 coefficient should be replaced with the 175 coefficient from the reexpressed MDRD equation.

‡‡Derived by using the original MDRD equation (with the 186 coefficient). For use with an SCr traceable to the SRM, the SCr should be replaced by SCr × 0.95, which represents the calibration factor relating the SCr assay in the Cleveland Clinic laboratory to the standardized SCr assay.

Reprinted with permission from Earley A, Miskulin D, Lamb EJ, et al.[85] Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. Ann Intern Med 2012; 156(11): 785-795.

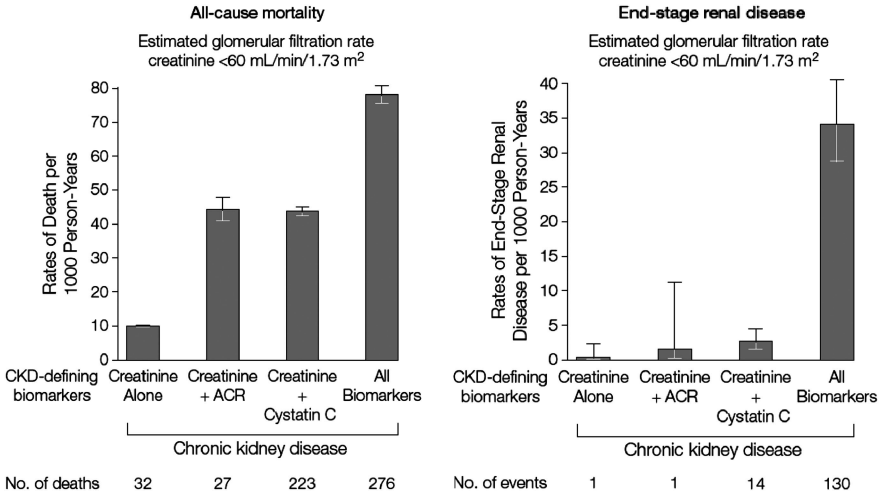


Figure 14 | Association of CKD definitions with all-cause mortality and ESRD. CKD, chronic kidney disease; ESRD, end-stage renal disease. Reprinted with permission from Peralta CA, Shlipak MG, Judd S, et al.[114] Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. JAMA 2011; 305(15): 1545-1552. Copyright © (2011) American Medical Association. All rights reserved.

Table 15 | Sources of error in GFR estimating using cystatin C

Source of error	Example
Non-steady state	• AKI
Non-GFR determinants of SCysC that differ from study populations in which equations were developed	
Factors affecting cystatin C generation	• Race/ethnicity other than US and European black and white • Disorders of thyroid function • Administration of corticosteroids • Other hypothesized factors based on epidemiologic associations (diabetes, adiposity)
Factors affecting tubular reabosrption of cystatin C	None identified
Factors affecting extra-renal elimination of cystatin C	Increased by severe decrease in GFR
Higher GFR	• Higher biological variability in non-GFR determinants relative to GFR • Higher measurement error in SCysC and GFR
Interference with cystatin C assay	• Heterophilic antibodies

Abbreviations: AKI, acute kidney injury; GFR, glomerular filtration rate, SCysC, serum cystatin C.

RATIONALE

Cystatin C is licensed for use in some countries in Europe and has been approved by the FDA as a measure of kidney function in the United States for nearly 10 years. In certain regions, notably Sweden and parts of China, eGFR is routinely estimated by both creatinine and cystatin C. As with creatinine, GFR estimates using cystatin C are more accurate in estimating measured GFR than the SCysC concentration alone. As with creatinine, sources of error in GFR estimation from SCysC concentration include non-steady state conditions, non-GFR determinants of SCysC, measurement error at higher GFR, and interferences with the cystatin C assays (Table 15).

Pediatric Considerations

For Recommendation 1.4.3.6, this guideline is fully applicable in pediatrics. See Recommendation 1.4.3.7 for details.

In terms of clinical settings where $eGFR_{cys}$ might be less accurate, it should be noted that Schwartz et al. determined that the only variable that explained the outlier values of estimated GFR (in both univariate and multivariate formulas) was heavier weight; race, high blood pressure, albumin levels and use of steroids did not contribute.[115]

1.4.3.7: We recommend that clinical laboratories that measure cystatin C should (*1B*):

- **measure serum cystatin C using an assay with calibration traceable to the international standard reference material.**
- **report eGFR from serum cystatin C in addition to the serum cystatin C concentration in adults and specify the equation used whenever reporting $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$.**
- **report $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$ in adults using the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C equations, respectively, or an alternative cystatin C-based GFR estimating equations if they have been shown to improve accuracy of GFR estimates compared to the 2012 CKD-EPI cystatin C and 2012 CKD-EPI creatinine-cystatin C equations.**

When reporting serum cystatin C:

- **We recommend reporting serum cystatin C concentration rounded to the nearest 100^{th} of a whole number when expressed as conventional units (mg/l).**

When reporting $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$:

- **We recommend that $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$ be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m^2 in adults using the units ml/min/1.73 m^2.**
- **We recommend $eGFR_{cys}$ and $eGFR_{creat\text{-}cys}$ levels less than 60 ml/min/1.73m^2 should be reported as "decreased."**

RATIONALE

As for SCr, reporting eGFR using cystatin C in addition to cystatin C will facilitate clinician's use of cystatin C for GFR estimation. It is important to acknowledge that calibration of assays is essential to interpretation of kidney function measures. Cystatin C is measured by a variety of immunoassays and, as for creatinine, there can be variation among methods in reported SCysC concentration but reported analytic variation appears less common than with creatinine. In June 2010 the Institute for Reference Materials and Measurements (IRMM) released a reference material (ERM-DA471/IFCC) for cystatin C measurement. Reagent manufacturers are in the process of recalibrating their assays against this standard which will enable standardized reporting of cystatin C and eGFR results. This recommendation is directed to laboratories with the intent to clarify the details of such calibration and the use of specific equations so as to facilitate international standardization.

Evidence Base

Numerous equations have been developed to estimate GFR. Some equations include cystatin C as the only variable, while others include, age, sex, or race, but the magnitude of coefficients for these variables are smaller than in creatinine-based equations, presumably reflecting less contribution of muscle to cystatin C generation than to creatinine generation. Equations without race are a potential advantage for cystatin C-based estimating equations in non-black, non-white populations.

For our review of GFR estimating equations, we only considered equations that were developed using assays that were traceable to the new reference methods and study populations in which SCysC concentration was measured using traceable assays. At this time, only the equations developed by CKD-EPI are expressed for use with standardized SCysC (Table 16), including equations developed in CKD populations in 2008[116,117] and re-expressed for use with standardized cystatin C in 2011, and equations developed in diverse populations in 2012.[113] Equations using assays that are not traceable to the the reference standard are listed in Supplemental Table 3.

The 2012 creatinine-cystatin C equation is more accurate than equations using creatinine or cystatin C separately (Figure 15), and more accurate than the 2008 creatinine-cystatin C equation (Table 17). The average of the GFR computed by the equations using creatinine and cystatin C separately is similar to the GFR computing using the creatinine-cystatin C equations. The 2012 cystatin C equation has similar accuracy to the 2009 creatinine equation described above but does not require use of race, and may be more accurate in non-black, non-white populations or in clinical conditions with variation in non-GFR determinants of SCr. We anticipate the development of additional equations using cystatin C in the future and recommend that they be compared with the CKD-EPI 2012 cystatin C and creatinine-cystatin C equations as well as with the CKD-EPI 2009 creatinine equation.

Pediatric Considerations

For Recommendation 1.4.3.7 this set of statements would need to be altered for application in pediatric practice in the following way:

- Measure SCysC using an immunonephelometrically determined method in which the assay is calibrated and traceable to the international standard reference material.
- Report $eGFR_{cys}$ in addition to the SCysC concentration in children.
- Report $eGFR_{cys}$ in children specifying the specific equation used.

Based on their recent work comparing particle-enhanced nephelometric to turbidometric immunoassays for cystatin C in a pediatric population with significant reduction in GFR (median GFR $\sim$45 ml/min/1.73 m^2), Schwartz et al. demonstrated less bias for the nepholometric value and that its reciprocal showed a substantially improved correlation to the iohexol GFR (0.87 versus 0.74) when compared to that of the

Table 16 | Equations based on IDMS traceable creatinine and IFCC traceable cystatin C assays

Equation name	Equation	*N*, Development and internal validation population	GFR measurement method	SCr and/or SCysC method	Reference
Cystatin C equations					
CKD-EPI cystatin C (alone) 2008 Re-expressed 2011	$76.7 \times (-0.105 + 1.13 \times \text{standardized SCysC})^{-1.19}$	2,980 participants from pooled individual-level patients data from the MDRD Study, African American Study of Kidney Disease (AASK), and Collaborative Study Group (CSG)	^{125}I-Iothalamate (U) [Mean GFR 51 ± 26 ml/min/1.73 m^2] Units for GFR in ml/min/1.73 m^2	SCr assays were calibrated to standardized SCr values at the Cleveland Clinic Research Laboratory (CCRL; Cleveland, OH). Results of the calibration procedure for the MDRD Study, AASK, and CSG were described previously. Samples for all studies had been frozen at -70°C until 2005 to 2006, when SCysC was measured at the CCRL by using a particle enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring, Deerfield, IL). Interassay coefficients of variation for the assay were 5.05% and 4.87% at mean concentrations of 0.97 and 1.90 mg/l (72.7 and 142.3 nmol/l), respectively. SCr in mg/dl SCysC in mg/l	Stevens LA, et al.[117] Inker LA, et al.[116]
CKD-EPI cystatin C 2008 Re-expressed 2011	$[127.7 * (-0.105 + 1.13 \times \text{standardized SCysC})^{-1.17} \times \text{age}^{-0.13} \times 0.91$ [if female] $\times 1.06$ [if black]]				
CKD-EPI creatinine-cystatin C 2008 Re-expressed 2011	$[177.6 * \text{SCr}^{-0.65} \times (-0.105 + 1.13 \times \text{standardized SCysC})^{-0.57} \times \text{age}^{-0.20} \times 0.82$ [if female] $\times 1.11$ [if black]]				
CKD-EPI cystatin C 2012	$133 \times \min(\text{SCysC}/0.8, 1)^{-0.499} \times \max(\text{SCysC}/0.8, 1)^{-1.328} \times 0.996^{\text{Age}} \times 0.932$ [if female] where SCysC is serum cystatin C, min indicates the minimum of SCysC/0.8 or 1, and max indicates the maximum of SCysC/0.8 or 1	5352 participants from 13 studies (7 RS and 6 CP)	^{125}I-Iothalamate (U) [Mean GFR 68 (39) ml/min/1.73 m^2 ; 51% GFR ≥60 ml/min/1.73 m^2; 49% GFR <60 ml/min/1.73 m^2] Units for GFR in ml/min/1.73 m^2	All assays were performed at the Cleveland Clinic Research Laboratory (Cleveland, OH). We calibrated SCr assays or measured serum SCr directly by the Roche enzymatic method (Roche-Hitachi P-Module instrument with Roche Creatininase Plus assay, Hoffman-La Roche, Ltd., Basel, Switzerland), that had been confirmed to be traceable to National Institute Standardized Technology (NIST) creatinine standard reference material 967. We calibrated SCysC assays or measured SCysC directly on the Siemens Dade Behring Nephelometer. We recently reported standardization of this assay to the recently released certified reference materials for cystatin C from the International Federation for Clinical Chemists (IFCC) Working Group for the Standardization of SCysC and the Institute for Reference Materials and Measurements (IRMM) at the University of Minnesota. SCr in mg/dl SCysC in mg/l	Inker LA, et al.[113]
CKD-EPI creatinine-cystatin C 2012	$135 \times \min(\text{SCr}/\kappa, 1)^{\alpha} \times \max(\text{SCr}/\kappa, 1)^{-0.601} \times \min(\text{SCysC}/0.8, 1)^{-0.375} \times \max(\text{SCysC}/0.8, 1)^{-0.711} \times 0.995^{\text{Age}} \times 0.969$ [if female] $\times 1.08$ [if black] where SCr is serum creatinine, SCysC is serum cystatin C, κ is 0.7 for females and 0.9 for males, α is -0.248 for females and -0.207 for males, min(SCr/κ,1) indicates the minimum of SCr/κ or 1, and max(SCr/κ,1) indicates the maximum of SCr/κ or 1; min(SCysC/0.8,1) indicates the minimum of SCysC/0.8 or 1 and max(SCysC/0.8,1) indicates the maximum of SCysC/0.8 or 1				

Abbreviations: AASK, African American Study of Kidney Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CP, clinical population; GFR, glomerular filtration rate; IDMS, isotope-dilution mass spectrometry; IFCC, International Federation for Clinical Chemists; IRMM, Institute for Reference Materials and Measurements; MDRD, Modification of Diet in Renal Disease; NIST, National Institute Standardized Technology, RS, Research study; SCr, serum creatinine; SCysC, serum cystatin C; U, urinary clearance.

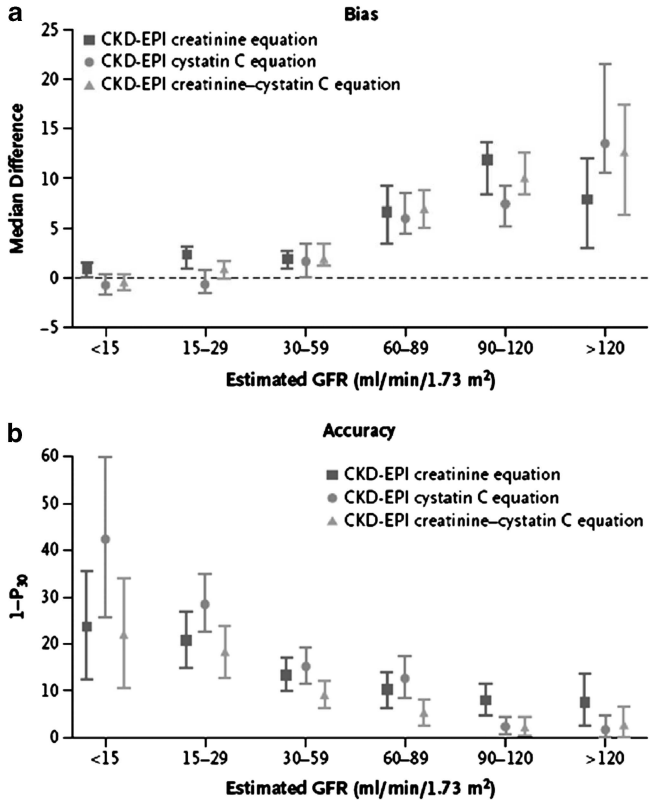


Figure 15 | Performance of three equations for estimating GFR. Panel **a** shows the median difference between measured and estimated GFR. The bias is similar with the equation using creatinine alone, the equation using cystatin C alone, and the combined creatinine–cystatin C equation. Panel **b** shows the accuracy of the three equations with respect to the percentage of estimates that were greater than 30% of the measured GFR ($1 - P_{30}$). Whiskers indicate 95% confidence intervals. GFR, glomerular filtration rate; P_{30}, percentage of estimated GFR values within 30% of measured GFR. From N Engl J Med, Inker LA, Schmid CH, Tighiouart H, et al.[113] Estimating glomerular filtration rate from serum creatinine and cystatin C. 367: 20-29. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

turbidometric assay.[115] This demonstrates the importance of using an assay calibrated and traceable to the international standard reference material.

Numerous pediatric specific and derived $eGFR_{cys}$ formulas have been published, the most current and recent by Schwartz[115] who derives the newest available from a validation set from the CKiD study and compares those results to 3 other well-recognized formulas from the literature, namely Zapitelli et al.,[118] Filler and Lepage,[119] and Hoek et al.[120]

Their results demonstrate that the newest univariate cystatin C formula derived from the CKiD cohort has excellent accuracy with 82.6% of $eGFR_{cys}$ within 30% of the true measured iohexol GFR and 37.6% within 10% of the true measured iohexol GFR. Likewise the bias of 0.3% and correlation of 0.85 are the best of all formulas reported to date. The formula they use to obtain these values is: $70.69 \times (\text{cystatin c})^{-0.931}$.

Of note, their final multivariate equation, when applied to the validation set and using height/SCr, nepholemetric cystatin C, BUN, sex, and an adjusted height term demonstrated the best accuracy reported in pediatric studies to date, 91% and 45% within 30% and 10% of the true GFR, respectively; with a bias of only −0.2 and correlation of 0.92.

1.4.3.8: We suggest measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact on treatment decisions. (*2B*)

RATIONALE

In clinical practice, there may be a requirement to measure GFR when the need for a 'truer' more precise value is identified (such as for organ donation or for dosing of toxic drugs). The intention of this statement is to recognize that specialty centers for kidney disease, usually tertiary referral centers, should have the capacity to measure GFR using exogenous filtration markers as a recognized specialist service. We recognize that this ability does not currently constitute the definition of specialty kidney referral centers and that it may be problematic, but resources to ensure accurate measurement ought to be made available. Given that these specific measurements require levels of rigor and reproducibility similar to those of laboratory calibration issues, specialist centers would be the right place to suggest that these facilities be made available.

Evidence Base

GFR is measured as the clearance of an exogenous filtration marker. The "gold standard" method is the urinary clearance of inulin during a continuous intravenous infusion. To simplify the procedure there are a number of alternative clearance methods and alternative filtration markers, with minor differences among them.[79] For all measurement methods, measured GFR should be reported as described for eGFR.

Table 18 summarizes the strengths and limitations of clearance methods and filtration markers for clearance measurements. Thus measured GFR may also be associated with error, and in evaluation of GFR estimating equations, random error in GFR measurement is a source of some of the imprecision in GFR estimating equations.[27,121] In principle, the magnitude of random error in GFR measurements is likely to be smaller than errors in GFR estimation using creatinine and cystatin C due to conditions listed in Tables 11 and 15.

International Relevance

The calculation of eGFR using these equations usually requires computer programming and some processes for quality monitoring. Nonetheless the statements are here to serve as 'best practice' recommendations so that these can be

Table 17 | Performance comparison of cystatin C-based estimating equations in North American and European populations

Study description			mGFR		GFR estimate		Results			
Author	Population (subgroup)	N	Reference standard	mGFR (SD)	Serum creatinine (SCr) calibration and assay detail	Cystatin C calibration and assay detail	Equations	Bias *ml/min/1.73* m^2*	Precision†	Accuracy‡
Inker LA et al.[113] Multi	RS/CP: 5 studies (2 RS and 3 CP) using equations developed in CKD population [3% black, Mean age 50y, 53% DM]	1119	Exogenous filtration markers other and urinary iothalamate (U)	70 (41)	Y (IFCC SRM 967)	Y (IRMM)	Re-expressed MDRD	-6.3 (-7.8, -5.4)	19.4 (17.4, 21.1)	83%
							CKD-EPI cystatin C 2011	-6.0 (-7.1, -4.9)	18.7 (17.5, 20.0)	84%
							CKD-EPI creatinine-cystatin C 2011	-4.9 (-5.9, -4.2)	15.3 (14.0, 16.3)	92%
	RS/CP: 5 studies (2 RS and 3 CP) using equations developed in diverse dataset [3% black, Mean age 50y, 53% DM]						CKD-EPI creatinine 2009	-3.7 (-4.6, -2.8)	15.4 (14.3, 16.5)	87%
							CKD-EPI cystatin C 2012	-3.4 (-4.4, -2.3)	16.4 (14.8, 17.8)	86%
							CKD-EPI creatinine-cystatin C 2012	-3.9 (-4.5, -3.2)	13.4 (12.3, 14.5)	92%
							Average of CKD-EPI creatinine 2009 and CKD-EPI cystatin C 2012	-3.5 (-4.1, -2.8)	13.9 (12.9, 14.7)	92%
Stevens, LA et al.[117] France	CP: Clinical population in Paris, France [29% women, 79% white, 8% black, 13% other, Mean age 59y, 22% DM, 16%]	438	^{51}Cr-EDTA	34 (17)	Y (IFCC SRM 967)	Y (IRMM)	Re-expressed MDRD	-2 (-3, -1)	0.229 (0.210, 0.247)	84% (83, 85)
							CKD-EPI cystatin C (alone) 2011	3 (2, 3)	0.264 (0.239, 0.289)	73% (72, 74)
							CKD-EPI cystatin C 2011	2 (1, 2)	0.248 (0.223, 0.271)	79% (78, 80)
							CKD-EPI creatinine-cystatin C 2011	0 (0, 1)	0.193 (0.174, 0.211)	90% (89, 91)

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CP, clinical population; Cr-EDTA, chromium-ethylenediamine tetraacetic acid; DM, diabetes mellitus; GFR, glomerular filtration rate; IFCC, International Federation of Clinical Chemistry; IQR, interquartile range; IRMM, International Reference Materials and Measurements; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate; RMSE, root mean square error; RS, Research study; SCr, serum creatinine; SRM, standard reference material; U, urine; Y, yes

Footnotes:

*Bias is computed as estimated GFR minus measured GFR. A positive number indicates estimated GFR overestimates measured GFR. A negative number indicates estimated GFR underestimates measured GFR. A smaller absolute value indicates lesser bias. A lower value for RMSE, IQR, or SD indicates greater precision.

†Precision is evaluated as IQR for the differences between estimated and measured GFR.

‡Higher values for P_{30} indicate greater accuracy. Values in parenthesis are 95% confidence intervals.

Table 18 | Strengths and limitations of GFR measurement methods and markers

Approach	Strengths	Limitations
Methods		
Urinary clearance		
Bladder catheter and continuous intravenous infusion of marker	• Gold standard method	• Invasive
Spontaneous bladder emptying	• Patient comfort • Less invasive	• Possibility of incomplete bladder emptying • Low flow rates in people with low levels of GFR
Bolus administration of marker	• Shorter duration	• Rapidly declining plasma levels at high levels of GFR • Longer equilibration time in extracellular volume expansion
24 h urinary collection		• Cumbersome • Prone to error
Plasma clearance	• No urine collection required • Potential for increased precision	• Overestimation of GFR in extracellular volume expansion • Inaccurate values with 1-sample technique, particularly at lower GFR levels • Longer duration of plasma sampling required for low GFR
Nuclear imaging	• No urine collection or repeated blood samples required • Relatively short duration	• Less accurate
Markers		
Inulin	• Gold standard • No side effects	• Expensive • Difficult to dissolve and maintain into solution • Short supply
Creatinine	• Endogenous marker, no need for administration • Assay available in all clinical laboratories	• Secretion can vary among and within individuals
Iothalamate	• Inexpensive • Long half life	• Probable tubular secretion • Requirement for storage, administration, and disposal of radioactive substances when ^{125}I used as tracer • Use of non-radioactive iothalamate requires expensive assay • Cannot be used in patients with allergies to iodine
Iohexol	• Not radioactive • Inexpensive • Sensitive assay allows for low dose	• Possible tubular reabsorption or protein binding • Use of low doses requires expensive assay • Cannot be used in patients with allergies to iodine • Nephrotoxicity and risk for allergic reactions at high doses
EDTA	• Widely available in Europe	• Probable tubular reabsorption • Requirement for storage, administration, and disposal of radioactive substances when ^{51}Cr is used as tracer
DTPA	• Widely available in the US • New sensitive and easy to use assay for gadolinium	• Requirement for storage, administration, and disposal of radioactive substances when ^{99m}Tc used as tracer • Requires standardization for ^{99m}Tc • Dissociation and protein binding of ^{99m}Tc • Concern for NSF when gadolinium is used as the tracer

Abbreviations: DTPA, diethylenetriamine pentaacetic acid; EDTA, ethylenediamine tetraacetic acid; GFR, glomerular filtration rate; NSF, nephrogenic systemic fibrosis.

aspired to over time in those locations where these recommendations are currently not able to be implemented.

The Work Group appreciated that not all laboratories have capabilities to assay cystatin C. Different countries and regions will have different availabilities for measurement of GFR. The statement about GFR measurements mostly applies to countries with tertiary care services such as kidney transplantation and oncology.

Implications for Clinical Practice and Public Policy

It is important for clinicians to understand various methods for estimating and measuring kidney function and the situations in which specific methods may be superior in clinical decision making about treatment and referral.

Standardized assays and robust equations are important for epidemiological and planning purposes so that public policy can be informed by more accurate estimates of CKD, which may be possible with improved standardization of both assays and equations.

In different parts of the world, different assays are used and equations for estimating eGFR may differ. Thus, appreciating and understanding local standards is important for individual patients who may travel, and for comparative research across countries or regions.

In the event that a clinician requires measurement of GFR instead of an estimate, knowledge of these different tests and availability of them is important. Situations in which measurement would be required are likely quite infrequent

but include donor evaluation in kidney transplantation and use of toxic drugs which have a narrow therapeutic range. We acknowledge that drug development and clinical observation programs may not define the various thresholds with sufficient granularity to require greater accuracy than is provided by $eGFR_{creat}$. Guidance is evolving regarding kidney function evaluation during drug development programs.[13] There are no direct implications for public policy for the statement about GFR measurement.

Areas of Controversy, Confusion, or Non-consensus

The Work Group recognizes that no single creatinine-based estimating equation will perform optimally in all clinical circumstances and that there may be changes in the performance of estimating equations over time and in different regions. However, for the purpose of eGFR reporting, it is important to select a single equation within a region or country. At the writing of this guideline, in North America, Europe, and Australia, the advantages of the CKD-EPI equation at higher GFR make it more applicable than the MDRD Study equation for general practice and public health.

While cystatin C offers some advantages over SCr as the basis of estimating equations, the cost of the assay and potential lack of standardization across laboratories for this 'newer' test limit our ability to recommend it as a preferred or even usual second test after creatinine. We recognize that these factors may lead to variations in implementation. The recommendation to consider confirmatory or additional testing if there is a need for more accurate determination of GFR is important. That there are other laboratory markers to estimate GFR (i.e., cystatin C) is stated here as there has been accumulating data to support its use in these situations. We have specifically mentioned cystatin C because of these data.

Clarification of Issues and Key Points

It is important for clinicians to appreciate the need for standardized assays and standardized equations for laboratory reporting of eGFR. Changes in laboratory assays or calculation methods should be reported to clinicians in order to avoid confusion when serially following individuals. This is because values in an individual might indicate a worsening or improvement in eGFR which may be attributable to different assays or calculation methods, rather than a reflection of true change.

When precise information about GFR is required, direct measurement using reliable methods should be pursued.

Pediatric Considerations

For Recommendation 1.4.3.8 this guideline is fully applicable in pediatrics.

1.4.4 Evaluation of albuminuria

1.4.4.1: We suggest using the following measurements for initial testing of proteinuria (in descending order of preference, in all cases an early morning urine sample is preferred) (*2B*):
(1) urine albumin-to-creatinine ratio (ACR);
(2) urine protein-to-creatinine ratio (PCR);
(3) reagent strip urinalysis for total protein with automated reading;
(4) reagent strip urinalysis for total protein with manual reading.

1.4.4.2: We recommend that clinical laboratories report ACR and PCR in untimed urine samples in addition to albumin concentration or proteinuria concentrations rather than the concentrations alone. (*1B*)

1.4.4.2.1: The term microalbuminuria should no longer be used by laboratories. (*Not Graded*)

1.4.4.3: Clinicians need to understand settings that may affect interpretation of measurements of albuminuria and order confirmatory tests as indicated (*Not Graded*):

- **Confirm reagent strip positive albuminuria and proteinuria by quantitative laboratory measurement and express as a ratio to creatinine wherever possible.**
- **Confirm ACR $\geq$ 30 mg/g ($\geq$ 3 mg/mmol) on a random untimed urine with a subsequent early morning urine sample.**
- **If a more accurate estimate of albuminuria or total proteinuria is required, measure albumin excretion rate or total protein excretion rate in a timed urine sample.**

RATIONALE

We recommend measurement of urinary albumin because it is relatively standardized and because it is the single most important protein lost in the urine in most chronic kidney diseases. Use of urinary albumin measurement as the preferred test for proteinuria detection will improve the sensitivity, quality, and consistency of approach to the early detection and management of kidney disease.

By contrast, laboratory tests purporting to measure urinary total protein are commonly flawed, often being standardized against, and predominantly sensitive to, albumin. They have poor precision at low concentrations and demonstrate poor between-laboratory agreement while being insensitive, non-specific, and susceptible to a range of false-positive and false-negative problems. There may occasionally

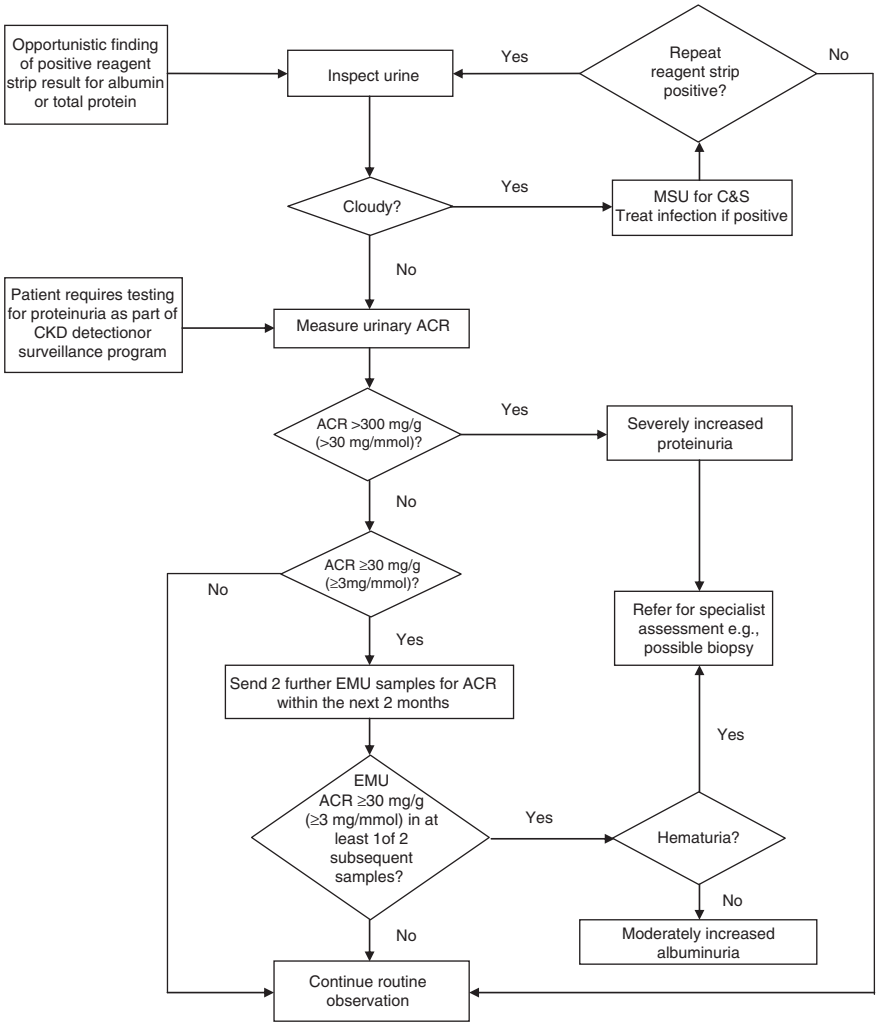


Figure 16 | Suggested protocol for the further investigation of an individual demonstrating a positive reagent strip test for albuminuria/proteinuria or quantitative albuminuria/proteinuria test. Reagent strip device results should be confirmed using laboratory testing of the ACR on at least two further occasions. Patients with two or more positive ($\geq$30 mg/g or $\geq$3 mg/mmol) tests on early morning samples 1-2 weeks apart should be diagnosed as having persistent albuminuria. The possibility of postural proteinuria should be excluded by the examination of an EMU. PCR measurement can be substituted for the ACR but is insensitive in the detection of moderately increased albuminuria/proteinuria. Approximate PCR equivalent to an ACR of 30 mg/mmol is 50 mg/mmol. ACR, albumin-to-creatinine ratio; C&S, culture and sensitivity; CKD, chronic kidney disease; EMU, early morning urine; MSU, mid-stream urine; PCR, protein-to-creatinine ratio. [a]Consider other causes of increased ACR (e.g., menstrual contamination, uncontrolled hypertension, symptomatic urinary tract infection, heart failure, other transitory illnesses, and strenuous exercise), especially in the case of type 1 diabetes present for less than 5 years. The presence of hematuria may indicate non-diabetic renal disease. This figure was published and adapted from Lamb EJ, Price CP.[122] Kidney function tests, in *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics*, eds Burtis CA, Ashwood E, Bruns DE, 5th edition, pp 669-708, 2012. Copyright Elsevier.

be clinical reasons for a specialist to use PCR instead of ACR to quantify and monitor significant levels of proteinuria (e.g., in patients with monoclonal gammopathies).

Commonly used reagent strip devices measuring total protein are insufficiently sensitive for the reliable detection of proteinuria, do not adjust for urinary concentration, and are only semi-quantitative. Furthermore, there is no standardization between manufacturers. The use of such strips should be discouraged in favor of quantitative laboratory measurements of albuminuria or proteinuria. When used, reagent strip results should be confirmed by laboratory testing (Figure 16).

The combination of reagent strips with automated reader devices can improve inter-operator variability. More recently launched reagent strip devices capable of producing albumin or total protein results as a ratio to urinary creatinine require further evaluation to provide evidence that they have equivalent sensitivity and specificity to laboratory tests and are economically advantageous.

Although the reference point remains the accurately timed 24-hour specimen, it is widely accepted that this is a difficult procedure to control effectively and that inaccuracies in urinary collection may contribute to errors in estimation of protein losses. In practice, untimed urine samples are a reasonable first test for ascertainment of albuminuria. An EMU ('first pass') sample is preferred since it correlates well with 24-hour protein excretion, has relatively low

intra-individual variability, and is required to exclude the diagnosis of orthostatic (postural) proteinuria. However, a random urine sample is acceptable if no EMU sample is available.

The concentration of protein or albumin in a urine sample will be affected by hydration (i.e., how diluted or concentrated a urine sample is). Creatinine excretion is considered to be fairly constant throughout the day and it has become customary to correct for urinary concentration by expressing either the protein or albumin concentrations as a ratio to the creatinine concentration in the same sample.

Timed urine collections may be used for confirmatory purposes but are not required except in circumstances in which untimed urine ACR is less accurate. It is worthwhile noting that albumin and protein excretion display considerable biological variability and may be increased by a variety of pathological and non-pathological factors. Consequently, confirmation of increased excretion rates is recommended.

Evidence Base

Why is albumin measurement being recommended instead of total protein? Urine albumin measurement provides a more specific and sensitive measure of changes in glomerular permeability than urinary total protein.[123–125] There is substantial evidence linking increased albuminuria to outcomes of CKD[4,30] (e.g., CKD Prognosis Consortium[2–5], Nord-Trøndelag Health Study [HUNT 2][125a], Prevention of Renal and Vascular Endstage Disease [PREVEND][125b]). There is also evidence that urinary albumin is a more sensitive test to enable detection of glomerular pathology associated with some other systemic diseases including diabetes, hypertension and systemic sclerosis.[126–129]

In health, relatively small amounts of albumin (<30 mg/24 hours) are lost in the urine. Because of this, and additionally because total protein assays are imprecise and insensitive at low concentrations, relatively large increases in urine albumin excretion can occur without causing a significant measurable increase in urinary total protein.[125]

Total protein measurement is problematic in urine due to: large sample-to-sample variation in the amount and composition of proteins; high and variable concentrations of non-protein interfering substances relative to the protein concentration; and high inorganic ion content. All these factors affect the precision and accuracy of the various methods. Most laboratories currently use either turbidimetry or colorimetry[130] to measure total protein and as with urine reagent strip analysis, these methods do not give equal analytical specificity and sensitivity for all proteins which can contribute to diverse estimates of proteinuria prevalence.[131,132] Most methods tend to react more strongly with albumin than with globulin and other non-albumin proteins.[34,133–135] There are significant interferences causing falsely high results.[136–138]. There is no reference measurement procedure and no standardized reference material for urinary total protein listed by the JCTLM. The variety of methods and calibrants in use means that there is inevitably significant between-laboratory variation.[139–141] Since a variable mixture of proteins is measured, it is difficult to define a standardized reference material.

How should albumin be measured and reported? Albumin should be measured using immunological assays capable of specifically and precisely quantifying albumin at low concentrations and of producing quantitative results over the clinically relevant range. Currently urinary albumin is predominantly measured by diagnostic laboratories using turbidimetric assays.[130] At present there is no reference measurement procedure or standardized reference material for urine albumin listed by the JCTLM, although the NKDEP and the International Federation of Clinical Chemistry and Laboratory Medicine have recently established a joint committee to address these issues.[142,143] At present, most assays are standardized against a serum-based calibrant (CRM 470) distributed by the IRMM of the European Commission, as has previously been recommended by KDIGO.[31]

Albumin concentration should be reported as a ratio to urinary creatinine concentration (mg/mmol or mg/g). ACR results should be expressed to one decimal place (mg/mmol) or whole numbers (mg/g). Both enzymatic and Jaffe assays are suitable for the measurement of creatinine in urine. We suggest that the term 'microalbuminuria' no longer be used because it can be misleading in suggesting that the albumin may be small or different in some way. The proposed albuminuria categories A1-3 are a more clinically meaningful way to express information about categories within the continuum of albumin excretion.

Reagent strip point-of-care testing devices capable of measuring low concentrations of albumin are also available producing both semi-quantitative and fully quantitative ACR results. Reasonable analytical[144–147] and diagnostic performance has been demonstrated.[148–150] While studies of these devices have been somewhat limited in size, they demonstrate their potential to play a significant role in the care pathway of patients suspected of having CKD.

Why are reagent strip devices for protein measurement considered less accurate than laboratory measurement? Reagent strip devices for proteinuria detection have been in use for more than 50 years. As discussed earlier, a positive reagent strip result is also associated with outcomes of CKD. Such devices have been used to support screening programs in some countries,[151–153] although there appears to be no evidence supporting such screening of unselected populations.[154]

Although purporting to measure total protein, the reagent pad is most sensitive to albumin.[155–157] There is evidence that strips from different manufacturers perform differently at the cutoff ('+') concentration of 300 mg/l and degrees of 'plusness' between different manufacturers don't always correspond to the same nominal concentration of protein in urine.[124] Concentrated urines may give a color change in the positive range of a reagent strip device even though protein loss remains normal and vice versa. False-positive results may occur if the urine is alkalinized (e.g., due to urinary tract

infection) or in the presence of quaternary ammonium compounds that alter the pH of the urine. The performance of reagent strips is operator-dependent[158] and affected by the presence of colored compounds such as bilirubin and certain drugs (e.g., ciprofloxacin, quinine, and chloroquine).[159] Reagent strips cannot reliably distinguish between proteinuria categories[124,157] and show relatively poor diagnostic accuracy for proteinuria detection.[160,161] In the Australian Diabetes, Obesity and Lifestyle (AusDiab) study, a reagent strip reading of + or greater had 58% and 99% sensitivity for detecting ACR $\geq$30 mg/g ($\geq$ 3 mg/mmol) and $\geq$300 mg/g ($\geq$30 mg/mmol), respectively. 47% of individuals who tested + or greater had an ACR $\geq$30 mg/g ($\geq$ 3 mg/mmol) on laboratory testing.[162]

Automated devices capable of reading the color changes of reagent strips using reflectance spectrometry are available. These reduce inter-operator variability and improve diagnostic accuracy.[150,158,163] A creatinine test pad has been added to some reagent strip systems to enable a PCR to be reported and so reduce the intra-individual variation seen with random urine collections. Such devices have been shown to be suitable for ruling out significant proteinuria (>300 mg/24 hours) in an outpatient setting.[149]

Correcting for urinary dilution. Since creatinine excretion in the urine is fairly constant throughout the 24-hour period, measurement of ACR (or PCR) allows correction for variations in urinary concentration.[164,165] ACR is a suitable alternative to timed measurement of urine albumin loss.[143,166–170] PCR on random or early morning untimed samples shows good diagnostic performance and correlation with 24-hour collection.[160,163,171–177]

Expressing albumin as a ratio to creatinine reduces intra-individual variability: lowest variability for the ACR has been reported in EMU samples as opposed to other untimed samples or timed collections.[142,178] In one study albumin variability was reduced from 80% to 52% when expressed as an ACR rather than an albumin concentration.[179] The within-subject biological variation for urinary ACR in an EMU has been reported to be 31%, compared to 36% for urinary albumin concentration.[180] The same study reported variability for ACR of 103% and 85% in random and timed 24-hour collections, respectively.[180] Intra-individual variation for protein loss is also significantly reduced when reported as a PCR compared to protein concentration in random urine samples collected throughout the day (a mean reduction from 97% to 39%).[179]

Why and how should a finding of albuminuria be confirmed?

Given the high biological variation and other pathological and physiological causes of albuminuria (Table 19),[143] repeat testing to confirm albuminuria, ideally using an EMU and laboratory testing, is recommended (Figure 16).

There has been extensive discussion in the literature about the appropriate urine sample to use for the investigation of protein loss. It is generally recognized that a 24-hour sample is the definitive means of demonstrating the presence of proteinuria. However, overnight, first void in the morning (i.e., EMU), second void in the morning, or random sample collections can also be used. In a systematic review random urine PCR was shown to have better performance as a test for ruling out significant proteinuria than as a "rule-in" test; the authors suggested that positive PCR results may still require

Table 19 | Factors affecting urinary ACR

Factor	Examples of effect
Preanalytical factors	
Transient elevation in albuminuria	Menstrual blood contamination Symptomatic UTI[181] Exercise[182] Upright posture (orthostatic proteinuria)[41,183] Other conditions increasing vascular permeability (e.g., septicemia)
Intraindividual variability	Intrinsic biological variability[180] Genetic variability[184]
Preanalytical storage conditions	Degradation of albumin before analysis[a]
Non-renal causes of variability in creatinine excretion	Age (lower in children and older people) Race (lower in Caucasian than black people) Muscle mass (e.g., lower in people with amputations, paraplegia, muscular dystrophy) Gender (lower in women)
Changes in creatinine excretion	Non-steady state for creatinine (AKI)
Analytical factors	
Antigen excess ('prozone') effect	Samples with very high albumin concentrations may be falsely reported as low or normal using some assays[124]

Abbreviations: ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; UTI, urinary tract infection.
[a]Samples for urinary albumin (or total protein) measurement may be analyzed fresh, stored at 4°C for up to one week, or stored at -70°C for longer periods. Freezing at -20°C appears to result in loss of measurable albumin and is not recommended. When analyzing stored samples, they should be allowed to reach room temperature and thoroughly mixed prior to analysis.[142]

confirmation with a 24-hour collection.[185] If an EMU is unavailable, subsequent samples can give a reliable indication of the 24-hour urine protein loss.[174]

International Relevance

The recommendation to replace urinary total protein with albumin as the test of choice in testing for proteinuria is consistent with most,[1,31,130,186,187] but not all,[188,189] current national and international guidance. It is accepted that cost pressures may affect implementation of this recommendation and may differ across the world.

Most international guidelines have also discouraged the use of reagent strip analysis for proteinuria detection.[186,189–191] Nevertheless, in the present guideline we acknowledge that these devices may have a role, particularly in settings where access to laboratory services may be limited.

ACRs in North America tend to be reported in mg/g whereas in other parts of the world usage of mg/mmol predominates. This difference appears unlikely to be resolved in the foreseeable future. When publishing data authors should ensure either that both units are cited or that a conversion factor is provided.

There is increasing adoption of the term 'albuminuria' instead of microalbuminuria by international and national laboratory and some clinical organizations.

Implications for Clinical Practice and Public Policy

Direct reagent costs of total protein measurement are generally lower than those of albumin measurement, which requires antibody-based reagents. It is often considered that reagent strip analyses are a cheaper option. Therefore some health-care systems may struggle to justify the recommendations in this guideline.

Costs of diagnostic tests vary depending on local financial agreements between hospitals and suppliers. In England, the National Institute for Health and Clinical Excellence (NICE) sampled a small random number of laboratories and estimated the average cost of an ACR to be £2.16 whereas a PCR cost £1.42.[186] It is acknowledged that increased use of ACR testing may reduce the unit cost on the basis of economies of scale. In Canada, laboratory analysis costs (Canadian dollars) of $2.81 for reagent strip, $11.67 for PCR, and $29.23 for ACR have been cited.[192] In relation to albumin-specific reagent strips, a cost of approximately $4 for a Micral test II (Roche Diagnostics) compared to $2 for a laboratory ACR has been reported.[193]

The cost- and clinical-effectiveness of an approach utilizing reagent strip testing followed by laboratory measurement compared to an approach in which samples are submitted directly to the laboratory (for either albumin or protein measurement) has recently been evaluated in a health economics model.[186] The model favored abandoning the use of reagent strips for identification of proteinuria.

Areas of Controversy, Confusion, or Non-consensus

Some data suggest that ACR is a poorer predictor of 24-hour total protein loss than PCR[194] and has no advantage over PCR as a predictor of renal outcomes and mortality in patients with CKD.[195,196] In the prediction of future transplant rejection, PCR has been reported to have equal utility to ACR,[192] although in a separate study ACR was found to be a better predictor.[197]

In the setting of preeclampsia, proteinuria is generally defined as $\geq$300 mg/24 hours or a PCR $\geq$300 mg/g ($\geq$30 mg/mmol).[175] Currently, there is insufficient evidence to substitute urine albumin measurement for total protein in this setting.[172]

Creatinine excretion is affected by a variety of non-renal influences (Table 19) and it therefore follows that different cutoffs for ACR (and PCR) may be required in different individuals.[194,198] While age-related cutoffs have not generally been applied in clinical practice, clinicians should bear this in mind when interpreting urine ACR data in older individuals or those with very low body mass, as these will impact the urine creatinine excretion.

While most guidelines agree that an ACR greater than approximately 3 mg/mmol (30 mg/g) is pathological in the setting of diabetes, in the non-diabetic population a higher threshold has commonly been used to define proteinuria. In the NICE guideline in England and Wales, proteinuria in non-diabetic individuals was defined as $\geq$30 mg/mmol ($\geq$300 mg/g), with higher level proteinuria being $>$70 mg/mmol ($>$700 mg/g).[186] Confirmation of results lying between 30 and 70 mg/mmol (300-700 mg/g) was recommended.[186] The present guideline proposes a lower threshold definition for albuminuria for use in both diabetic and non-diabetic individuals.

A study from Italy in type 2 diabetes has reported that, although intra-individual biological variation of albuminuria is large, a single sample (either ACR or timed collection) can accurately classify patients into albuminuria categories, negating the need for multiple collections.[178]

Some data suggest that a significant proportion of albumin present in urine may be non-immunoreactive,[199–202] although this finding has been questioned.[203,204]

There is a substantial existing literature using the term microalbuminuria and many existing guidelines use this term especially in the context of diabetes and cardiovascular risk, as its presence confers risk. Nonetheless, the Work Group believes that it is important for this international guideline to foster 'best practices' and clarity of communication, and since the risk of adverse events is continuous throughout the spectrum of albuminuria, we encourage adoption of the term 'albuminuria' with subsequent quantification of the level or amount.

Pediatric Considerations

For Recommendation 1.4.4.1, this set of statements would need to be altered for application in the pediatric practice as follows:

We suggest using the following measurements for initial testing of proteinuria in children (in descending order of preference):

(1) urine PCR, EMU sample preferred;
(2) urine ACR, EMU sample preferred;

(3) reagent strip urinalysis for total protein with automated reading;
(4) reagent strip urinalysis for total protein with manual reading.

For Recommendations 1.4.4.2 and 1.4.4.3, this set of statements would need to be altered for application in the pediatric practice as follows:

Currently the urinary PCR should be favored over the urine ACR in children. Unlike in adults where powerful evidence exists in support of the use of measures of albumin rather than total protein to predict adverse outcomes, this level of evidence is currently lacking in children.[205] However, current longitudinal trials such as CKiD[55] and European 4C[78] may eventually shed light on this issue.

In children the underlying conditions associated with the diagnosis of CKD are also important considerations as to which form of testing is most valuable. Unlike adults where the majority of patients with CKD are attributed to an underlying glomerular disease or hypertensive damage, the vast majority of children have underlying developmental abnormalities often referred to as CAKUT (congenital anomalies of the kidney and urinary tract).[70] This relative paucity of glomerular conditions makes the use of albumin excretion a less sensitive test for diagnostic purposes as many children will have underlying tubular conditions and hence tend to excrete more Tamm-Horsfall protein and other low-molecular-weight proteins that will not be captured by the albumin-to-creatinine (or formal albumin excretion) assay.

For Recommendations 1.4.4.2 and 1.4.4.2.1 this guideline is fully applicable in pediatrics. The recommendation that clinical laboratories report ACR and PCR in untimed urine samples in addition to albumin concentration or proteinuria concentrations rather than the concentrations alone is valid and useful in the pediatric population. As per Recommendation 1.2.4, however, note should be made that age-related normal values for urinary protein losses must be considered when laboratories choose to report either ACR or PCR.

Albuminuria in children, whether measured as an absolute value per day, an excretion rate, or as an albumin to creatinine ratio is fraught with more uncertainity than in adults as they are known to vary across categories of age, sex, height, weight, and Tanner staging.[206]

In two recent reviews by Rademacher[206] and Tsioufis et al.,[205] both groups examined the results of all relevant studies on normative values of AER or ACR. Rademacher's paper in particular provides detailed information on the mean AER values (with SD) across a variety of studies, ages, sex, and race, and provides a normative estimate for overnight AER of between 2-6 μg/minute or a 95th percentile value from 4.5–28 μg/minute. Similarly, they summarize results for ACR in normal children and suggest that the mean for children older than 6 years would seem to fall between 8-10 mg/g (0.8-1.0 mg/mmol).

For Recommendation 1.4.4.3, this guideline is fully applicable in pediatrics.

1.4.4.4: If significant non-albumin proteinuria is suspected, use assays for specific urine proteins (e.g., α_1-microglobulin, monoclonal heavy or light chains, [known in some countries as "Bence Jones"proteins]). (*Not Graded*)

RATIONALE

Testing for tubular proteinuria using a total protein approach almost certainly has very poor sensitivity for detecting tubular disease. When an isolated tubular lesion is suspected (Table 3), this is probably best investigated by measuring a specific tubular protein (e.g., α_1-microglobulin) using an immunoassay approach.

Evidence Base

There have been concerns that replacing urinary total protein measurement with albumin measurement may cause non-albuminuric (effectively tubular and overproduction) proteinuria to be missed. Low-molecular-weight proteinuria is a defining feature in some uncommon kidney diseases (e.g., Dent's disease).[207] However, for some of the reasons already discussed, total protein assays will also be poor at detecting tubular proteinuria. When investigating patients for tubular proteinuria, it is advisable to use assays targeted at specific tubular proteins.

In the AusDiab study, of those with proteinuria (2.4% of the general population, defined as a PCR >23 mg/mmol [230 mg/g]) 92% had albuminuria (defined as an ACR >3.4 mg/mmol [34 mg/g]); 8% had an ACR within the reference range.[208] These individuals were less likely to have diabetes than those with both proteinuria and albuminuria, but no further information is available as to the nature of the proteinuria in these individuals or its likely significance. The authors speculate that these individuals could have had light chain proteinuria or interstitial nephropathies. Using albuminuria testing to identify proteinuria had a specificity of 95%. The negative predictive value was 99.8% and the positive predictive value was 32.4%. The authors concluded that testing for albuminuria rather than proteinuria was supported.

As discussed above, quite significant increases in urinary albumin loss have to occur before such an increase is detectable on the background of a total protein assay. The situation is even more extreme for tubular proteins which, in health, are present in urine at lower concentrations than albumin (e.g., normal daily losses of retinol binding protein, α_1-microglobulin and β_2-microglobulin are 0.08, 3.6, and 0.1 mg/d, respectively).[209] This problem will be exacerbated by the fact that the recognition of tubular proteins by some total protein assays is poor.[210]

In disease states concentrations of tubular proteins, at least collectively, can reach levels detectable by total protein assays. For example, among patients with tubulointerstitial disease but without renal insufficiency, median concentrations of α_1-microglobulin were 37 mg/l, with concentrations up to 100 mg/l being observed; higher concentrations were seen in patients with decreased GFR.[211] Among a group of patients with acute

tubular necrosis requiring dialysis treatment, median α_1-microglobulin concentration was 35 mg/mmol of creatinine.[212] However, although tubular proteinuria is characterized by a relative increase in low-molecular-weight protein concentrations, generally albumin still remains a significant component of the total protein concentration. Indeed, it is thought that tubular disease results in an increase in albumin loss as a result of decreased tubular reabsorption of filtered albumin. For example, it has been estimated that when tubular absorption fails completely, β_2-microglobulin loss increases to 180 mg/24 hours (approximately 1800-fold normal) but there will also be an increase in urinary albumin loss to about 360 mg/24 hours (approximately 20-fold normal).[209] In a series of patients with Dent's disease, a classical tubular disorder, 21 of the 23 patients demonstrating increased urinary α_1-microglobulin and β_2-microglobulin loss also had increased urinary albumin loss: those who did not had borderline increases in tubular protein losses that would not have been detectable using a total protein measurement approach.[207] The authors comment that in those patients in whom proteinuria was marked (>1 g/d), urinary albumin loss was also markedly increased. In some situations, however, tubular proteinuria in the absence of albuminuria has been reported (e.g., in some children with type 1 diabetes[213] and in kidney scarring in reflux nephropathy[214]).

International Relevance

There is no reason to believe that there are significant differences around the world with respect to incidence or prevalence of conditions in which measurement of non-albumin proteins would be required. The availability of reliable tests for these alternative proteins, however, may be different in different regions.

Implications for Clinical Practice and Public Policy

The incidence and prevalence of tubular disorders will vary geographically with the clinical setting (e.g., adult or pediatric practice) and factors such as occupational exposure. Clinicians should agree with their local laboratories a suitable approach to the detection of tubular proteinuria and laboratories should be able to advise on suitable sample handling procedures. It is acknowledged that many laboratories do not currently offer assays of tubular proteins.

In patients with suspected myeloma, monoclonal heavy or light chains (known in some countries as Bence Jones) protein should be sought in concentrated urine using electrophoresis with immunofixation of any identified protein bands in accordance with current myeloma guidelines.[215] Simultaneous albumin measurement is needed when the possibility of immunoglobulin light chain (AL) amyloid or light chain deposition disease is suspected.

Non-albumin proteinuria may also be suspected in patients with disorders of tubular function (see Table 3).

Areas of Controversy, Confusion, or Non-consensus

Testing for proteinuria using a urine albumin rather than total protein first-line approach may occasionally miss cases of tubular proteinuria but the significance of this problem is probably overestimated and should be the subject of further research.

Earlier guidance from KDOQI[1] suggested that proteinuria in children should be detected with total protein rather than albumin assays due to the higher prevalence of non-glomerular diseases in this group of patients. For the reasons outlined above, we do not think total protein assays are suitable for this purpose and would ideally recommend testing for albumin and for specific tubular proteins when non-glomerular disease is suspected.

Pediatric Considerations

For Recommendation 1.4.4.4, this statement is fully applicable in pediatrics. In children the likelihood of any form of overflow proteinuria such as seen in conditions of heavy or light chain production is extremely low; however a significant number of underlying genetic tubular disorders do exist and protein electrophoresis can assist the practitioner in determining the presence of such a condition or the concurrent finding of severe tubular injury in addition to a glomerular condition.

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SUPPLEMENTARY MATERIAL

Supplemental Table 1: Search strategy.
Supplemental Table 2: Equations based on serum creatinine assays in adults that are not traceable to the standard reference material.
Supplemental Table 3: Equations based on serum cystatin C assays in adults that are not traceable to standard reference material.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/ckd.php

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Chapter 2: Definition, identification, and prediction of CKD progression

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2.1: DEFINITION AND IDENTIFICATION OF CKD PROGRESSION

2.1.1: Assess GFR and albuminuria at least annually in people with CKD. Assess GFR and albuminuria more often for individuals at higher risk of progression, and/ or where measurement will impact therapeutic decisions (Figure 17). (*Not Graded*)

RATIONALE

The statement is worded this way to remind the practitioner to use both GFR and albuminuria in order to assess progression and is consistent with the definition offered in Chapter 1 regarding definitions of CKD which include both parameters. There is increasing evidence which supports that both parameters are valuable. Lower GFR and greater albuminuria are both associated with an increased rate of progression and are synergistic.

More frequent measures of eGFR and albuminuria should be considered in patients with a lower GFR and greater albuminuria as these people are more likely to progress. Frequency of measurement should also be individualized based on the patient history and underlying cause of kidney disease.

In specific conditions (e.g., GN or increased levels of albuminuria), frequent (every 1–3 months) assessment may guide therapeutic decisions. Regular monitoring of stable patients may include more frequent monitoring than annually, but will be dictated by underlying cause, history, and estimates of GFR and ACR values obtained previously.

Evidence Base

There is variability in the presence of or rate of decline of kidney function in those with CKD. The rate at which

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category

GFR categories (ml/min/1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

Figure 17 | GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). Green reflects stable disease, with follow-up measurements annually if CKD is present; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements at 3 times per year while deep red may require closest monitoring approximately 4 times or more per year (at least every 1—3 months). These are general parameters only based on expert opinion and must take into account underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient. CKD, chronic kidney disease; GFR, glomerular filtration rate. Modified with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, et al.[30] The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17–28; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

Table 20 | Decline in kidney function in various populations (longitudinal studies only)

Reference	Population	*N*	GFR decline
	Healthy		
Slack TK[216]	Healthy kidney donors	141	0.40 ml/min/year
Rowe JW et al.[217]	Healthy males	293	0.90 ml/min/1.73 m^2/year (CrCl)
Lindeman RD[218]	Healthy males	254	0.75 ml/min/year (CrCl)
Halbesma N et al.[219]	PREVEND cohort (all participants)	6894	0.55 ml/min/1.73 m^2/year
Imai E et al.[220]	Annual health exam participants in Japan	120,727	0.36 ml/min/1.73 m^2/year
Matsuchita K et al.[221]	Atherosclerosis Risk In Communities Cohort	13,029	0.47%/year (median)
Kronborg J et al.[222]	Healthy adults from Norway	4441	1.21 ml/min/1.73 m^2/year (men) 1.19 ml/min/1.73 m^2/year (women)
	With comorbidity		
Lindeman RD[218]	Males with renal/urinary tract disease	118	1.10 ml/min/year (CrCl)
Lindeman RD[218]	Males with hypertension	74	0.92 ml/min/year (CrCl)
Halbesma N et al.[219]	PREVEND cohort – adults with macroalbuminuria (>300 mg/24 hours)	86	1.71 ml/min/1.73 m^2/year
Halbesma N et al.[219]	PREVEND cohort - Adults with impaired renal function (5% lowest CrCl/MDRD GFR)	68	0.05 ml/min/1.73 m^2/year
Imai E et al.[220]	Annual health exam participants in Japan with hypertension	16,722	0.3 to 0.5 ml/min/1.73 m^2/year
Imai E et al.[220]	Annual health exam participants in Japan with proteinuria (⩾1+ dipstick proteinuria)	2054	0.6 to 0.9 ml/min/1.73 m^2/year
	Older adults		
Hemmelgarn B et al.[223]	Males age >65 with diabetes	490	2.7 ml/min/1.73 m^2/year
Hemmelgarn B et al.[223]	Males age >65 without diabetes	2475	1.4 ml/min/1.73 m^2/year
Hemmelgarn B et al.[223]	Females age >65 with diabetes	445	2.1 ml/min/1.73 m^2/year
Hemmelgarn B et al.[223]	Females age >65 without diabetes	3163	0.8 ml/min/1.73 m^2/year
Keller C et al.[224]	Cardiovascular Health Study	4128	1.83 ml/min/1.73 m^2/year (based on cystatin C-based eGFR)

Abbreviations: CrCl, creatinine clearance; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; PREVEND, Prevention of Renal and Vascular End-Stage Disease.

this decline occurs also varies based on the underlying population, cause of CKD, presence of albuminuria/proteinuria, comorbidities and age. The Work Group searched the literature for longitudinal studies that evaluated decline in kidney function. As outlined in Table 20 the study populations included healthy adults, those with comorbidity, as well as a subgroup of adults aged 65 and older.

Data from the PREVEND study, a prospective, population-based cohort study, provides important information on decline in kidney function at the population level.[219] The PREVEND study evaluated 6894 people over a 4-year period and reported loss in eGFR of 2.3 ml/min/1.73 m^2/4 years in the whole population, 7.2 ml/min/1.73 m^2/4 years in participants with macroalbuminuria (>300 mg/24 hours) and 0.2 ml/min/1.73 m^2/4 year in participants with impaired renal function. The yearly decline in eGFR among a Japanese general population over 10 years was slightly lower at 0.36 ml/min/1.73 m^2/year.[220] The rate of eGFR decline was approximately two times higher in participants with proteinuria, and about 1.5 times higher among participants with hypertension.[220] Among adults aged 65 and older, progression (median follow-up 2 years) varied by sex and presence of diabetes.[223] In general these studies suggest progression rates of approximately 0.3 to 1 ml/min/1.73 m^2/year among participants without proteinuria or comorbidity and rates of approximately two to three times higher among participants with proteinuria or comorbidity. The somewhat surprising finding that eGFR had low rates of progression among the group with impaired renal function at baseline[219] has been shown in other studies[225] and may relate to the statistical phenomenon of regression to the mean. There is also a concern that it is hard to maintain consistent calibration of the SCr assay over time and progression results are highly sensitive to drift in the creatinine assay.

Studies evaluating rate of decline in eGFR among populations with CKD specifically are outlined in Table 21 and typically demonstrate a slightly more rapid rate of decline in this subgroup, thus requiring more frequent assessment of GFR and albuminuria.

Data from the MDRD Study during a mean 2.2 year follow-up showed that the average rate of decline in GFR ranged from 2.3 to 4.5 ml/min/year, depending on the baseline GFR and protein/MAP treatment assignments.[227] Similarly, a more recent study of 4231 patients with GFR categories G3a-G5 (GFR<60 ml/min/1.73 m^2) referred to a nephrologist showed a mean decline in GFR of 2.65 ml/min/1.73 m^2/year,[231] and variability in the rates of decline in this referred cohort.

Note that there have been no studies which evaluate the utility of more or less frequent monitoring in CKD cohorts.

International Relevance

Frequency of measurements of GFR and albuminuria may vary by country and so are economic resources available to support such testing, and the ability to implement therapeutic strategies to address changes. Nonetheless, given the availability of simple monitoring tools like urine reagent

Table 21 | Decline in kidney function in CKD populations

Study	Study population	*N*	Baseline GFR ml/min/1.73 m^2	Mean Follow-up years	GFR decline Mean (SD) or (95% CI) ml/min/1.73 m^2/year
MDRD Study Group[226]	Study A: GFR 25-80 ml/min/1.73 m^2	28	Mean (SD) 37.1 (8.7)	1.2	3.7 (7.6)
	Study B: GFR 7.5-24 ml/min/1.73 m^2	63	15.0 (4.5)		4.3 (4.7)
Klahr S et al.[227]	Study 1: GFR 25-55 ml/min/1.73 m^2		Mean (SD)	2.2 years	
	- Usual protein, usual MAP	145	37.6 (9.0)		4.5 (3.7 – 5.3)
	- Usual protein, low MAP	149	38.2 (8.6)		3.3 (2.5 – 4.1)
	- Low protein, usual MAP	140	38.9 (8.8)		3.3 (2.5 – 4.2)
	- Low protein, low MAP	151	39.7 (9.1)		2.3 (1.5 – 3.0)
	Study 2: GFR 13-45 ml/min/1.73 m^2				
	- Low protein, usual MAP	62	18.7 (3.1)		4.9 (3.8 – 5.9)
	- Low protein, low MAP	67	18.8 (3.3)		3.9 (3.2 – 4.7)
	- Very low protein, usual MAP	61	18.3 (3.7)		3.6 (2.8 – 4.4)
	- Very low protein, low MAP	65	18.4 (3.5)		3.5 (2.6 – 4.5)
Wright J et al.[228]	African Americans with hypertension and GFR 20-65 ml/min/1.73 m^2		Mean (SD)	4 years	Mean (SE)
	- Low MAP	380	46.0 (12.9)		2.21 (0.17)
	- Usual MAP	374	45.3 (13.2)		1.95 (0.17)
Eriksen B[229]	GFR categories G3a and G3b (GFR 30–59 ml/min/1.73 m^2)	3047	Median (IQR) 55.1 (50.8 – 57.9)	Median 3.7 years	Mean 1.03 ml/min/1.73 m^2/year
Jones C et al.[230]	Nephrology referrals with GFR categories G3a-G5 (GFR < 60 ml/min/1.73 m^2)	726	Median (IQR) 29 (18-38)	Median (IQR) 2.9 years (1.3 – 4.1)	Median 0.35 ml/min/1.73 m^2/year
Levin A et al.[231]	Nephrology referrals with GFR categories G3a-G5 (GFR < 60 ml/min/1.73 m^2)	4231	Median 33 ml/min/1.73 m^2	Median (IQR) 2.6 years (1.6-3.6)	Mean 2.65 ml/min/1.73 m^2/year

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; IQR, interquartile range; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; SD, standard deviation; SE, standard error.

strips, consideration may be given to implementation of this assessment in high-risk groups.

Implications for Clinical Practice and Public Policy

Practitioners must incorporate underlying category of GFR and albuminuria as well as cause of kidney disease and individual patient characteristics in determining the frequency of ongoing assessment. The implications for practice include the incorporation of regular monitoring of both GFR and albuminuria into clinical care for patients with CKD.

There are no immediate implications for public policy of this statement.

Areas of Controversy, Confusion, or Non-consensus

There are many who would like more definitive guidance on frequency of measurement according to specific categories of risk. However this is not possible at the current time given the lack of evidence to guide such statements and the extreme number of individual circumstances that would mitigate any proposed protocol.

We recommend further research to more accurately define the frequency with which GFR and albuminuria measurements should be performed based on their ability to inform strategies which prevent adverse outcomes (e.g., progression of kidney disease and death).

Clarification of Issues and Key Points

a) Assessment of both GFR and albuminuria should be undertaken to evaluate progression.
b) More frequent assessment is required as kidney disease progresses.
c) Not all individuals with CKD require close surveillance and monitoring; clinical context remains an important modifier for all recommendations.
d) While cause of CKD is an important predictor of progression, it is the values of GFR and albuminuria that are used to assess progression.

Pediatric Considerations

Currently there is no evidence as to the value of increasing the frequency of assessment of either GFR or proteinuria in children with CKD. Eventually more complete longitudinal data from the CKiD cohort[55] and hence better granularity of individual and group rates of decline in GFR may provide the data required to strengthen proof of this guideline in children.

As described in detail in the *Pediatric Considerations* for Recommendation 1.3.1, there is good observational evidence acknowledging the importance of level of GFR and proteinuria at baseline on predicting rates of progression and it may be that interventional opportunities would exist if closer monitoring and earlier recognition of worsening in these values for the individual were available. Future studies may examine this.

2.1.2: Recognize that small fluctuations in GFR are common and are not necessarily indicative of progression. (*Not Graded*)

2.1.3: Define CKD progression based on one of more of the following (*Not Graded*):

- **Decline in GFR category ($\geq$90 [G1], 60-89 [G2], 45-59 [G3a], 30-44 [G3b], 15-29 [G4], $<$15 [G5] ml/min/1.73 m^2). A certain drop in eGFR is defined as a drop in GFR category accompanied by a 25% or greater drop in eGFR from baseline.**
- **Rapid progression is defined as a sustained decline in eGFR of more than 5 ml/min/1.73 m^2/year.**
- **The confidence in assessing progression is increased with increasing number of serum creatinine measurements and duration of follow-up.**

RATIONALE

This statement serves to inform clinicians that some consistent definition of progression is required and should be implemented based on an appreciation of baseline values for an individual. There is considerable controversy as to what constitutes normal progression of CKD. The potential for biological and analytical variation associated with use of SCr measurements should be taken into account as they represent reversible fluctuations in GFR and are not necessarily indicative of progression. Further, it is important to recognize that the degree of precision with which progression is able to be estimated is highly dependent upon two factors: the number of SCr measurements used to define progression and the duration of follow-up. Estimating risk of ESRD based on extrapolation of the previous rate of change in GFR required substantial information ($\geq$4 measurements over $\geq$3 years in most cases) to add to the risk information in the most recent GFR. Further, it should be recognized that some reno-protective treatments (e.g., BP lowering and RAAS antagonists) result in a slower rate of GFR decline long-term but often lower GFR in a stepwise fashion as a result of hemodynamic effects. Even substantial (5-25%) reductions in GFR may be protective, complicating the interpretation of progression in these individuals. Finally, underlying disease activity should be considered when assessing patients for progression of kidney dysfunction.

The importance of determining the rate of decline in kidney function over time is to identify individuals who are progressing at a more rapid rate than anticipated, which is associated with increased morbidity and mortality. Individuals who are "rapid progressors" should be targeted to slow their progression and associated adverse outcomes. A progressive decline in kidney function is influenced by baseline GFR category and albuminuria category.

Evidence Base

Unfortunately few studies are available to guide us regarding the optimal definition of "rapid progression." Such studies require serial follow-up of patients to calculate change in GFR over time, with more frequent measurements and longer duration of follow-up providing more accurate estimates. The Work Group reviewed cohort studies of the general population that have evaluated rapid progression of kidney function (Table 22).

Approaches to define decline in kidney function included absolute rate of loss[232,233,235] as well as percent change.[221,234] Studies consistently demonstrate that a more rapid rate of loss of kidney function was associated with an increased risk of adverse clinical outcomes including death and vascular related events. These studies have been limited however by relatively few patients with GFR levels $<$60 ml/min/1.73 m^2, few measurements of SCr, and relatively short duration of follow-up to obtain accurate estimates of the rate of decline in kidney function. The precision of the estimate of the slope depends on a number of factors including the number of measurements of kidney function, biological variability, measurement error, and duration of follow-up. In general at least three measures of kidney function are required to permit an estimate of slope.[1]

None of these studies assessed the impact of albuminuria on rate of "rapid decline" in kidney function. However as noted in Recommendation 2.1.1, the presence of proteinuria has been associated with a faster rate of kidney function decline compared with people without proteinuria.[236–238] Two of the largest prospective cohort studies have shown an approximate two-fold increase in the rate of decline in GFR in the presence of proteinuria.[219,220] Further evidence regarding the potential adverse effects of albuminuria on outcomes has been reported among patients with diabetes. The AER is one of the best indicators of diabetic nephropathy risk in both type 1 and type 2 diabetes, and patients with microalbuminuria have been reported to have 200 to 400% higher risk for progression to proteinuria than patients with normal albuminuria.[239,240] Long-term follow-up studies have also demonstrated the increased risk of ESRD associated with albuminuria among patients with both type 1 and type 2 diabetes.[241,242]

Given the recognized limitations in defining rapid progression, the Work Group aimed to provide options for determination of progression, based on their clinical utility, and ease of use. One approach included an assessment of change in GFR category, combined with a minimal percent change. A criterion requiring both a change in GFR category (e.g., change from G2 to G3a) and percent change would

Table 22 | Studies evaluating rapid progression (general population studies only)

Study	Study population	*N*	Categories for decline in kidney function	Outcome	Follow-up	Results (95% CI)	
Al-Aly Z et al.[232]	Veterans Affairs - GFR categories G3a and G3b (GFR 30–59 ml/min/1.73 m^2) with $\geq$2 eGFR measurements	4171	No decline: eGFR 0 ml/min/yr Mild decline: 0 to 1 Moderate decline: 1 to 4 Severe decline: >4	Death	5.7 yrs (median)	HR (multivariate): No decline: 1.15 (0.99-1.24) Mild: Reference Moderate: 1.10 (0.98-1.30) Severe: 1.54 (1.30-1.82)	
Shlipak et al.[233]	Cardiovascular Health Study - Age 65+ - eGFR measurements at baseline, years 3 and 7	4378	Rapid decline: eGFR >3 ml/min/1.73 m^2/yr Not rapid decline: $\leq$3 ml/min/1.73 m^2/yr	Incident: HF MI Stroke PAD	Subsequent 8 years after enrollment in year 7	HR (multivariate): HF: 1.40 (1.20-1.65) MI: 1.42 (1.14-1.76) Stroke: 1.11 (0.89-1.37) PAD: 1.67 (1.02-2.75)	
Matsushita et al.[221]	ARIC study - eGFR measurements at baseline and 3 years	13,029	Quartiles of % annual change in eGFR: Q1 (-52.76 to -5.65) Q2 (-5.65 to -0.47) Q3 (-0.47 to -0.33) Q4 (-0.33 to 42.94)	CHD & all cause mortality	Up to Jan 1, 2006 (Baseline 1987-89)	HR (multivariate): CHD: Q1: 1.30 (1.11-1.52) Q2: 1.16 (1.00-1.35) Q3: Reference Q4: 1.04(0.90-1.22)	Mortality: Q1: 1.22 (1.06-1.41) Q2: 1.05 (0.92-1.21) Q3: Reference Q4: 1.10 (0.96-1.27)
Cheng et al.[234]	Taiwanese civil servant & school teachers	7968	% decrease: <20% decrease $\geq$20% decrease	All cause, CVD, CHD, & stroke mortality	Up to Dec 31, 2005 (Baseline 1989-94)	HR (multivariate): All death: 1.45 (1.13-1.86) CVD death: 2.48 (1.58-3.89) CHD death: 2.14 (1.07-4.29) Stroke death: 2.79 (1.45-5.36)	
Rifkin et al.[235]	Cardiovascular Health Study - Age 65+ - eGFR measurements at baseline, years 3 and 7	4380	Rapid decline: eGFR >3 ml/min/1.73 m^2/yr Not rapid decline: <3 ml/min/1.73 m^2/yr	All cause, & CVD mortality	Mean follow-up 9.9 yrs	HR (multivariate): All death: 1.73 (1.54-1.94) CVD death: 1.70 (1.40-2.06)	

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; PAD, peripheral arterial disease; yr, year.

ensure that small changes GFR from 61 to 59 ml/min/1.73 m^2 for example, which represents a change in category but a minimal change in GFR, would not be misinterpreted to represent progression. A change of $<25\%$ in a pair of GFR estimates may reflect physiologic variation rather than true progression.

Additional work to inform this definition has been undertaken, using data from the Alberta Kidney Disease Network (AKDN).[243] In this analysis 598,397 adults with at least two out-patient measures of SCr spaced at least 6 months apart were included. Progression was defined as "certain" (rise or drop) if during the median follow-up time of 2.4 years there was a change in GFR category combined with a 25% or greater change in GFR from the baseline measurement (constituting a certain rise or a certain drop). Participants who changed GFR category but did not meet the criterion of 25% change in GFR were categorized as "uncertain" rise or drop. The reference group was comprised of participants who did not change GFR category over the follow-up period. As outlined in Table 23, compared to participants with stable eGFR, those with a certain drop had an almost two-fold increase in the risk of all-cause mortality (HR 1.89; 95% CI 1.83–1.95)[244] and a five-fold increase in the risk of ESRD (HR 5.11; 95% CI 4.56–5.71).[245] Lesser degree of risk was present for those with an uncertain drop (reflecting a change in category only). It is worth noting that once progression occurs, the last eGFR which has a lower level often contains much of the information about risk of ESRD and extrapolation of progression using information from prior progression and the most recent eGFR is only useful if the information about progression is precise and the patient's trajectory is linear.

Table 23 | CKD progression and risk of all-cause mortality and ESRD using baseline (first) eGFR

Definition of progression	All-cause mortality HR** (95% CI)	ESRD* HR** (95% CI)
Certain rise	1.51 (1.46–1.56)	0.33 (0.26–0.42)
Uncertain rise	1.12 (1.08–1.16)	0.39 (0.30–0.51)
Stable (reference)	**Ref**	**Ref**
Uncertain drop	0.98 (0.95–1.01)	2.13 (1.84–2.47)
Certain drop	1.89 (1.83–1.95)	5.11 (4.56–5.71)

Abbreviations: CI, confidence interval; eGFR, glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio.
Data from Turin et al.[244,245]
*ESRD defined as requiring renal replacement therapy.
**Adjusted for age, gender, hypertension, diabetes, proteinuria, Charlson comorbidities and baseline (first) eGFR.

The second approach to define progression takes into account the rate of change in kidney function based on a slope analysis. In this approach the rate of loss is defined by both the absolute rate of change and the percent change, as determined among a cohort of 529,312 adults who had at least 3 outpatient SCr measurements over a four year period (AKDN databases). Two indices of change in eGFR were estimated: the absolute annual rate of change (categorized as: increase, stable and -1, -2, -3, -4, and $\geq$ -5 ml/min/1.73 m^2/year decline); and the annual percentage change (categorized as: increase, stable, -1 to -2, -3 to -4, -5 to -6, and $\geq$-7 percent decline/year). The adjusted ESRD risk associated with each category of change in eGFR was estimated, using stable eGFR (no change in eGFR) as the reference. The results were adjusted in two ways: for eGFR and covariates at the time of the first eGFR measurement, and at the time of the last eGFR measurement. As outlined in Table 24, the risk of ESRD increased almost two-fold for every 1 ml/yr decline in eGFR, when adjusted for covariates and eGFR at the time of the first eGFR measurement. The risk remained significant, but was less pronounced, when adjustments were performed at the time of the last eGFR measurement. This suggests that extrapolation of kidney function beyond the last measurement of eGFR is still informative, but identifies a lesser risk. Similar results were obtained when change in eGFR was defined by a percentage.

Table 24 | Association between absolute and percentage change in kidney function and risk of ESRD*, based on adjustment for eGFR at the first and last measurement

Absolute rate of change (over a median of 3.5 years)	Adjusted for eGFR at first creatinine measurement HR** (95% CI)	Adjusted eGFR at last creatinine measurement HR** (95% CI)
Increasing eGFR	0.64 (0.48-0.86)	1.20 (0.90–1.61)
Stable (0 ml/min/1.73 m^2/year)	Ref	Ref
-1 ml/min/1.73 m^2/year	2.05 (1.56–2.69)	1.45 (1.11–1.90)
-2 ml/min/1.73 m^2/year	2.71 (2.08–3.53)	1.58 (1.21–2.06)
-3 ml/min/1.73 m^2/year	3.98 (3.06–5.17)	1.63 (1.25–2.13)
-4 ml/min/1.73 m^2/year	5.82 (4.45–7.61)	1.90 (1.45–2.48)
-5 ml/min/1.73 m^2/year or more	12.49 (10.04–15.53)	1.70 (1.36–2.12)
Percentage Change:		
Increasing	0.76 (0.55–1.07)	1.11 (0.80 – 1.55)
Stable	Ref	Ref
-1 to -2%/year	1.17 (0.81–1.68)	0.97 (0.67–1.40)
-3 to -4%/year	1.79 (1.25–2.56)	1.19 (0.83–1.71)
-5 to -6%/year	2.26 (1.55–3.29)	1.21 (0.83–1.78)
-7%/year or more	11.30 (8.53–14.97)	2.17 (1.60–2.93)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stge renal disease; HR, hazard ratio.
Data from the Alberta Kidney Disease Network.
*ESRD defined as requiring renal replacement therapy.
**Adjusted for age, gender hypertension, diabetes, proteinuria, Charlson comorbidities and eGFR at the first or last measurement.

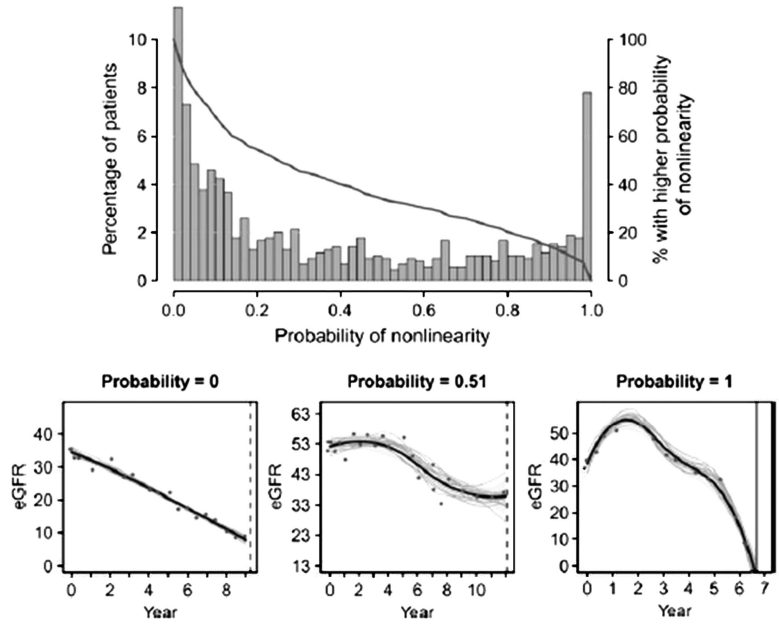


Figure 18 | Distribution of the probability of nonlinearity (top) with three example trajectories demonstrating different probabilities of nonlinearity (bottom). Reprinted from Li L, Astor BC, Lewis J, et al. Longitudinal Progression Trajectory of GFR Among Patients With CKD. Am J Kidney Dis 2012; 59: 504-512 with permission from the National Kidney Foundation.[247]; accessed http://download.journals.elsevierhealth.com/pdfs/journals/0272-6386/PIIS0272638611017896.pdf

With respect to the impact of changes in albuminuria over time, a study from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint trial (ONTARGET) investigators showed that a greater than or equal to twofold increase in albuminuria from baseline to 2 years associated with a nearly 50% higher mortality (HR 1.48; CI 1.32-1.66), while a greater than or equal to twofold decrease in albuminuria associated with 15% lower mortality (HR 0.85; CI 0.74-0.98) compared with those with lesser changes in albuminuria, after adjustment for baseline albuminuria, BP, and other potential confounders. Increases in albuminuria also significantly associated with renal outcomes, defined as ESRD or doubling of SCr (HR 1.40; CI 1.11-1.78), while a decrease in albuminuria was associated with a decrease of the combined renal outcome (HR 0.73; CI 0.57-0.95).[246] However, preliminary analysis of cohort studies is limited and suggests that further research is required to more accurately determine the change in albuminuria associated with an increased risk of kidney disease progression.

There is accumulating evidence that the trajectories of GFR decline are non-linear, and may take a number of different courses over time. The longer an individual is followed over time, the more likely they are to experience non-linear change in trajectory.[247,248] The non-linearity of a trajectory may be due to intercurrent illness, changes in medication, intrinsic to the disease process, or any combination of these factors. Li et al.[247] described individual GFR progression trajectories over twelve years of follow-up among participants in the African American Study of Kidney Disease (AASK) (Figure 18). The authors reported that 41.6% of patients exhibited a greater than 90% probability of having a non-linear trajectory; in 66.1% the probability of non-linearity was $>50\%$.

International Relevance

Studies to date evaluating rapid progression of kidney disease have been limited to North American (White and African American), European, and Asian populations. Given the differences in the prevalence of CKD by ethnic group, there may also be variations in rate of progression by ethnicity, and in particular ethnic groups with high rates of comorbid conditions leading to ESRD such as the Aboriginal population. Thus, the definition of rapid progression may vary according to country or region. However, by using a general definition of progression, which includes change of category of eGFR or albuminuria or both, as well as a numeric change over an established period of time, we believe that the definition of progression can be used in all cohorts.

Implications for Clinical Practice and Public Policy

Practitioners should monitor the GFR and albuminuria at regular intervals to identify rates of decline which exceed that normally demonstrated. The rate of GFR decline may be relatively constant over time in an individual; however the rate of GFR decline is highly variable among people and over long periods of observation, within individuals. Thus clinicians are encouraged to evaluate changes in GFR or albuminuria in the context of multiple observations over time, and with attention to clinical events which may have impacted the change. A number of factors influence assessment of rate of progression including frequency and duration of GFR and albuminuria measurements as well as

factors related to the patient (e.g., baseline GFR, comorbidities, age etc.).

There are no implications for public policy at this time.

Areas of Controversy, Confusion, or Non-consensus

The practical issue in clinical practice and clinical trials is how to define progression (as inferring true deterioration in kidney function) with meaningful thresholds that are easy to understand for the non-nephrologist. While changes in proteinuria may signify change in clinical condition, there are no data yet to suggest that change in proteinuria is itself reliably associated with progression of CKD *per se*. This may be confusing to practitioners, since a change in quantity of proteinuria is an indication for referral.

We recommend research to confirm rates which can be classified as slow, moderate, and rapid progression of kidney disease. The rate to define "rapid progression" may vary depending on the outcome considered, such as kidney failure versus mortality for example. It will be important for researchers to determine methods by which reproducible classification systems for describing rates of progression can be developed. There are increasing data to suggest the non-linearity of progressive disease in many individuals. This makes extrapolation risky and warrants continued assessment of the slope on a regular basis.

Clarification of Issues and Key Points

Small fluctuations in GFR are common and should not be misinterpreted to represent progressive decline in kidney function. Many factors can cause a small change in GFR including medications, volume status, measurement error, and biological variability. Assessment of progressive decline in GFR needs to take into account the number of measurements considered and time period of assessment.

In pediatrics, information about utilty of serial creatinine measurements over periods of time during which growth (and muscle mass increase) is occurring, for the diagnosis of progression or regression, remains problematic.

Pediatric Considerations

Applying strict GFR criteria in order to develop cutoff values associated with 'true' progression in terms of any one individual child is not currently possible. Conceptually the movement from various levels of renal function downward, in particular if that movement is associated with increasing comorbidities or intensity of such, is a reasonable approach.

The most informative data available in children comes from the longitudinal GFR data from CKiD.[72] Examination of the whole cohort reveals an annual decline in GFR of −4.2%; median GFR decline was −1.8 ml/min/1.73 m^2 (interquartile range [IQR] −6.6 to 1.6); this can be expressed as a median absolute decline in GFR of −4.3 ml/min/1.73 m^2 (IQR −11.9 to 1.1) and −1.5 ml/min/1.73 m^2 (IQR −5.0 to1.8).

Given that the lower IQR in each of the overall cohort and both sub-groups is equal to or exceeds the suggested decline of 5 ml/min/1.73 m^2 as stated here, we suggest that it is reasonable to adopt this definition at least for the purpose of classification as it relates to 'rapid' progression; note the above values all relate to measured GFR.

Increasing numbers of any given measurement of an event generally allow for greater precision and accuracy. However, the simple repeated measurements of creatinine over time are less likely to be valuable in children than in adults with CKD. Unlike adults with static muscle mass and hence expected stability in creatinine values, or adults with expected declining muscle mass and hence expectations of declining creatinine if renal function has remained stable, pediatric populations have a situation of increasing muscle mass with expectation of increasing creatinine in the otherwise normal child without CKD. In a child with CKD who is growing therefore, and in particular one going through puberty, the simple comparison of creatinine values over time will likely not be sufficient to presume CKD progression or regression has occurred. The two exceptions to this would be a) a series of creatinine measurements demonstrating significant increase over a short period of time wherein there is no demonstrable or expected gain of muscle mass; b) values of creatinine that over time demonstrate an increase to levels above that which is expected of the child's age and sex based on population normative value for the lab and method of measurement.

2.1.4: In people with CKD progression, as defined in Recommendation 2.1.3, review current management, examine for reversible causes of progression, and consider referral to a specialist. (*Not Graded*)

RATIONALE

This statement intends to reassure patients and practitioners that not all patients necessarily require referral to specialists, but that this should be considered in the event that the patient or clinician requires further guidance or prognostic information. CKD progression, contextualized for the individual circumstance, does not always require referral, and earlier guidelines may not have been so overt in stating this. Faster or unusual trajectories of progression should alert the patient and physician to assess for potentially reversible causes of progression.

Progressive kidney disease requires the need for more aggressive assessment and treatment, which may include referral to a nephrologist or specialist (if they are not currently being managed by a nephrologist).

Evidence Base

Decline in GFR may not be constant, with acute decline superimposed on CKD (see Chapter 2.2 for discussion of factors associated with progression of a more chronic nature). The most common risk factors identified for acute decline in GFR for patients with established CKD include: obstruction of the urinary tract; volume depletion; nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX 2) inhibitors; select antimicrobial agents

such as aminoglycosides and amphotericin B; radiocontrast agents; and angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin-receptor blockers (ARBs).[249–252] Readers are also referred to the *KDIGO Clinical Practice Guideline for Acute Kidney Injury*[7] which contains additional relevant details regarding risk factors for rapid progression and management strategies.

Rapid sustained decline in GFR could also be considered an indication for referral once potentially reversible factors as outlined above have been assessed and treated. The principles guiding referral include additional input from a nephrologist into management of CKD and preparation for RRT, such as that which may be required with rapidly declining GFR. The NICE guidelines for CKD also recommend referral for "rapidly declining GFR" although the definition of rapidly declining is not provided.[186] Most studies assessing nephrology referral have focused on early versus late referral, and not considered the impact or implications of nephrology referral in situations associated with rapid decline in GFR.[253] The evidence that such referral will change outcomes is not clear but given that nephrologists often have access to education and specialized services, which are essential for optimal preparation for RRT, referral to a specialist is recommended. Additional discussion of when to consider a referral to a nephrologist can be found in Chapter 5.

International Relevance

Risk factors for acute deterioration in kidney function may vary slightly by country of origin, although the common categories in general (e.g., medications, volume depletion and urinary tract obstruction) would be relevant irrespective of country. This set of statements serves to ensure that attention to changes in kidney function in those identified with kidney disease is part of the usual care of these individuals.

Implications for Clinical Practice and Public Policy

Practitioners should be aware of the common risk factors for acute-on-chronic kidney disease resulting in a rapid loss of kidney function. Acute rapid deterioration in kidney function should alert the practitioner to assess for these potentially reversible causes of progression. This assessment would include an evaluation for potential urinary tract obstruction as well as a volume assessment and detailed medication review.

Areas of Controversy, Confusion, or Non-consensus

Readers are referred to the *KDIGO Clinical Practice Guideline for Acute Kidney Injury*[7] for a detailed discussion of issues related to definition, diagnosis, and treatment of rapid progression of kidney dysfunction, as defined by AKI.

Clarification of Issues and Key Points

There are no specific numeric values to define "rapid loss" as this varies within and between disease states, individuals, and populations. The key point for practitioners is to serially review individual trajectories of changes in kidney function so as to determine stability or not, identify changes in previous stable trajectories, and to be aware of the importance of circumstances where AKI changes the course of CKD. Further studies are required to determine the rate of loss of GFR that constitutes rapid loss of kidney function. In children, interpretation of serial changes in SCr requires understanding of normative value ranges and drivers of change in SCr which are different than in adults.

2.2: PREDICTORS OF PROGRESSION

2.2.1: Identify factors associated with CKD progression to inform prognosis. These include cause of CKD, level of GFR, level of albuminuria, age, sex, race/ethnicity, elevated BP, hyperglycemia, dyslipidemia, smoking, obesity, history of cardiovascular disease, ongoing exposure to nephrotoxic agents, and others. (***Not Graded***)

RATIONALE

The rationale for estimating the risk of kidney failure is that it may inform referral, care plans, and other therapeutic strategies, including frequency of monitoring and follow-up. Previous guidelines have not been able to suggest risk equations or relative and absolute risks of specific outcomes but with the data currently available, this is now possible. There are several factors that influence the likelihood and rate of CKD progression including GFR and albuminuria category, the degree of albuminuria, the cause of kidney disease, ongoing exposure to nephrotoxic agents, obesity, hypertension, age, race/ethnicity and laboratory parameters such as Hb (hemoglobin), albumin, calcium, phosphate, and bicarbonate.

As some of these risk factors are modifiable they should be actively identified and, if present, be treated as they may impact long-term outcomes including cardiovascular conditions, QOL, and progression of CKD.

It is not yet clear what the relative weight of each of these factors is in predicting in an individual whether he/she will have progressive CKD.

Evidence Base

As progression of CKD is defined as either a progressive decrease in GFR or a progressive increase in albuminuria, we should consider separately whether different factors would predict these two components of CKD differently. Given the limited evidence, this will not be discussed separately. It is however clear that a subject with a lower GFR to start with will progress more rapidly to a GFR <15 ml/min/1.73 m^2, just as a subject with already elevated albuminuria will progress more rapidly to an ACR >300 mg/g (>30 mg/mmol). Similarly, it is well-known that a subject with membranous glomerulopathy is more likely to progress to nephrotic syndrome, while a subject with adult polycystic kidney disease is more likely to progress to ESRD.

Although there are many cross-sectional studies that describe factors associated with a low GFR and factors associated with a high albuminuria, the number of studies evaluating which

factors are associated with progressive decreases in GFR and progressive increases in albuminuria are more limited. In general, it can be argued that most of the above-mentioned factors are associated with a more progressive rise in albuminuria and a more progressive fall in GFR. Most recently, studies have focused on the development of risk scores for identifying progressive decreases in GFR and progressive increases in albuminuria. It has not yet been established which prediction formula could best be used. Some formulas use just simple demographic and clinical measures, while others also include laboratory tests. Some were developed for high-risk populations, such as people with known underlying CVD,[254] with CKD in general,[255] or with specific causes of CKD, such as IgA nephropathy,[256] diabetic nephropathy,[257] or renal artery stenosis.[258] Others developed a risk prediction model in the general population.[259] This latter model included age, race, gender, and in dichotomized version, the presence of anemia, hypertension, diabetes, and CVD history. More recently, two studies used more accurate laboratory parameters in addition to demographic characteristics. The first study was in patients with an eGFR of 15-60 ml/min/1.73 m^2/year, and included age, gender, eGFR, albuminuria, and serum calcium, phosphate, bicarbonate and albumin.[260] The second study was in subjects from the general population and included age, eGFR, albuminuria, measured levels of BP and C-reactive protein (CRP).[261] The results from these predictive models require validation in future studies but they demonstrate the potential and the capabilities of developing clinically meaningful classification of risk for individual patients. Further research is required to establish whether prediction formulas may differ for different ethnicities.

International Relevance

Studies describing factors associated with lower GFR and higher ACR have been described from all over the world. In general, there is much overlap between these data. It may be that in different parts of the world the relative weight of each of the factors predicting progressive increases in albuminuria or decreases in GFR may substantially differ.

Implications for Clinical Practice and Public Policy

It is important to realize that some factors predicting progression of CKD are modifiable. This holds true for lifestyle measures such as cessation of smoking and prevention of obesity. It also subtends to lowering of BP, lowering of albuminuria and prevention of hyperglycemia. A further factor that may be modifiable is the underlying cause of CKD. As various causes may respond to targeted treatment, finding the cause of CKD is the starting point of the work-up of a subject with CKD. If this causal disease is modifiable, for example by immunosuppressive treatment, then such treatment is the first step to consider. Management of patients with CKD and delay of progression are dealt with in Chapter 3 and more fully in other guidelines (see *KDIGO Clinical Practice Guideline for Glomerulonephritis*[8] and *KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update*.[262])

Areas of Controversy, Confusion, or Non-consensus

While there are prediction equations available using combinations of eGFR, albuminuria, cause of CKD, and some or all of the laboratory abnormalities listed, they have not been used in clinical practice to guide therapy as yet. Furthermore, while the associated abnormalities clearly increase in severity with worsening kidney function, normalizing them in some instances has not changed progression to ESRD. The need for prediction equations to take into account changes over time (trajectories) and stability or instability of specific factors has been raised by many. Nonetheless, the ability to determine progression versus stability should be of value for patients and clinicians.

Clarification of Issues and Key Points

Clinicians should attempt to determine stability or progression of patients with CKD for the purposes of informing care. Further research is required to determine which formula best predicts who will have progressive increases in albuminuria and progressive decreases in GFR. The key components of prediction equations for ESRD may well be different than prediction equations for cardiovascular events or death.

Pediatric Considerations

A more complete discussion of the evidence in children supporting these factors as potentially related to risk of progression, in addition to the pediatric specific risk of growth/puberty, can be found in the *Pediatric Considerations* for Recommendation 1.3.1.

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Chapter 3: Management of progression and complications of CKD

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DELAYING PROGRESSION OF CKD

The following section describes key recommendations and guidance for people with CKD with respect to delaying progression of CKD. General lifestyle recommendations are provided as well as caveats given for those with diabetes. Cardiovascular risk reduction including management of hypertension, dyslipidemia, and hyperuricemia is further addressed. Unless otherwise stated, the guidance is intended to apply to adults with CKD.

For the practicing clinician, ideally working with a team of health-care professionals, it is important to institute general lifestyle modification practices in people with CKD so that they may gain the benefit of these in addition to more kidney-specific strategies. Often these general measures are overlooked or disregarded in people with CKD, thus their utility is underscored here.

3.1 PREVENTION OF CKD PROGRESSION

The management of progression of CKD is aimed at addressing a multiplicity of factors known to be associated with progression. There are general measures which have been shown to address cardiovascular health and CKD together, or each separately. Addressing CVD risk factors may indirectly and directly impact CKD progression. Strategies include general lifestyle measures which improve cardiovascular health, BP control, and interruption of the RAAS. In addition, control of other metabolic parameters such as blood sugar, uric acid, acidosis, and dyslipidemia may also be important. This section deals with management of BP, RAAS interruption, glycemic control and dietary/lifestyle manipulations which have been examined in the context of delaying progression of CKD.

BP and RAAS interruption

The following statements are excerpted and where necessary, condensed, from the *KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD.*[10]

3.1.1: Individualize BP targets and agents according to age, coexistent cardiovascular disease and other comorbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes), and tolerance of treatment as described in the KDIGO 2012 Blood Pressure Guideline. (*Not Graded*)

3.1.2: Inquire about postural dizziness and check for postural hypotension regularly when treating CKD patients with BP-lowering drugs. (*Not Graded*)

3.1.3: Tailor BP treatment regimens in elderly patients with CKD by carefully considering age, comorbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to BP treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *(Not Graded)*

3.1.4: We recommend that in both diabetic and non-diabetic adults with CKD and urine albumin excretion <30 mg/24 hours (or equivalent*) whose office BP is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic. *(1B)*

3.1.5: We suggest that in both diabetic and non-diabetic adults with CKD and with urine albumin excretion of ≥ 30 mg/24 hours (or equivalent*) whose office BP is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently ≤ 130 mm Hg systolic and ≤ 80 mm Hg diastolic. *(2D)*

3.1.6: We suggest that an ARB or ACE-I be used in diabetic adults with CKD and urine albumin excretion 30-300 mg/24 hours (or equivalent*). (*2D*)

3.1.7: We recommend that an ARB or ACE-I be used in both diabetic and non-diabetic adults with CKD and urine albumin excretion >300 mg/24 hours (or equivalent*). (*1B*)

3.1.8: There is insufficient evidence to recommend combining an ACE-I with ARBs to prevent progression of CKD. (*Not Graded*)

3.1.9: We recommend that in children with CKD, BP-lowering treatment is started when BP is consistently above the 90th percentile for age, sex, and height. (*1C*)

3.1.10: We suggest that in children with CKD (particularly those with proteinuria), BP is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. (*2D*)

*Approximate equivalents for albumin excretion rate per 24 hours—expressed as protein excretion rate per 24 hours, albumin-to-creatinine ratio, protein-to-creatinine ratio, and protein reagent strip results— are given in Table 7, Chapter 1

3.1.11: We suggest that an ARB or ACE-I be used in children with CKD in whom treatment with BP-lowering drugs is indicated, irrespective of the level of proteinuria. (*2D*)

These statements are worded to maintain consistency with the *KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD*,[10] where the full rationale and evidence behind the statements may be found. In detailing BP targets, we recognize that we have not made recommendations or suggestions concerning lower limits of BP. The risks of overtreatment should be specifically considered when making decisions about BP lowering and this is encapsulated in the first two guideline statements.

CKD and risk of AKI

3.1.12: We recommend that all people with CKD are considered to be at increased risk of AKI. (*1A*)

3.1.12.1: In people with CKD, the recommendations detailed in the KDIGO AKI Guideline should be followed for management of those at risk of AKI during intercurrent illness, or when undergoing investigation and procedures that are likely to increase the risk of AKI. (*Not Graded*)

RATIONALE

Observational data suggest a strong association between pre-existing CKD and AKI. The appreciation that CKD patients may be more susceptible to AKI is the purpose of the above set of statements. However, methodological issues such as how CKD and AKI are defined in clinical studies and the statistical adjustments for non-uniformity of comorbidities among various studies may affect the validity of observed associations. These statements would be applicable in pediatrics, though the data are not available for this specific issue.

Evidence Base

CKD is designated as a risk factor for AKI because of the epidemiological association between the two.[263,264] A number of studies in a variety of settings report an association between pre-existing CKD and AKI.[265–271] CKD is a potent predictor of acute decline in kidney function following exposure to radiocontrast,[272] major surgery,[273] and other medical conditions.[274]

Hsu et al.[14] compared the pre-hospitalization MDRD GFR of 1764 adult members of the Kaiser Permanente Northern California health-care system who developed dialysis-requiring AKI during hospitalization with 600,820 individuals who did not. Compared with a reference baseline GFR of ≥ 60 ml/min/1.73 m^2, a baseline GFR of 45–59 ml/min/1.73 m^2 was associated with an adjusted odds ratio (OR) of in-hospital AKI of 1.66 (95% CI 1.40–1.97). For GFR values of 15–29 ml/min/1.73 m^2, the adjusted OR for in-hospital AKI was 20.42 (95% CI 17.40–23.96). The presence of diabetes, hypertension, and proteinuria increased the likelihood of developing in-hospital AKI, with adjusted OR of 1.99 (95% CI 1.78–2.23), 1.55 (95% CI 1.37–1.76) and 2.84 (95% CI 2.52–3.19), respectively. The authors concluded that CKD is the main risk factor for AKI during hospitalization. A contrasting approach by Singh et al. defined AKI as dialysis-requiring acute renal failure.[275] Because the clinical decision to dialyze a patient is frequently influenced by a higher overall SCr, presence of hemodialysis access, or consideration of inevitable progression to ESRD, this definition of AKI could bias toward capturing more AKI cases in CKD patients. Moreover, in patients with advanced CKD, the progression of CKD to ESRD may sometimes be difficult to separate from acute-on-chronic renal failure. A cohort study by Lafrance et al. followed a referred CKD population in British Columbia for a median of 19.4 months after achieving a GFR of ≤ 30 ml/min/1.73 m^2. Forty-five percent had at least one episode of AKI.[276] In another cohort study of 920,985 adults in Alberta, Canada with at least one outpatient measurement of SCr and proteinuria and not requiring chronic dialysis, risk of admission with AKI increased with heavier proteinuria and reduced GFR.[16]

International Relevance

The incidence of AKI in CKD populations may be different around the world, or have different etiologies. It is not yet clear what the recovery rates from AKI are in the CKD population, and how these vary around the world dependent on cause and duration of AKI.

Areas of Controversy, Confusion, or Non-consensus

Interpretation of published data examining the influence of pre-existing CKD on the increased likelihood of AKI is potentially confounded by a number of issues. These include the comorbidities associated with CKD, influenced by repeated exposure to various nephrotoxic insults or in-hospital errors,[57,277] or primarily due to the altered physiology in CKD. There are also methodological issues such as how CKD and AKI are defined in clinical studies and the varying statistical adjustments for comorbidities.

A further important issue to clarify is whether pre-existing CKD influences the outcome of AKI. Currently, there is no single biomarker that can differentiate 'acute' from 'chronic' kidney disease and help to address this issue. Several large observational and database studies report, surprisingly, lower in-hospital mortality in patients with AKI superimposed on CKD compared with controls.[278–283] Data from the Program to Improve Care in Acute Renal Disease (PICARD) reveal lower in-patient mortality and median length of stay in intensive-care unit (ICU) subjects with acute-on-chronic renal injury compared with non-CKD subjects with AKI, though the post-discharge dialysis rates were higher in subjects with pre-existing CKD.[284]

Clarification of Issues and Key Points

AKI is relatively common in CKD populations and impacts progression adversely. Clinicans should attempt to minimize

avoidable episodes of AKI (see Chapter 4 for more details) as part of a holistic approach to delaying progression.

RESEARCH RECOMMENDATIONS

Prospectively designed clinical studies with a clear and uniform definition of CKD and AKI and adjusted for comorbidities are needed to determine the:

- frequency of AKI events in a CKD population;
- outcome of AKI in patients with CKD;
- importance of proteinuria in addition to low GFR in the risk of AKI.

Protein intake

3.1.13: We suggest lowering protein intake to 0.8 g/kg/day in adults with diabetes (*2C*) or without diabetes (*2B*) and GFR <30 ml/min/ 1.73 m^2 (GFR categories G4-G5), with appropriate education.

3.1.14: We suggest avoiding high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression. (*2C*)

RATIONALE

These statements are worded to reflect the potential benefits and dangers of varying dietary protein intake (DPI) in people with CKD. Excess dietary protein leads to the accumulation of uremic toxins, conversely insufficient protein intake may lead to loss of lean body mass, and malnutrition (the latter more frequent in the elderly). The benefits of dietary protein restriction include reduction of accumulation of metabolic waste products that may suppress the appetite and stimulate muscle protein wasting. The role of dietary protein restriction in slowing progression of CKD is more controversial and advanced CKD is associated with a protein wasting syndrome which is directly correlated with morbidity and mortality. Note that statements about reduction in dietary protein do not apply to pediatric populations given issues related to growth and nutrition.

Evidence Base

A number of systematic reviews and meta-analyses have pooled the available RCT data.[285–289] Pedrini et al.[288] compared a low-protein diet (LPD), defined as a DPI of 0.4 to 0.6 g/kg/day, with a usual diet (5 RCTs, N = 1413) over a period of follow-up ranging between 18-36 months in people with non-diabetic CKD and GFR <55 ml/min/1.73 m^2. Fouque et al.[285] updated this analysis to include 8 RCTs in people with non-diabetic CKD (N = 1524). DPI in their low-protein group was between 0.3-0.6 g/kg/day and follow-up ranged from 12-24 months (5 of 8 studies were in people with GFR categories G4-G5 (GFR <30 ml/min/ 1.73 m^2). Roberston et al.[289] compared diabetic subjects (8 studies in type 1 diabetes, N = 322; 1 study in type 2 diabetes, N = 263). DPI in the low-protein subjects was 0.3-0.8 g/kg/day and usual protein intake ranged from 1-2 g/kg/day. Mean follow-up ranged from 4.5 months to 4 years. In all studies, compliance with a low DPI was poor. There was no convincing or conclusive evidence that long-term protein restriction delayed the progression of CKD.

The largest RCT to date was the MDRD Study.[227] The MDRD Study compared the effects of LPD and BP control on the progression of CKD in over 800 subjects split into 2 groups. Study A compared a DPI of 1.3 g/kg/day (usual protein intake) with 0.58 g/kg/day (LPD) in 585 subjects with a measured GFR of 25-55 ml/min/1.73 m^2 and the actual DPIs were 1.11 and 0.73 g/kg/day, respectively. Study B randomized 255 patients with a measured GFR 13-24 ml/min/1.73 m^2 to DPIs of 0.58 g/kg/day (LPD) or 0.28 g/kg/day supplemented by keto-aminoacids (denoted by VLPD-KA), actual DPIs were 0.69 and 0.46 g/kg/day, respectively. In each of the randomization groups ACE-Is were allowed and were used by 32-44% of patients. Mean follow-up was 2.2 years and the loss of GFR was estimated by the slope of ^{125}I-iothalamate clearance measured over 2 years. There was no difference in GFR decline between groups in Study A and in Study B. Although there was a somewhat faster decline in GFR in the LPD group compared with the VLPD-KA group, this was not significant.

A follow-up study of the original MDRD Study followed those subjects recruited to Study B between 1989-1993 up until the year 2000. Median duration of follow-up until kidney failure, death, or administrative censoring was 3.2 years and median time to death was 10.6 years.[290] The authors concluded that assignment to a very LPD did not delay progression to kidney failure, but appeared to increase the risk of death in the long-term. The chief limitation of this follow-up study was the lack of measurements of DPI and nutritional measurements during the course of the long-term follow-up period and it is therefore not known how many patients continued with the LPD or the VLPD-KA diets after the study concluded.

There is some evidence to suggest that higher protein diets above the recommended daily intake may accelerate renal functional decline in people with early CKD. In a study of 1624 women enrolled in the Nurses' Health Study, Knight et al. described the effect of protein intake over an 11-year period in women with eGFR ≥ 80 ml/min/1.73 m^2 (normal renal function) at baseline and those with eGFR 55-80 ml/min/1.73 m^2.[291] DPI was measured twice during the study period at intervals of 4 years using a semiquantitative food-frequency questionnaire that inquired about the average intake of specified foods and beverages during the previous year. In women with normal renal function at baseline high protein intake was not significantly associated with change in eGFR. However in those with eGFR 55-80 ml/min/1.73 m^2 at baseline, protein intake was significantly associated with a change in eGFR of -1.69 ml/min per 1.73 m^2 (95% CI, -2.93 to -0.45 ml/min per 1.73 m^2) per 10 g increase in protein intake. The effect was greatest in those with the highest intake of non-dairy animal protein.

Dietary protein restriction of <0.80 g/kg/day appears to offer no advantage and any dietary protein restriction should

include careful monitoring of clinical and biochemical markers of nutritional deficiencies. A high total protein intake, particularly high intake of non-dairy animal protein, may accelerate renal function decline in people with CKD and should be avoided.

International Relevance

Studies on protein restriction have not been widely tested in different ethnicities or within cultures with low baseline proten intake or purely vegetarian diets. Thus, the applicability of statements to all regions of the world is limited.

Implications for Clinical Practice and Public Policy

Clinicians should be aware of different sources of protein, and if lowering of protein is recommended, education and monitoring for malnutrition should be implemented. Appropriate dietary counseling for CKD patients may have healthcare resource implications, although as part of a combined strategy to manage obesity, salt intake, and diabetes may be considered cost-effective on a population basis in certain countries. Avoidance of malnutrition is important.

Areas of Controversy, Confusion, or Non-consensus

Data are mixed on the value of protein restriction, the values which are achievable in general populations, and the level of GFR at which they should be instituted. Nonetheless, the Work Group felt that on balance there is enough data to support a reduction in dietary protein in selected individuals. It is important to avoid this advice in those with evidence of or at risk of malnutrition.

Pediatric Considerations

A Cochrane review addresses this issue in children[292] by examining two RCTs with a total of 250 children to determine the effect of protein restriction on a number of variables. The RR of progression to ESRD in the low-protein restricted versus normal group was 1.12 (95% CI 0.54-2.33). At two years, progression of kidney disease was not significant as measured by change in CrCl: mean difference 1.47 ml/min/1.73 m^2 (95% CI −1.19–4.14) or growth as measured by mean weight difference: −0.13 kg (95% CI −1.10–0.84) or mean height difference: −1.99 cm (95% CI −4.84–0.86). The conclusion of the authors was that a low-protein diet did not delay progression to kidney failure in children, but it may be detrimental to growth.

Glycemic control

Diabetes is the leading cause of CKD worldwide. Diabetic nephropathy occurs in 25–40% of patients with type 1 or type 2 diabetes within 20–25 years of disease onset and is an independent risk factor for early death due to CVD. The mortality rate in people with diabetes and urinary ACR >30 mg/g (>3 mg/mmol) is more than twice that in those with normal urinary albumin levels.

The National Kidney Foundation (NKF) *KDOQI Clinical Practice Guideline for Diabetes and CKD*[293] has been updated in 2012. The first three recommendations below are reproduced verbatim from this guideline.

3.1.15: We recommend a target hemoglobin A_{1c} (HbA_{1c}) of ~7.0% (53 mmol/mol) to prevent or delay progression of the microvascular complications of diabetes, including diabetic kidney disease. (*1A*)

3.1.16: We recommend not treating to an HbA_{1c} target of <7.0% (<53 mmol/mol) in patients at risk of hypoglycemia. (*1B*)

3.1.17: We suggest that target HbA_{1c} be extended above 7.0% (53 mmol/mol) in individuals with comorbidities or limited life expectancy and risk of hypoglycemia. (*2C*)

3.1.18: In people with CKD and diabetes, glycemic control should be part of a multifactorial intervention strategy addressing blood pressure control and cardiovascular risk, promoting the use of angiotensin-converting enzyme inhibition or angiotensin receptor blockade, statins, and antiplatelet therapy where clinically indicated. (*Not Graded*)

RATIONALE

These statements are included to reflect the current evidence that achieving a hemoglobin A_{1c} (HbA_{1c}) level of ~7.0% (53 mmol/mol) is able to prevent the microvascular complications of diabetes, although recognizing that the major risk for patients attaining HbA_{1c} levels <7.0% (<53 mmol/mol) is hypoglycemia, and that this risk will be higher in people with lower levels of kidney function.

Evidence Base

The evidence base for these statements is reviewed in the NKF *KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 Update*[293] and will not be reiterated in full here. It should be noted that the evidence that intensive glycemic control reduces the microvascular complications of diabetes is based almost exclusively on prevention of development of albuminuria (ACR >30 mg/g or >3 mg/mmol) and prevention of increasing albuminuria. Evidence from the three most recent studies, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),[294] Action to Control Cardiovascular Risk in Diabetes (ACCORD),[295] and the Veterans Affairs Diabetes Trial (VADT),[296] is summarized in Table 25.

ADVANCE, ACCORD, or VADT did not show significant benefits of more intensive glycemic control on creatinine-based estimates of GFR. However, in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study, 1.4% of participants in the previously intensive treatment group and 3.6% of those in the previously conventional treatment group developed SCr concentrations >2.0 mg/dl (177 μmol/l) ($P=0.01$) and 0.6% versus 1.9% required kidney replacement therapy ($P<0.03$).[297] For patients with type 2 diabetes, intensive treatment in the United Kingdom

Table 25 | Intensive versus normal glycemic control and albuminuria outcome

Study	Intensified treatment versus normal treatment HbA_{1C} goals	Albuminuria outcome
ADVANCE[294]	6.5% (48 mmol/mol) versus 7.3% (56 mmol/mol)	9% ↓ in new ACR 3-30 mg/mmol (30-300 mg/g) 30% ↓ in ACR progression to >30 mg/mmol (>300 mg/g)
ACCORD[295]	6.3% (45 mmol/mol) versus 7.6% (60 mmol/mol)	21% ↓ in new ACR 3-30 mg/mmol (30-300 mg/g) 32% ↓ in ACR progression to >30 mg/mmol (>300 mg/g)
VADT[296]	6.9% (52 mmol/mol) versus 8.4% (68 mmol/mol)	32% ↓ in new ACR 3-30 mg/mmol (30-300 mg/g) 37% ↓ in ACR progression to >30 mg/mmol (>300 mg/g)

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACR, albumin-to-creatinine ratio; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; HbA_{1C}, hemoglobin A_{1C}; VADT, Veterans Affairs Diabetes Trial.

Prospective Diabetes Study (UKPDS) was associated with a 67% risk reduction for a doubling of plasma creatinine levels at 9 years (0.71% of the intensive group and 1.76% of the conventional group, $P = 0.027$).[298]

International Relevance

The incidence and prevalence of diabetes is rising around the world and at rapid rates in developing countries. Glycemic control is therefore one of the most important strategies for delaying progression of CKD, irrespective of region or country. It is recognized that not all hypoglycemic strategies or treatments are available in all countries.

Implications for Clinical Practice and Public Policy

Practitioners should encourage glycemic control in all people with CKD and diabetes, including referral to education sessions and diabetic clinics where available. Public health policies and diabetic strategies should include screening in high-risk populations such as those with diabetes, as the presence of CKD would confer higher risk of adverse events, and could represent an opportunity for intensified intervention with large implications for health-care.

Areas of Controversy, Confusion, or Non-consensus

Recommendations on the use of specific medications for glycemic control (e.g., metformin and glyburide) remain variable depending on different perspectives. These are covered more fully in Chapter 4 on medication dosing and AKI.

Clarification of Issues and Key Points

Glycemic control improves outcomes in people with diabetes, with or without CKD. Those with diabetes and CKD have higher risk of adverse outcomes and therefore presumed higher benefit from control. Many agents are renally excreted and therefore adjustments to doses may be necessary as GFR declines or if patients are acutely unwell (see Chapter 4 on medication dosing).

Caveats in measuring glycemic control with HbA_{1C}

HbA_{1C} may not be reflective of glucose control in people with CKD who have reduced red cell life span, and thus should be interpreted with caution. Review of blood sugar daily logs may be more reliable.

Clinicians should be aware that HbA_{1C} measurements that inform glycemic control are based on an assumed red cell life span of 90 days. In people with CKD the RBC life span is shortened, even if receiving erythropoiesis-stimulating agents (ESAs). As such, measurement may only reflect glycemic control over a shorter time period than the presumed 3 months and thus, HbA_{1C} measurements may be falsely low. Awareness of this may alter clinicians' reliance on this measurement as a long-term measure.[299–304] Ongoing research intitiatives comparing HbA_{1C} with glycated albumin using continuous glucose monitoring suggest that glycated albumin may provide a more reliable index of glycemic control in people with advanced CKD.

Pediatric Considerations

It is recommended that the Guidelines of the American Diabetes Association[305] or similar national guidelines for diabetes management in children and adolescents, be reviewed to address issues related to management of diabetic children either with, or at risk of, CKD.

Salt intake

3.1.19: We recommend lowering salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) in adults, unless contraindicated (see rationale). (*1C*)

3.1.19.1: We recommend restriction of sodium intake for children with CKD who have hypertension (systolic and/or diastolic blood pressure >95th percentile) or prehypertension (systolic and/or diastolic blood pressure >90th percentile and <95th percentile), following the age-based Recommended Daily Intake. (*1C*)

3.1.19.2: We recommend supplemental free water and sodium supplements for children with CKD and polyuria to avoid chronic intravascular depletion and to promote optimal growth. (*1C*)

RATIONALE

In subjects with CKD, impaired excretion of sodium is often present. High sodium intake increases BP and proteinuria, induces glomerular hyperfiltration and blunts the response to RAAS blockade. Lowering salt intake not only reduces BP, but also lowers albuminuria. The importance of salt intake in the general management of CKD patients cannot be overemphasized, hence the need for specific statements here. We appreciate that there are some conditions in which salt

restriction may be harmful, and hence the qualifier "unless contraindicated.' These conditions include salt losing nephropathies and those prone to hypotension and volume contraction who do not have heart failure.

Evidence Base

A systematic review of 16 studies addressing salt intake and kidney disease set out to establish whether variations in dietary sodium consumption influence renal outcomes in people with CKD.[306] Despite marked heterogeneity, the review suggested that increased salt intake was associated with worsening albuminuria and an increased likelihood of reduction of GFR. Although the quality of the studies included was insufficient to support the authors' hypothesis that increased salt intake is nephrotoxic, the results were strong enough to suggest modest dietary avoidance of salt should be encouraged in people with CKD, especially those with hypertension and/or proteinuria. In a randomized, double-blind, placebo-controlled trial of salt reduction in 40 Afro-Caribbean hypertensives, a salt-restricted diet (approximately 5 g daily) significantly reduced 24-hour urinary protein excretion by 19% and led to a fall in systolic and diastolic BP of 8 mm Hg and 3 mm Hg, respectively.[307] The fall in urinary protein excretion correlated with a reduction in urinary sodium excretion, not with BP reduction. Individuals with metabolic syndrome may be especially sensitive to the effects of sodium intake. Hoffman and Cubeddu examined the role of salt intake in increased BP in 109 subjects with metabolic syndrome.[308] Salt restriction from an average usual intake of 8.2 g/day to nearly 2.3 g/day reduced the percentage of hypertensive patients from 23.8% to 8.2%. In a six-month prospective controlled trial, 110 patients with GFR categories G4 or G5 (GFR $<$ 30 ml/min/1.73 m^2) followed a low-sodium (circa 1 g/day) diet as part of either a LPD (0.6 g/kg/day) or very low-protein diet (VLPD) supplemented with essential amino acids (0.35g/kg/day), or a free diet.[309] BP fell significantly in the VLPD group from $143 \pm 19/84 \pm 10$ to $128 \pm 16/78 \pm 7$ mm Hg ($P < 0.0001$), despite reduction of antihypertensive drugs. The improved BP correlated with decreased urinary sodium and the authors concluded that the antihypertensive effect was due to reduction of salt intake independent of actual protein intake. Finally, a randomized controlled crossover trial in 52 non-diabetic subjects with CKD compared the effects of a low-sodium diet (target 50 mmol [1.15 g] sodium per day) versus a regular sodium diet (target 200 mmol [4.60 g] sodium per day) on lowering of proteinuria through RAAS blockade.[310] The reduction of proteinuria by the addition of a low-sodium diet to angiotensin-converting enzyme inhibition was significantly larger ($P < 0.001$) than the addition of angiotensin receptor blockade to angiotensin-converting enzyme inhibition and similarly the reduction of systolic BP by the addition of a low-sodium diet was significantly larger ($P = 0.003$) than the addition of angiotensin receptor blockade. The authors concluded that sodium restriction to a level recommended in guidelines was more effective than dual renin-angiotensin blockade for reduction of proteinuria and BP in non-diabetic nephropathy.

International Relevance

Salt intake has been identified as an important driver of high BP in all countries and in adults, thus this recommendation is of international relevance and applicability. The relevance and caveats to children in different situations around the world merits further review.

Implications for Clinical Practice and Public Policy

In most developed countries, a reduction in salt intake can be achieved by a gradual and sustained reduction in the amount of salt added to foods by the food industry. In other countries where most of the salt consumed comes from salt added during cooking or from sauces, a public health campaign is needed to encourage consumers to use less salt. The range of sodium intake associated with improved long-term outcomes is easily achievable and may have the potential to greatly improve health outcomes in patients with CKD around the world.

Areas of Controversy, Confusion, or Non-consensus

While salt restriction is of benefit on a population-basis, and in most people with hypertension and CKD, there may be individual conditions in which salt restriction might be detrimental (e.g., those with salt wasting tubular disorders; those either hypotensive in the absence of heart failure or those prone to volume contraction). Thus while this general statement applies to the majority of people, individualization is required based on clinical circumstance. This may be particularly relevant to children.

Pediatric Considerations

The suggested relative salt restrictions for children with CKD and/or hypertension are age-based with consideration given to both average intakes and upper limit values. The recommended upper limit for sodium intake from which a reduced intake could be derived is provided in Table 26.

It must also be recognized that children with CKD often have underlying tubular conditions that predispose to numerous electrolyte losses, including sodium. For these children a supplemental rather than restricted sodium intake will be required.

Table 26 | Recommended Daily Intake of sodium for healthy children

Age	Upper Limit
0-6 months	No data
7-12 months	No data
1-3 years	1500 mg
4-8 years	1900 mg
9-13 years	2200 mg
14-18 years	2300 mg

Hyperuricemia

3.1.20: There is insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD. (*Not Graded*)

Hyperuricemia is common in people with CKD and is defined by urate concentrations above 7.0 mg/dl (420 μmol/l) as measured by automated enzymatic (uricase) laboratory methods. Concentrations obtained with colorimetric methods are approximately 1 mg/dl (60 μmol/l) lower. The Work Group believe it important to acknowledge the accumulating body of evidence describing the association of hyperuricemia with CKD and adverse cardiovascular outcomes, and thus list hyperuricemia as a potential contributor to progression. However, at the time of current writing, there is not a reliable body of evidence from which to recommend treatment of hyperuricemia for the specific goal of delaying progression of CKD. Thus, the wording of this ungraded statement is very deliberate.

RATIONALE

Observational data had implicated uric acid in the progression of CKD suggesting that adverse outcomes in people with CKD may be improved by specific uric acid lowering therapy. Small studies using appropriate RCT design have shown reduced left ventricular mass, improved endothelial function, and reduced progression of CKD in people with either symptomatic or asymptomatic hyperuricemia and CKD. Thus, the specific statement is intended to ensure and foster RCTs to properly assess the risk and benefits of uric acid lowering strategies in people with CKD.

Evidence Base

Published data implicate elevated serum uric acid (SUA) concentrations in the progression of CKD.[311–315] Reduction of SUA by allopurinol has been reported to delay progression of CKD in people with both diabetic and nondiabetic CKD.[316,317] Treatment of asymptomatic hyperuricemia has also been reported to improve kidney function even in subjects with normal levels of GFR.[318,319] Both GFR and endothelial function significantly improved in asymptomatic hyperuricemic subjects randomly assigned to 300 mg/day of allopurinol in comparison to placebo.[318] A separate double-blind, placebo-controlled, parallel-group study in 67 people with CKD (GFR 30-60 ml/min/1.73 m^2) and left ventricular hypertrophy (LVH) randomly assigned subjects to treatment with allopurinol (300 mg/day) or placebo for 9 months.[320] In comparison to placebo, the allopurinol-treated subjects had significant reductions in left ventricular mass assessed by magnetic resonance imaging (MRI), and improvements in endothelial function assessed by flow-mediated dilation of the brachial artery and in central arterial stiffness assessed by pulse-wave analysis. Another study randomized 70 subjects with known hyperuricemia or SUA concentrations $\geq$7.0 mg/dl ($\geq$420 μmol/l) to treatment with either allopurinol monotherapy (100-200 mg/day) or a combination of allopurinol and a citrate preparation (3 g/day).[321] SUA concentrations were decreased in both groups but to a significantly lower level by combination treatment. GFR assessed by CrCl increased in the combination therapy group but remained unchanged in those treated with allopurinol alone. Other uric acid lowering agents have also been reported to improve outcomes in people with CKD. In an 8-week, placebo-controlled group comparison of rasburicase and placebo, a single 4.5 mg dose of rasburicase significantly lowered SUA and resulted in a significant improvement in kidney function assessed by CrCl.[322] In a *post hoc* analysis of 1342 patients with type 2 diabetes mellitus and nephropathy participating in the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial, Miao et al. examined the relationship between change in SUA concentration after 6 months of treatment with losartan and doubling of SCr or ESRD.[323] Baseline SUA was 6.7 mg/dl (400 μmol/l) in placebo and losartan-treated subjects. During the first 6 months, losartan lowered SUA by 0.16 mg/dl (9.5 μmol/l) [95% CI 0.30-0.01; $P = 0.031$] as compared with placebo. The risk of doubling of SCr or ESRD was decreased by 6% (95% CI 10%-3%) per 0.5-mg/dl (30-μmol/l) decrement in SUA during the first 6 months. This effect was independent of other risk markers, including albuminuria.

International Relevance

There are no data to support or refute the importance of hyperuricemia in different geographical reasons or ethnic groups. Further study is needed.

Implications for Clinical Practice and Public Policy

There is insufficient evidence to recommend the use of uric acid lowering agents in asymptomatic individuals for the specific purpose of delaying CKD progression. Further large trials are required to better understand the potential benefit of uric acid lowering for this purpose.

Lifestyle

3.1.21: We recommend that people with CKD be encouraged to undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 minutes 5 times per week), achieve a healthy weight (BMI 20 to 25, according to country specific demographics), and stop smoking. (*1D*)

RATIONALE

People with CKD have self-reported reduced physical functioning and are not as aerobically fit as the general population. Frailty, impaired physical performance, disability, and geriatric syndromes are common among older adults even with mild kidney disease. Reduced physical functioning and inactivity are associated with increased mortality and poor QOL. Obesity is associated with increased morbidity,

mortality, and reduction in life expectancy and leads to an increase in the incidence of diabetes, hypertension, and dyslipidemia. Associations between smoking and CKD suggest that smoking increases the risk of kidney failure and that smoking cessation decreases that risk. Thus, this statement reflects the importance of ensuring lifestyle recommendations.

Evidence Base

CKD patients have a reduced exercise capacity and impaired physical functioning.[324–326] Moreover, reduced physical activity is associated with increased mortality and poor QOL in people with CKD.[327–329] Regular exercise leads to increased exercise capacity, decreased morbidity, and improved health-related QOL.[330–332] Exercise may reduce cardiovascular risk through its beneficial effects on BP, triglycerides, high-density lipoprotein cholesterol (HDL-C), insulin resistance, and glycemic control. In ESRD, exercise has been shown to improve arterial stiffness, BP, cardiorespiratory function, and QOL.[333–339] Less data are available on the beneficial effects of exercise on early CKD. However, as cardiovascular risk gradually increases with both a lower GFR and a higher ACR, it is expected that exercise will also help to prevent progressive CVD in less severe CKD. Indeed, in subjects with GFR categories G3a-G4 (GFR 15–59 ml/min/1.73 m^2), long-term exercise training improved physical impairment, arterial stiffness, and health-related QOL.[340] It has therefore been argued that exercise training is imperative in CKD patients[341] and that support programs including self-monitoring, verbal reinforcement, and motivation should be applied[342–344] in an attempt to prevent the high cardiovascular risk in CKD. A prospective study compared the benefits of 6 months of regular walking in 40 predialysis patients with GFR categories G4-G5 (GFR $<$ 30 ml/min/1.73 m^2) (20 in an exercising group and 20 patients who continued with usual physical activity for comparison). Improvements noted after 1 month were sustained to 6 months in the 18 of 20 who completed the exercise study. These included improvements in exercise tolerance (reduced exertion to achieve the same activity), weight loss, improved cardiovascular reactivity, avoiding an increase in BP medication and improvements in quality of health and life and uremic symptom scores as assessed by questionnaire.[345]

In the absence of diabetes, hypertension or other cardiovascular risk factors there has been a lack of evidence to support a causal link between obesity and CKD. Observational studies suggest that obesity is an independent risk factor for CKD.[346–348] The evidence in population studies is conflicting; some studies have failed to link obesity with decreased GFR,[349,350] possibly because BMI in isolation is a poor measure, while others suggest that CKD is independently associated with BMI.[351] It has been known for some time that obesity is associated with secondary focal and segmental glomerulosclerosis,[352] yet significant associations between obesity and CKD in large observational studies such as The Framingham Heart Study disappear after adjustment for age, gender, and cardiovascular risk factors.[353] However, systematic review and meta-analysis of weight loss interventions in CKD have shown weight loss to be associated with significant decrease in proteinuria and systolic BP with no further decrease in GFR in people with CKD during a mean follow-up of 7.4 months.[354] A further systematic review drew very similar conclusions. Weight loss interventions were associated with decreased proteinuria and albuminuria by 1.7 g (95% CI 0.7-2.6 g) and 14 mg (95% CI 11-17 mg), respectively ($P < 0.05$).[355] Each 1-kg weight loss was associated with 110 mg (95% CI 60-160 mg; $P < 0.001$) decrease in proteinuria and 1.1 mg (95% CI 0.5-2.4 mg; $P = 0.011$) decrease in albuminuria, respectively, independent of reduction in BP.

Multiple studies document a clear association between smoking and renal damage in the general population, patients with diabetes, and hypertensive patients.[356] Smoking is causally linked to cardiovascular events in the general population and is also associated with an increased risk for cardiovascular events in patients with CKD.[357–360] Studies investigating the beneficial effects of smoking cessation on kidney function have all been positive.[361–365]

International Relevance

Exercise, weight loss and smoking cessation in CKD are equally important in all countries and thus this recommendation is of international relevance and applicability.

Implications for Clinical Practice and Public Policy

Implementation of this recommendation has no public health cost but has the potential to make far-reaching public health gains both in terms of population health and health-care economics.

Additional dietary advice

3.1.22: We recommend that individuals with CKD receive expert dietary advice and information in the context of an education program, tailored to severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake where indicated. (*1B*)

RATIONALE

International Relevance

The importance of lifestyle recommendations and dietary counseling cannot be overstated. It is however recognized that within the context of different countries, health-care systems and jurisdictions, the degree to which these can be implemented is variable. These recommendations serve as a 'best practice' suggestion.

3.2 COMPLICATIONS ASSOCIATED WITH LOSS OF KIDNEY FUNCTION

People with CKD are prone to develop a variety of complications which reflect loss of endocrine or exocrine function of

Table 27 | Prevalence of CKD complications by GFR category* derived from CKD cohorts

Complication	GFR category (ml/min/1.73 m^2)					Reference
	≥90	60-89	45-59	30-44	<30	
Anemia[1]	4.0%	4.7%	12.3%	22.7%	51.5%	[366]
Hypertension[2]	18.3%	41.0%	71.8%	78.3%	82.1%	[366]
25(OH) Vit D deficiency[3]	14.1%	9.1%	10.7%		27.2%	[367]
Acidosis[4]	11.2%	8.4%	9.4%	18.1%	31.5%	[366]
Hyperphosphatemia[5]	7.2%	7.4%	9.2%	9.3%	23.0%	[366]
Hypoalbuminemia[6]	1.0%	1.3%	2.8%	9.0%	7.5%	[366]
Hyperparathyroidism[7]	5.5%	9.4%	23.0%	44.0%	72.5%	[366]

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Note that modification of prevalence according to albuminuria categories data is not yet available to inform this table adequately, though there are limited data to suggest increasing prevalence of hypoalbuminemia, hypertension, anemia, and acidosis as albuminuria category increases
[1]Defined as hemoglobin levels <12 g/dl (120 g/l) for women; <13.5 g/dl (135 g/l) for men
[2]Defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-reported use of antihypertensive medication
[3]Less than 15 ng/ml [37 nmol/l] (as defined in Study for the Evaluation of Early Kidney disease [SEEK])
[4]Defined as serum bicarbonate less than 21 mEq/l
[5]Defined as serum phosphate ≥4.5 mg/dl (≥1.5 mmol/l)
[6]Defined as serum albumin less than 3.5 g/dl (35 g/l)
[7]Defined as PTH levels ≥70 pg/ml; (≥7.4 pmol/l)

the kidneys. The incidence and prevalence of these complications increase with severity of CKD as defined predominantly by GFR categories (Table 27).

It is beyond the scope of this guideline to describe each of the complications and the proposed treatment options for them in detail as guidance for these conditions can be found in other documents. However, for the purpose of completeness, the key complications and management recommendations for people with CKD are addressed in this section.

In addition to these complications, we have described strategies to delay progression of CKD which are in part predicated on the identification and management of the clinical, metabolic, and hematologic complications. Note that not all people with CKD will have all of the complications and complications may not occur at the same rate or to the same degree in individuals with the same categories of GFR or albuminuria. Nonetheless knowledge of the common complications and treatment options is important in the care of CKD.

Management of Complications

Anemia in CKD. Anemia is an important complication of CKD because it contributes significantly to the heavy symptom burden of CKD. It has a major impact on the lives of people with CKD but it is potentially reversible with appropriate treatment. The guideline statements included here are those we consider to be the key considerations for people with non-dialysis CKD. Interested readers are referred to the *KDIGO Clinical Practice Guideline for Anemia in CKD*[11] for comprehensive guidance on this topic.

Table 28 | Hemoglobin thresholds used to define anemia

Age or gender group	Hemoglobin threshold: g/dl (g/l)
Children	
6 mo-5 yr	11.0 (110)
5-12 yr	11.5 (115)
12-15 yr	12.0 (120)
Non-pregnant females >15 yr	12.0 (120)
Pregnant females >15 yr	11.0 (110)
Men >15 yr	13.0 (130)

Abbreviations: mo, month; yr, year.
Reproduced with permission from World Health Organization. Worldwide prevalence of anaemia 1993-2005: WHO global database on anaemia.[368] In: de Benoist B, McLean E, Egli I and Cogswell M (eds), 2008; accessed: http://whqlibdoc.who.int/publications/2008/9789241596657_eng.pdf.

Definition and identification of anemia in CKD

3.2.1: Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl (<130 g/l) in males and <12.0 g/dl (<120 g/l) in females. (*Not Graded*)

3.2.2: Diagnose anemia in children with CKD if Hb concentration is <11.0 g/dl (<110 g/l) in children 0.5-5 years, <11.5 g/dl (115 g/l) in children 5-12 years, and <12.0 g/dl (120 g/l) in children 12-15 years. (*Not Graded*)

RATIONALE

These statements reflect the need to measure Hb in people with CKD in order to detect if anemia is present, given its association with poor outcomes and its use in prediction models. Anemia is a common occurrence in CKD patients, though variable in its time of presentation and severity within individuals. Thus, the guidelines stress that evaluation and treatment of anemia in people CKD should be undertaken as in other individuals, and emphasize that anemia due to CKD is a diagnosis of exclusion. Furthermore, the guidelines stress that laboratory values used for diagnosis do not imply therapeutic thresholds or targets. For details, consult *KDIGO Clinical Practice Guideline for Anemia in CKD*.[11]

Evidence Base

Conventionally anemia is defined as a Hb concentration lower than the established cutoff defined by the WHO.[368] Different biological groups have different cutoff Hb values below which anemia is said to be present, ranging from 11 g/dl (110 g/l) for pregnant women and for children between 6 months and 5 years of age, to 12 g/dl (120 g/l) for non-pregnant women, and to 13 g/dl (130 g/l) for men (Table 28).

International Relevance

Globally the prevalence of anemia is 24.8% of the population, much of this is linked to nutritional deficiency exacerbated by

infectious disease. However, altitude, race, and smoking will each also have an impact on Hb concentration. Hb concentration can be expected to increase by about 0.6 g/dl (6 g/l) in women and 0.9 g/dl (9 g/l) in men for each 1000 m of altitude above sea level.[369] Hb concentrations also vary between races, with African-American individuals consistently showing concentrations 0.5 to 0.9 g/dl (5 to 9 g/l) lower than those of whites or Asian populations.[370–372] Smoking is associated with elevated carboxyhemoglobin levels, which are associated with a compensatory increase in total Hb concentration. Hence, the US Centers for Disease Control and Prevention have recommended a downwards adjustment of 0.3 g/dl (3 g/l) for smokers.[373] Thus, specific Hb levels expected for different levels of eGFR should be contextualized within the normal distribution of the population.

Implications for Clinical Practice and Public Policy

The recommended thresholds for diagnosis and evaluation of anemia should not be interpreted as being thresholds for treatment of anemia but simply for the identification of this complication. Practice preferences with respect to treatment strategies should be directed according to local resources.

Evaluation of anemia in people with CKD

3.2.3: To identify anemia in people with CKD measure Hb concentration (*Not Graded*):

- **when clinically indicated in people with GFR $\geq$60 ml/min/1.73 m^2 (GFR categories G1-G2);**
- **at least annually in people with GFR 30-59 ml/min/1.73 m^2 (GFR categories G3a-G3b);**
- **at least twice per year in people with GFR $<$30 ml/min/1.73 m^2 (GFR categories G4-G5).**

RATIONALE

The recommendation that patients be evaluated at least annually rests on observations from clinical trials that (in the absence of ESA therapy) the natural history of anemia in patients with CKD is a gradual decline in Hb concentration over time.[374–376] The exact frequency of monitoring of Hb concentration will be influenced by kidney function, underlying disease process, the initial Hb concentration, and the rate of change in Hb concentration. The latter will also be influenced by whether or not anemia is being treated and what type of treatment is undertaken. The statements specifically address the need to measure Hb concentrations at a minimum and are not intended to deter the clinician from more frequent measurements as required for individual circumstances.

The initial evaluation of anemia in CKD is geared towards the exclusion of causes other than those directly related to kidney disease (relative iron and erythropoietin deficiency); see *KDIGO Clinical Practice Guideline for Anemia in CKD*[11] for details.

Evidence Base

Anemia as defined above is found in people with CKD in increasing proportions as GFR declines (Table 27). This is due to a number of reasons, including loss of erythropoietic hormone efficacy, production, substrate deficiency (most notably iron), and other conditions which may contribute to the lack of effective erythropoiesis. For a full description of the evidence behind this statement please refer to the *KDIGO Clinical Practice Guideline for Anemia in CKD.*[11]

International Relevance

Frequency of Hb concentration monitoring and the initial evaluation of anemia should not differ by country, except that causes of anemia other than those related to CKD do differ. Nutritional deficiencies in resource-poor areas are common, particularly iron deficiency, which is frequently exacerbated by infectious diseases.

Implications for Clinical Practice and Public Policy

Anemia is associated with increased morbidity, mortality, and consumption of health-care resources. The major health consequences include poor pregnancy outcome, impaired physical and cognitive development, increased risk of morbidity in children, and reduced work productivity in adults.

Treatment of anemia in CKD. The last 30 years have seen a major transition in approach to the treatment of anemia in people with CKD beginning with the introduction of erythropoietin therapy into clinical practice and the subsequent resurgence of interest in iron therapies. The promise of early intervention with anemia treatment in non-dialysis CKD suggested by observational study has been tempered with the reality of risks of adverse cardiovascular outcomes in RCTs. Nevertheless treatment of anemia with iron and ESAs has an important positive role to play in the lives of people with CKD. For the treatment of anemia in people with CKD, we suggest clinicians refer to the *KDIGO Clinical Practice Guideline for Anemia in CKD* for further details.[11]

The key points for practitioners to remember include the following:

1. Work-up for anemia in CKD should include assessment of secondary causes including iron deficiency.
2. Iron replacement is often effective in anemia of CKD as initial therapy and routes of administration (intravenous or oral) will be determined by clinicians, patient preferences, and local available resources.
3. ESA therapy is not recommended in those with active malignancy, or recent history of malignancy.
4. In most people with CKD, ESAs should not be used to intentionally increase the Hb concentration above 11.5 g/dl (115 g/l)
5. For pediatric patients, the selection of Hb concentration at which ESA therapy is initiated should be individualized after taking into account the potential benefits (e.g., improvement in QOL, school

attendance/performance, and avoidance of transfusion) and potential harms.

3.3 CKD METABOLIC BONE DISEASE INCLUDING LABORATORY ABNORMALITIES

Changes in bone mineral metabolism and alterations in calcium and phosphate homeostasis occur early in the course of CKD and progress as kidney function declines (Table 27). These changes are grouped under the umbrella term Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) which includes renal osteodystrophy and extraskeletal (vascular) calcification related to abnormalities of bone mineral metabolism. Renal osteodystrophy is the component of CKD-MBD that is identified and quantified through bone biopsy histomorphometry and includes osteitis fibrosa (hyperparathyroidism), osteomalacia, and adynamic bone disease.

The evidence on which existing recommended guideline treatment targets for serum concentrations of calcium, phosphate, and parathyroid hormone (PTH), and the strategies to achieve these targets, is exclusively observational and thus problematic for that reason. Furthermore, very little of the evidence is derived from patients with non-dialysis CKD. Nevertheless we feel it is important to include here some of the key statements relating to mineral metabolism abnormalities in patients with non-dialysis CKD from the *KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)* published in 2009.[9] These statements will be qualified where new data since the publication of the CKD-MBD guidance have become available.

3.3.1: We recommend measuring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity at least once in adults with GFR <45 ml/min/1.73 m^2 (GFR categories G3b-G5) in order to determine baseline values and inform prediction equations if used. (*1C*)

RATIONALE

As kidney function declines, abnormalities of serum calcium, phosphate, and circulating hormones related to CKD-MBD progress. These include PTH; 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), and other vitamin D metabolites; fibroblast growth factor-23 (FGF-23); and growth hormone. At the tissue level there is down regulation of vitamin D receptors and resistance to the actions of PTH. Immunohistochemical abnormalities in bone also occur early and generally precede changes in mineral homeostasis. Extraskeletal calcification may result from deranged mineral and bone metabolism and from the therapies used in an attempt to correct these abnormalities. Associations between disorders of mineral metabolism and CVD have widened the focus of CKD-MBD to include abnormal mineral metabolism, abnormal bone, and extraskeletal calcification. Once baseline values have been obtained, the subsequent frequency of testing will be determined on an individual basis by the actual value and any intervention that may be introduced.

Evidence Base

There are observational studies which describe the abnormalities of each of these parameters at relatively high values of eGFR in general and high-risk population cohorts.[367,377,378] Importantly, abnormalities of calcium and phosphate appear to occur relatively later in the course of CKD than do abnormalities in values of $1,25(OH)_2D$, 25(OH)D, and PTH. Thus, the recommendation is to evaluate these parameters relatively early in the trajectory of CKD, as an assessment of burden of illness. In dialysis patients, the highest risks for mortality have been reported with combinations of high serum phosphate and calcium together with either high PTH (RR 3.71; 95% CI 1.53-9.03; $P = 0.004$) or low PTH (RR 4.30; 95% CI 2.01-9.22; $P < 0.001$) compared with the combination of high PTH with normal serum calcium and phosphate which had the lowest mortality and was used as the index category.[379] The importance of examining combinations of parameters of mineral metabolism is likely to be no different in patients with less severe CKD, but this has not been tested in non-dialysis populations.

There are also racial differences in the parameters of mineral metabolism. In a multicenter cohort of 227 black and 1633 non-black patients with early CKD, blacks had similar $1,25(OH)_2D$ levels compared with non-blacks but significantly lower levels of 25(OH)D with higher levels of calcium, phosphate, and PTH, and were significantly more likely to have hyperphosphatemia than non-blacks.[380] In multivariable analyses adjusted for age, gender, eGFR, BMI, and diabetes, blacks had significantly lower 25(OH)D and higher PTH levels than non-blacks. Examining the relationships between 25(OH)D and PTH in 8415 adult participants (25% black and 24% Mexican-American) in NHANES 2003–2004 and 2005–2006, and the relationship between 25(OH)D and bone mineral density (BMD) in 4206 adult participants (24% black and 24% Mexican-American) in the 2003–2004 NHANES sample, Guitierrez et al. found significant racial differences.[381] Blacks and Mexican-Americans had significantly lower 25(OH)D and higher PTH concentrations than whites ($P < 0.01$ for both). Bone mineral density significantly decreased ($P < 0.01$) as serum 25(OH)D and calcium intake declined among whites and Mexican-Americans, but not among blacks ($P = 0.2$).

International Relevance

The association between black race and Hispanics and secondary hyperparathyroidism, independent of known risk factors, suggests that novel mechanisms may contribute to secondary hyperparathyroidism in non-whites with CKD. Testing for these parameters would therefore be informed by the demographics of the population. In different countries and regions, the ability to measure these parameters may

vary, thus the authors of the guideline statements appreciate that implementation of regular measurements of all these parameters may not be possible in all jurisdictions.

Implications for Clinical Practice and Public Policy

Given there remains no clear recommendation as to 'expected' values in CKD nor consensus on thresholds regarding treatment, the testing of PTH, and vitamin D parameters would lead to substantial costs to the health-care system. Abnormal values lead to repeat testing. There are no data to suggest how effective or useful repeated monitoring of abnormal values is, nor what an acceptable interval of monitoring should be to inform care. Laboratory testing for phosphate and calcium is relatively inexpensive, but treatment and ongoing monitoring may be expensive. At the current time, recommendations for testing frequency may be problematic for clinical practice.

Areas of Controversy, Confusion, or Non-consensus

The inter-relationship of calcium, phosphate, and PTH, and the potential impact of vitamin D on these mineral metabolites and extraskeletal calcification remains an area of research and debate among clinicians. Newer research examining the role of FGF-23, an important molecule in phosphate, PTH, and vitamin D homeostasis, has caused many to question the previous focus on PTH values as misplaced. The questions of whether vitamin D therapies are toxic in some or all patients and what values of phosphate are pathologic have yet to be resolved.

Pediatric Considerations

Application of guidelines related to bone health, growth, and CKD in children is extremely complex. Numerous issues arise, including age-related variation in normative values, comparisons across age, sex, size, and the need to account for pubertal changes etc., when one considers the options and targets for evaluation and treatment.

It is recommended that in the application of any of these specific guidelines, the reader carefully reviews the publications as they relate to pediatrics, starting with the following two documents and then accessing the most currently available pediatric CKD resources for the topic(s).

Recommended primary pediatric CKD-MBD resources:

- *KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 Update*[382]
- *KDIGO Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD*[9]

3.3.2: We suggest not to perform bone mineral density testing routinely in those with eGFR <45 ml/min/1.73 m^2 (GFR categories G3b-G5), as information may be misleading or unhelpful. (*2B*)

RATIONALE

While there is an appreciation that BMD is measured in many elderly, this statement is intended to highlight for the clinician the fact that the information gained from BMD in those with reduced GFR may be false, leading to either under- or over-treatment. Although fractures rates and fracture-related mortality are elevated in CKD, bone densitometry does not reliably predict fracture risk in patients with GFR <45 ml/min/1.73 m^2 and neither does it predict the type of renal osteodystrophy. Thus, BMD measurements do not provide the information usually sought from such testing, which is usually the basis of interventions.

Evidence Base

Decreased bone mass and changes in bone microarchitecture occur early in CKD and worsen with progression of disease such that patients with CKD are at increased risk of bone fracture.[383] Bone strength is determined by the density and quality of the bone. Dual-energy x-ray absorptiometry (DXA) scanning measures density of bone but is not able to determine bone quality (cortical and trabecular microarchitecture). Studies using high-resolution peripheral quantitative computed tomography (HR-pQCT) demonstrate abnormalities in the cortical and trabecular microarchitecture of patients with early CKD compared with healthy control subjects.[384] Although abnormalities of both DXA and HR-pQCT associate with fractures in patients with CKD, receiver operator characteristic curve analysis suggests that neither technique is predictive of fracture (area under the curve <0.75), although this improved for patients with longer duration of CKD.[385] In a cross-sectional study, the combination of these imaging techniques with markers of bone turnover improved prediction of fracture.[386]

Implications for Clinical Practice and Public Policy

A major component of fracture risk is related to fall risk, thus reduction in fall risk may be achieved through establishment of falls prevention programs. Such programs include medication review; prevention of postural hypotension; cardiac pacing, where appropriate; home hazard assessment and modifications; muscle strengthening and retraining; and treatment of vitamin D deficiency.

Areas of Controversy, Confusion, or Non-consensus

The combination of measurements of bone thickness, BMD of femoral neck, and a history of fracture may be useful to identify CKD patients who might benefit from fracture prevention strategies. Prospective studies are needed to assess the utility of these parameters for fracture prediction in the CKD population.

Treatment of CKD-MBD

Disturbances of calcium, phosphate, vitamin D, and PTH develop early during the course of CKD and are associated with adverse outcomes. Studies of these and other markers of bone mineral metabolism have improved our understanding of disease mechanisms governing adverse outcomes of CKD-MBD but clinical studies have yet to indicate whether or not manipulation of these markers improves patient-level

outcomes. In making recommendations for therapeutic targets for mineral metabolism abnormalities, we have been careful not to reach beyond the evidence.

3.3.3: In people with GFR <45 ml/min/1.73m^2 (GFR categories G3b-G5), we suggest maintaining serum phosphate concentrations in the normal range according to local laboratory reference values. (*2C*)

3.3.4: In people with GFR <45 ml/min/1.73m^2 (GFR categories G3b-G5) the optimal PTH level is not known. We suggest that people with levels of intact PTH above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency. (*2C*)

RATIONALE

Higher serum phosphate concentrations are associated with mortality and experimental data suggests that serum phosphate concentration is directly related to bone disease, vascular calcification and CVD. Serum phosphate, calcium, and PTH concentrations are all inter-related in patients with CKD. Randomized studies linking manipulation of these parameters to clinical outcomes are lacking but systematic review indicates that earlier phosphate control may help reduce the early clinical consequences of CKD-MBD. Similarly there is insufficient evidence that any specific phosphate binder significantly impacts patient-level outcomes.

Evidence Base

Systematic review of serum concentrations of calcium, phosphate, and PTH and the risk of death and CVD in people with CKD showed that the risk of death increased 18% for every 1 mg/dl (0.33 mmol/l) increase in serum phosphate concentration (RR 1.18; 95% CI 1.12-1.25).[387] There was no association seen with either PTH or serum calcium and all-cause mortality (Figure 19). Of the 327,644 subjects included in the review only 16,247 were not receiving dialysis and of these only 8990 were people with GFR <60 ml/min/1.73 m^2 not receiving RRT. In these subjects the risk of all-cause mortality for each 1 mg/dl (0.33 mmol/l) increase in serum phosphate concentration was very similar (RR 1.29; 95% CI 1.12-1.48). As with all subjects included there was no evidence of an association between serum calcium concentration and all-cause mortality in people with CKD not receiving RRT (RR 1.02; 95% CI 0.81-1.29). Data for associations of calcium, phosphate, and PTH with cardiovascular death were only available in one of the studies included.

In the Multi-Ethnic Study of Atherosclerosis (MESA) study, the associations of serum phosphate concentrations with vascular and valvular calcification were examined in 439 people with GFR <60 ml/min/1.73 m^2. Each 1 mg/dl (0.33 mmol/l) increase in serum phosphate concentration was associated with a 21% ($P=0.002$), 33% ($P=0.001$), 25% ($P=0.16$), and 62% ($P=0.007$) greater prevalence of coronary artery, thoracic, aortic valve, and mitral valve calcification, respectively.[388] The strength of the associations did not differ by age, race, or diabetes. Adjustment for serum concentrations of PTH and $1,25(OH)_2D$ did not alter the strength of the associations.

Factors affecting gastrointestinal phosphate absorption include $1,25(OH)_2D$, food content, phosphate bioavailability and phosphate binders (natural and prescribed). Sources of dietary phosphate are protein-rich foods, including dairy products, meat, and fish as well as legumes, nuts, chocolates and inorganic phosphate additives such as those found in carbonated drinks. In a non-vegetarian Western diet, over half the dietary intake of phosphate comes from animal protein. Although the phosphate content of plant-derived phosphate is higher than animal derived, its bioavailability in terms of gastrointestinal absorption is lower.[389] Inorganic phosphate additives have the highest bioavailability. A number of clinical studies detail benefit from dietary phosphate and protein control in terms of secondary hyperparathyroidism and progression of CKD in people with moderate CKD.[390] Few studies have evaluated the impact of dietary phosphate restriction on bone disease or vascular calcification and only one has addressed survival. In people on hemodialysis, a *post hoc* analysis suggested that more restrictive prescribed dietary phosphate was associated with poorer indices of nutritional status and a greater need for nutritional supplementation.[391] There was a stepwise trend toward greater survival with more liberal phosphate prescription, which reached statistical significance among subjects prescribed 1001 to 2000 mg/d and those with no specified phosphate restriction, raising concerns about protein energy malnutrition with dietary phosphate restriction. The means used to achieve phosphate restriction may therefore be important.

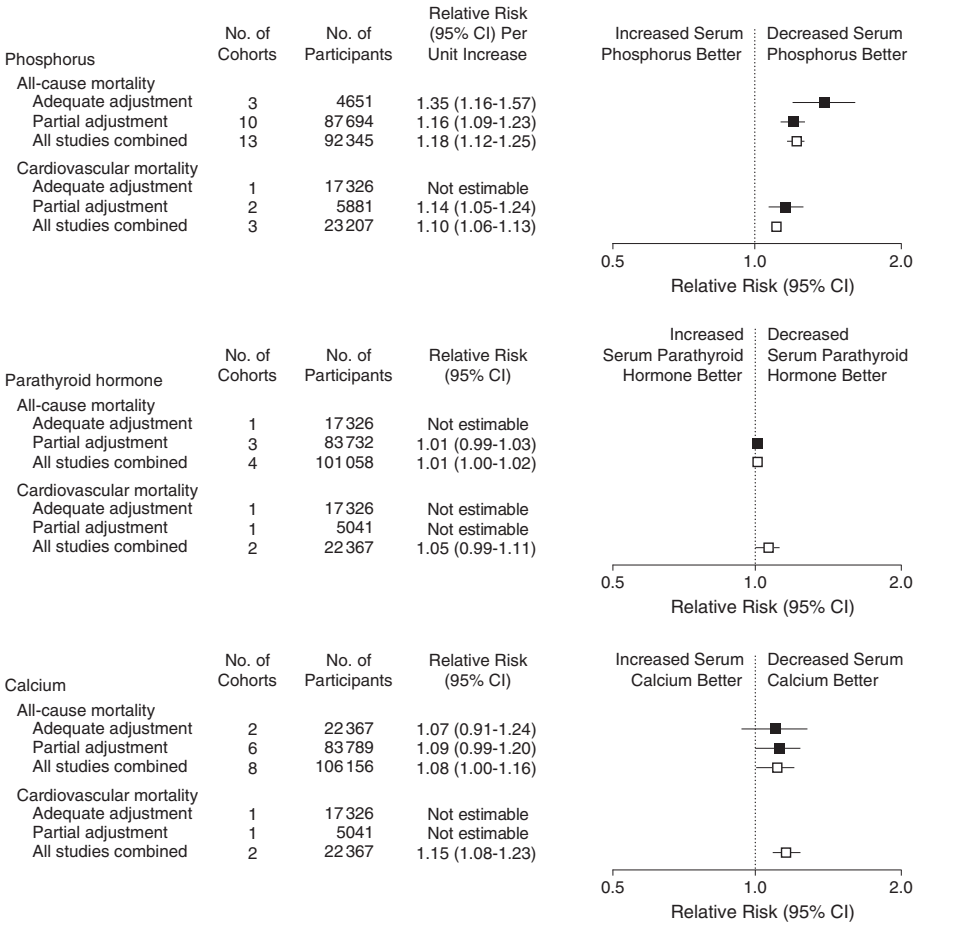
Table 29 details the relative cost comparisons of phosphate binders currently in clinical use for which there is observational or study trial data demonstrating their efficacy. Data concerning comparative patient-level outcomes such as mortality are not available.

There are a number of agents available for phosphate binding which are listed in the table ranked in order of relative cost, appreciating that both availability and specific costs are country- and era-specific.

A Cochrane meta-analysis considered 60 RCTs or quasi-RCTs (7631 participants) that assessed the effects of various phosphate binders in adults with CKD.[392] The authors concluded that all available phosphate-binders reduced serum phosphate concentrations in comparison to placebo but that data to date do not support superiority of novel non-calcium binding agents for patient-level outcomes such as all-cause mortality and cardiovascular end points in CKD.

International Relevance

Availability of different phosphate binders differs around the globe. Thus, recommendations as to specific agents are not possible within the context of these statements. Similarly, dietary phosphate intake may be different around the world,



Risks of all-cause mortality, cardiovascular mortality, and nonfatal cardiovascular events are shown per 1-mg/dL increase in serum levels of phosphorus, 100-pg/mL increase in serum parathyroid hormone, and 1-mg/dL increase in serum calcium. Summary estimates are not reported when only a single cohort contributed data. CI indicates confidence interval.

Figure 19 | Summary estimates for risks of all-cause mortality and cardiovascular mortality associated with levels of serum phosphorus, PTH, and calcium. PTH, parathyroid hormone. Reprinted with permission from Palmer SC, Hayen A, Macaskill P, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. JAMA 2011; 305(11): 1119-1127.[387] Copyright © (2011) American Medical Association. All rights reserved. Accessed http://jama.jamanetwork.com/data/Journals/JAMA/18301/jrv15003_1119_1127.pdf

rendering this problem of greater or lesser significance in different jurisdictions. Measurement of specific hormones (PTH, vitamin D) is expensive and may not inform care sufficiently to warrant the expense at this time.

Implications for Clinical Practice and Public Policy

Existing data support prevention of hyperphosphatemia and associated secondary hyperparathyroidism in CKD. In the absence of hypercalcemia, there is no indication to prescribe phosphate-binders that are less cost-effective than calcium-based agents. Current data are insufficient to make recommendations about target levels of serum calcium or PTH concentrations that should be achieved in order to reduce mortality or cardiovascular morbidity in people with CKD not requiring dialysis. Assay variability of PTH and vitamin D remains problematic and this issue is beyond the scope of this document. The practitioner and health-care administrators are advised to appreciate this problem in developing targets for care or thresholds for treatment.

Areas of Controversy, Confusion, or Non-consensus

As per comments above, the data to support levels of laboratory values for interventions, types of interventions, and target values remain problematic. Thus recommendations for therapy remain similarly problematic and practice varies depending on location and resource availability. Likely correlation of symptoms with blood values and addressing laboratory abnormalities within that context is a pragmatic approach at the current time. The non-specialist is asked to seek advice from local experts for best advice for specific individuals.

The KDIGO guidelines on this subject have not been updated at the time of the writing of this CKD guideline.

Table 29 | Phosphate binding agents in routine clinical practice and their ranked cost

Agent	Dose/day	Clinical experience and evidence base	Ranked cost*
Aluminium hydroxide	1.425-2.85 g	Extensive clinical experience in CKD and ESRD, no RCT comparison versus placebo. Aluminium accumulates in bone and neural tissue with long-term use, avoids calcium	1
Calcium citrate	1.5-3 g	Limited trial evidence in ESRD. Reduction in phosphate and elevation in calcium dose-dependent	2
Magnesium carbonate	0.7-1.4 g (plus calcium carbonate 0.33-0.66 g)	Short-term RCT evidence in ESRD, less hypercalcemia	3
Calcium acetate and Magnesium carbonate combination	Calcium acetate 435 mg plus Magnesium carbonate 235 mg, 3-10 tablets daily	Short-term RCT evidence in ESRD, less hypercalcemia	3
Calcium carbonate	3-6 g	Extensive clinical experience in CKD and ESRD, limited RCT evidence versus placebo. Reduction in phosphate and elevation in calcium both dose-dependent	4
Calcium acetate	3-6 g	Extensive clinical experience in ESRD; RCT evidence comparing to other binders. Reduction in phosphate and elevation in calcium dose-dependent but less than with calcium carbonate	4
Lanthanum carbonate	3 g	Extensive prospective cohort evidence, RCT evidence compared to other phosphate binders. Potential for accumulation in bone and other tissues, avoids calcium	5
Sevelamer-HCl	4.8-9.6 g	Extensive prospective cohort evidence in ESRD; RCT evidence compared to other phosphate binders; surrogate and patient-centered outcomes, avoids calcium	6
Sevelamer carbonate	4.8-9.6 g	RCT evidence compared to other phosphate binders; equivalency studies compared to sevelamer-HCl, avoids calcium	6

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; RCT, randomized controlled trial.
*The average annual cost of aluminium hydroxide in the UK, for example, is £51/year equivalent to US$84/year. The cost of lanthanum and sevelamer in the UK is 38-42 times higher and the cost of calcium and magnesium-based binders 5-7 times higher than aluminium hydroxide (All drug costs derived from 2011 British National Formulary list prices).

We have attempted to balance current knowledge with published guidance statements in non-CKD populations.

Clarification of Issues and Key points

Clinical trials comparing strategies such as vitamin D replacement, dietary phosphate restriction, phosphate binders, and calcimimetics with placebo are needed to address patient-level outcomes such as mortality and cardiovascular morbidity in people with CKD.

Measurement of vitamin D levels is problematic and expensive and is not advocated here.

Vitamin D supplementation and bisphosphonates in people with CKD

3.3.5: We suggest not to routinely prescribe vitamin D supplements or vitamin D analogs, in the absence of suspected or documented deficiency, to suppress elevated PTH concentrations in people with CKD not on dialysis. (*2B*)

RATIONALE

This statement is intended to highlight the lack of robust data to support either the measurement or the treatment of vitamin D deficiency in non-dialysis CKD populations. The statement asks the clinician to more fully evaluate the individual situation. The internationally accepted definition of vitamin D deficiency is a blood concentration <20 ng/ml (<50 nmol/l). Low 25(OH)D levels are common in patients with non-dialysis dependent CKD; concentrations of <15 ng/ml (<37 nmol/l) occur in at least 12-15% of patients with CKD and are more prevalent at lower GFR levels, in institutionalized subjects, at extremes of age, and in certain racial groups. Deficiency of 25(OH)D increases fracture risk and is associated with increased mortality. As CKD progresses, levels of $1,25(OH)_2D$ progressively fall and are closely associated with increasing PTH concentrations. In vitamin D-deficient subjects supplementation with vitamin D increases BMD and muscle strength, reduces risk for fractures and falls, and reduces PTH. In the absence of deficiency, treatment with vitamin D and related compounds has not been shown to improve either mortality or cardiovascular outcomes.

Evidence Base

There is a substantial amount of data to support 25(OH)D deficiency in general and CKD populations[367,393] which is likely multifactorial. In addition to 25(OH)D deficiency, note has been made that there is a progressive increase in prevalence of $1,25(OH)_2D$ deficiency with lower GFR category, which occurs earlier than 25(OH)D deficiency (Figure 20).

No relationship between 25(OH)D levels and $1,25(OH)_2D$ levels was apparent but there was a strong association between $1,25(OH)_2D$ deficiency and PTH concentration. Of particular note, a higher urinary ACR was associated with lower levels of $1,25(OH)_2D$ at GFR values of <60 ml/min/1.73 m^2.

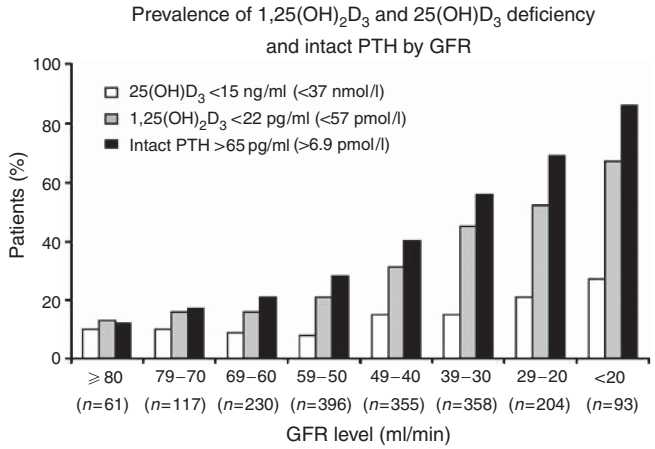


Figure 20 | Prevalence of deficiency of $1,25(OH)_2D_3$, $25(OH)D_3$, and secondary hyperparathyroidism by GFR intervals. GFR, glomerular filtration rate; PTH, parathyroid hormone. Adapted by permission from Macmillan Publishers Ltd: *Kidney International*. Levin A, Bakris GL, Molitch M, et al.[367] Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int 2007; 71: 31-38; accessed http://www.nature.com/ki/journal/v71/n1/pdf/5002009a.pdf

The potential importance of these deficiencies has been illustrated in a number of studies examining the relationship between low levels of 25(OH)D and $1,25(OH)_2D$ and all-cause and cardiovascular mortality in a different cohorts.[393,394]

Despite the associations with mortality, systematic review of published data to date on vitamin D supplementation in patients with CKD not on dialysis has only shown an improvement in biochemical end points. A series of publications[395,396] have attempted to summarize the efficacy of vitamin D therapy on biochemical, bone, cardiovascular, and mortality outcomes in people with CKD and not requiring dialysis. No formulation, route, or schedule of vitamin D compound was found to alter the mortality risk or need for dialysis although vitamin D compounds significantly lowered serum PTH concentrations. None of the studies assessed reported outcomes related to CVD, bone disease, or mortality.

International Relevance

The importance of vitamin D deficiency has been addressed in both general and CKD populations. Specific populations have been identified as more likely to be vitamin D deficient depending on cultural and environmental factors; estimates of worldwide prevalence of vitamin D deficiency range from 25-60%. CKD populations within high-risk areas may be particularly vulnerable. The interplay between loss of kidney function and exacerbation of vitamin D deficiency is not known.

Implications for Clinical Practice and Public Policy

Vitamin D supplementation improves biochemical end points similar to active vitamin D analogs with a lower burden of costs and side effects. Measurement of serum 25(OH)D is expensive and in the CKD population with vitamin D deficiency, simple vitamin D replenishment is all that is indicated until new evidence becomes available. Except for education or research purposes, there is no need to measure vitamin D levels in general practice.

Areas of Controversy, Confusion, or Non-consensus

The appropriate dose and formulation of vitamin D, target range for treatment, frequency, route of administration, and safety at different severities of CKD remain to be determined.

3.3.6: We suggest not to prescribe bisphosphonate treatment in people with GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5) without a strong clinical rationale. (*2B*)

RATIONALE

The risk-benefit ratio of bisphosphonates has not been well studied in CKD populations. Indications for bisphosphonate therapy include osteoporosis, corticosteroid therapy, malignant disease and Paget's disease. In people with CKD and GFR categories >60 ml/min/1.73 m^2 with osteoporosis and/or at high risk of fractures, and in people with GFRs between 30-60 ml/min/1.73 m^2 with normal PTH, osteoporosis and/or at high risk of fracture, treatment should be the same as for the general population (although dose modification may be necessary, see Table 30).

In people with CKD at lower categories of GFR ($<$30-35 ml/min/1.73 m^2), the correct diagnosis of osteoporosis becomes increasingly complex and other forms of renal osteodystrophy requiring alternative management strategies to osteoporosis require exclusion before treatment with bisphosphonates is considered. In people with adynamic renal bone disease, more likely at lower GFR categories, there is a lack of evidence of either harm or benefit of bisphosphonates on bone strength or vascular calcification.

Evidence Base

Bisphosphonates increase BMD, reduce bone turnover, and reduce the risk of fragility fractures. The bioavailability of intravenous bisphosphonate formulations is 100% but the bioavailability of oral formulations is only 1-5%. Approximately 50-80% of available bisphosphonate is taken up by bone and the remaining 20-50% is excreted in urine without being metabolized. Although oral bisphosphonates have not been shown to adversely affect kidney function in people with GFRs as low as 15 ml/min/1.73 m^2, in *post hoc* analysis of clinical trial data their safety and efficacy below GFRs of 30 ml/min/1.73 m^2 have not been well-validated and intravenous bisphosphonates have been implicated in nephrotoxicity, especially when rapidly infused (Table 30).[9,397,398] Thus, from a patient's safety perspective, the statement serves to limit exposure of those with abnormal kidney function to these agents.

International Relevance

Given cost and clinical practice variation, the use of bisphosphonates varies around the world. Thus, this statement may be less applicable in different jurisdictions.

Table 30 | Summary data for bisphosphonates and CKD

Agent	Indications	Dose, frequency and route of administration	Special considerations for CKD and clinical trial notes
Alendronate	Postmenopausal osteoporosis Corticosteroid use	10 mg daily, oral 70 mg weekly, oral	GFR <35 ml/min/1.73 m^2: not recommended No reported adverse events specific to CKD
Clodronate	Malignancy-related bone disease	1.6-3.2 g daily, oral	GFR <10 ml/min/1.73 m^2: contraindicated GFR 10–30 ml/min/1.73 m^2: reduce dose by 50%
Etidronate	Postmenopausal osteoporosis Corticosteroid use Paget's disease	400 mg daily for 14 days, oral 5-10 mg/kg daily for up to 6 months	Mild renal impairment: reduce dose Moderate or severe renal impairment: avoid No data in CKD
Ibandronate	Malignancy-related bone disease Postmenopausal osteoporosis	150 mg monthly, oral 3 mg every 3-months intravenous	GFR <30 ml/min/1.73 m^2: not recommended No reported adverse events specific to CKD
Pamidronate	Malignancy-related bone disease Paget's disease	15-60 mg single dose, intravenous 30 mg weekly for 6 weeks, intravenous	GFR <30 ml/min/1.73 m^2: avoid AKI reported
Risedronate	Postmenopausal osteoporosis Corticosteroid use Paget's disease	5 mg daily, oral 35 mg weekly, oral	GFR <30 ml/min/1.73 m^2: contraindicated No reported adverse events specific to CKD
Tiludronate	Paget's disease	400 mg daily for 3 months	CrCl <30 ml/min: contraindicated No data in CKD
Zoledronate	Malignancy-related bone disease Postmenopausal osteoporosis Paget's disease	4-5 mg single dose, intravenous	GFR <30 ml/min/1.73 m^2: avoid GFR <60 ml/min/1.73 m^2: graded dose reduction No data in CKD, AKI reported in non-CKD

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CrCl, creatinine clearance; GFR, glomerular filtration rate.

Implications for Clinical Practice and Public Policy

Given the widespread use of bisphosphonates in developed countries, especially in older women who are also likely to have some degree of kidney dysfunction, the cessation of bisphosphonates in that group may be problematic. There is a need to monitor clinical practice and understand the implications of this recommendation for large populations, who may or may not be deriving benefit from these agents.

Areas of Controversy, Confusion, or Non-consensus

Despite these concerns, primary care data from the USA suggest that prescription of bisphosphonates is common in people with CKD. Even in the subset with GFR <30 ml/min/1.73 m^2, bisphosphonate use was no less prevalent than in the non-CKD population.[399] People with CKD in this study were nearly seven times more likely to receive a bisphosphonate than active vitamin D. Similar uncertainty about the efficacy and safety of such treatment for people with CKD was demonstrated in a study of people under the care of a UK renal unit.[400] Half of all people prescribed bisphosphonates had a GFR <30 ml/min/1.73 m^2 and yet 50% of people with higher GFRs and documented osteoporosis were not prescribed bisphosphonates.

Clarification of Issues and Key Points

Further study is required to elucidate whether or not bisphosphonates, through reduction of bone turnover in people with pre-existing low bone turnover states, would be beneficial or harmful both for bone and vascular calcification.

3.4 ACIDOSIS

The prevalence and severity of metabolic acidosis in people with CKD progressively rises as GFR falls (Table 27). Adaptations in acid excretion by the kidneys initially prevent a fall in serum bicarbonate concentration but as GFR continues to decline below 40 ml/min/1.73 m^2, metabolic acidosis commonly develops.

3.4.1: We suggest that in people with CKD and serum bicarbonate concentrations <22 mmol/l treatment with oral bicarbonate supplementation be given to maintain serum bicarbonate within the normal range, unless contraindicated. (*2B*)

RATIONALE

Serum bicarbonate concentrations less than 22 mmol/l are associated with increased risk of CKD progression and increased risk of death. Conversely, high serum bicarbonate concentrations greater than 32 mmol/l are associated with increased risk of death irrespective of the level of kidney function. Small studies of alkali supplementation have shown reduction in progression of CKD and improved nutritional status in people with CKD. This statement is therefore worded to reflect the potential benefits of oral bicarbonate supplementation to maintain serum bicarbonate concentrations within the normal range, but the word 'suggest' in the statement reflects the lack of robust evidence base on which to support this statement.

Evidence Base

Chronic metabolic acidosis is associated with increased protein catabolism, uremic bone disease, muscle wasting, chronic inflammation, impaired glucose homeostasis, impaired cardiac function, progression of CKD, and increased mortality.[401–410] The suggestion that treatment of acidosis may be beneficial was first made by Richard Bright,[411] later

taken up enthusiastically by Arthur Osman[412] and further explored by Lyon et al. who conducted a form of crossover study of supplementation with bicarbonate in 17 people with moderate kidney failure and suggested that treatment with alkali might preserve kidney function.[413] Rustom et al. described a reduction in proximal renal tubular catabolism and markers of tubular injury after oral $NaHCO_3$ in 11 people with mild/moderate renal impairment (mean ^{51}Cr-EDTA GFR 46.2 ± 6.0 ml/min/1.73 m^2) and proteinuria (3.2 ± 0.8 g/24 hours).[414] They suggested that oral sodium bicarbonate may protect the proximal renal tubule and help delay kidney disease progression. Mathur et al. randomized 40 subjects with mild to moderate CKD to oral bicarbonate (1.2 mEq/kg of body weight) or placebo for 3 months and suggested that correction of metabolic acidosis significantly attenuates the rise in blood urea.[415] A larger study randomly assigned 134 adults with moderate to severe CKD (CrCl 15 to 30 ml/min/1.73 m^2) and serum bicarbonate 16 to 20 mmol/l to either supplementation with oral sodium bicarbonate (1.82 ± 0.80 g/day) or standard care for 2 years.[416] Primary end points were rate of kidney function decline, the proportion of subjects with rapid decline of kidney function (>3 ml/min/1.73 m^2/yr), and ESRD (CrCl <10 ml/min [<0.17 ml/s]). Secondary end points were DPI, normalized protein nitrogen appearance, serum albumin, and mid-arm muscle circumference. Serum bicarbonate increased significantly in the bicarbonate group but despite the associated sodium load there was no difference in BP control, prescription of antihypertensives and loop diuretics, or hospitalization for heart failure compared with the control group. The decline in CrCl was significantly slowed in the bicarbonate group compared with controls (5.93 versus 1.88 ml/min/1.73 m^2, $P<0.0001$), rapid progression was less prevalent (9 versus 45%, RR 0.15; 95% CI 0.06-0.40; $P<0.0001$), and fewer subjects developed ESRD (6.5 versus 33%, RR 0.13; 95% CI 0.04-0.40; $P<0.001$). Nutritional parameters also improved significantly with bicarbonate supplementation. In a non-randomized study the effects of supplementation of 1 mmol of bicarbonate equivalent per kg body weight per day for 2 years using oral sodium citrate in 30 subjects with hypertensive nephropathy was compared with 29 control subjects.[417] There were no statistically significant differences in baseline demographic data, systolic BP, venous bicarbonate levels, or parameters of kidney function between the two groups. All subjects were receiving angiotensin-converting enzyme inhibition throughout the study and BP was controlled to similar levels in both groups in a 6-month run-in period prior start of study. In those treated with oral sodium citrate, urine endothelin-1 excretion and N-acetyl-β-D glucosaminidase were each significantly lower while the rate of GFR decline was significantly slower after 24 months of treatment compared to the control group.

International Relevance

Alkali supplementation appears to be a promising low-cost, high-benefit adjunct treatment for patients with CKD and may be accessible to all populations. It is not known how prevalent acidosis is among different communities or countries around the world.

Implications for Clinical Practice and Public Policy

The use of sodium bicarbonate or calcium carbonate as a source of alkali should not present financial hardships in most practices or jurisdictions.

Areas of Controversy, Confusion, or Non-consensus

A potential concern regarding treatment of patients with CKD with sodium bicarbonate or sodium citrate is the possible associated sodium loading. A crossover study of 200 mmol/day (17 g/day) of sodium bicarbonate versus 200 mmol/day (12 g/day) of sodium chloride in 10 subjects with severe CKD (CrCl 2.5-16.8 ml/min [0.04-0.28 ml/s]) on an extremely low-sodium diet showed that sodium chloride but not sodium bicarbonate produced an increase in weight and BP.[418] A subsequent follow-up study suggested that if dietary sodium chloride intakes are near maximum tolerance, then sodium bicarbonate supplementation should be accompanied by reductions in sodium chloride intake to maintain sodium balance.[419] Given the lack of large and long-term trials, many are still not convinced that this is a reasonable recommendation, and is thus controversial. We would like to ensure that individual clinicians are aware of the controversy rather than making no statement at all.

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Chapter 4: Other complications of CKD: CVD, medication dosage, patient safety, infections, hospitalizations, and caveats for investigating complications of CKD

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This section addresses a series of important topics which impact the outcomes of people with CKD. Specifically CVD, interpretation of tests for CVD, infections, vaccinations and hospitalizations, medications, and patient safety are addressed. This section is designed to help the practitioner appreciate the specific nuances related to testing and drug administration in people with CKD and to alert all clinicians to the fact that many common tests may not be as useful in people with CKD to diagnose or evaluate therapies. It was beyond the scope of the guideline and evidence review to thoroughly evaluate all tests with respect to sensitivity and specificity in different groups of people with CKD but future research may consider this as a useful direction.

4.1 CKD and CVD

Population-based studies have demonstrated an increased risk of death and cardiovascular mortality as GFR falls below 60 ml/min/1.73 m^2 or when albumin is detected on urinalysis. This is not explained by an increase in traditional risk factors. There are CKD-specific risk factors associated with more advanced CKD which drive the high rates of mortality and morbidity even at young ages. People with CKD are more likely to experience a cardiovascular event than to progress to ESRD, have a worse prognosis with higher mortality after acute myocardial infarction (MI), and have a higher risk of recurrent MI, heart failure and sudden cardiac death. Management of modifiable cardiovascular risk factors, such as improved BP and diabetes control, also reduces CKD progression.

4.1.1: We recommend that all people with CKD be considered at increased risk for cardiovascular disease. (*1A*)

RATIONALE

This statement is worded in this way to reflect the strong and independent associations between GFR and albuminuria categories and risk of CVD in people with CKD and applies to both adult and pediatric populations.

Evidence Base

Large cohort studies have demonstrated the strong and independent associations between CVD (acute coronary syndrome [ACS], stroke, heart failure and sudden cardiac death) and CKD by category of eGFR, after adjusting for known CVD risk factors, history of CVD events, and proteinuria. In those with an eGFR of 45-59 ml/min/1.73 m^2, risk is increased by 43% and in those with eGFR below 15 ml/min/1.73 m^2, risk is increased by 343%.[58] Although people with GFR category G5 (GFR $<$ 15 ml/min/1.73 m^2) are at the highest risk of a CVD event, there will be more events in people with GFR categories G3a-G3b (GFR 30–59 ml/min/1.73 m^2) because of the much higher prevalence at these categories.[420] These events occur at a younger age in people with CKD suggesting that CKD promotes CVD at an accelerated rate.[421] The prognosis after an acute event is related to level of GFR with a significant rise in mortality when eGFR falls below 45 ml/min/1.73 m^2.[422–424]

Albuminuria is associated with duration and severity of hypertension; an adverse lipid profile with higher levels of total cholesterol, triglycerides and lipoprotein(a) and low HDL-C levels;[425] and abnormalities of coagulation. The presence of higher levels of proteinuria increases the risk of mortality and MI independently of level of eGFR.[426] Many studies have demonstrated low levels of urinary albumin to be associated with the increased risk of CVD in people with diabetes independent of renal function; however population studies of non-diabetic individuals have confirmed that even small amounts of albuminuria are associated with increased CVD risk. In the Third Copenhagen study, in people with microalbuminuria, risk of coronary heart disease was increased independently of age, sex, renal function, diabetes, hypertension, and plasma lipids.[427] The Chronic Kidney Disease Prognosis Consortium demonstrated that in general practice cohorts there was an increase in cardiovascular mortality when ACR is higher than 30 mg/g (3 mg/mmol).[4] Analysis of data from the Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that any degree of albuminuria is a risk factor for cardiovascular events in individuals with or without diabetes.[428] The lack of a threshold of albuminuria for cardiac risk was also confirmed in the HUNT 2 Study[429] and the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study in patients with LVH.[430] Albuminuria and low eGFR were synergistic cardiovascular mortality risk factors in the HUNT 2 study and using both ACR and eGFR improved

cardiovascular risk stratification at all age levels, but particularly in persons 70 years and over.[429]

In the MDRD Study cohort of patients with GFR categories G3a-G4 (GFR 15–59 ml/min/1.73 m^2), cystatin C level was strongly associated with all-cause and cardiovascular mortality particularly in the elderly.[431] Analysis of data from MESA and the Cardiovascular Health Study (CHS) demonstrated that the worst prognosis of CVD, heart failure, and progressive CKD was found in those subjects with CKD diagnosed using the cystatin C-based equation.[432]

LVH is common with CKD, is known to reflect target organ damage, and is associated with increased cardiovascular mortality in CKD.[360] It is also important to consider the role of CKD-specific risk factors particularly in patients with more severe CKD (GFR <30 ml/min/1.73 m^2) and correct them where possible. Anemia has been thought to have a particular role in the early development of CVD in people with CKD. Although treatment of anemia is associated with improved well-being and greater exercise capacity, the results of several RCTs of anemia correction have suggested that complete correction of anemia is not advisable in people with lower GFR (<60 ml/min/1.73 m^2). A meta-analysis of 9 RCTs comparing different target Hb levels suggests an increase in mortality and worse BP control with the higher treatment targets, independent of the GFR category.[433,434] Those patients with LVH at baseline, a sign of target organ damage and which was present in 47% of the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta Trial (CREATE) cohort, had significantly worse cardiovascular outcomes when treated to the higher targets.[435]

Abnormalities of mineral metabolism with low 1,25-dihydroxyvitamin D and PTH were found to occur early in CKD in the Study for the Evaluation of Early Kidney disease [SEEK] study, however serum calcium and phosphate were usually normal until eGFR fell below 40 ml/min/1.73 m^2.[367] An association between elevated serum phosphate and cardiovascular mortality was demonstrated in a prospective study of people with CKD and this was also thought to be associated with low vitamin D levels.[436]

Pediatric Considerations

While the majority of data for, and evidence of, the high risk of cardiovascular morbidity and mortality in the pediatric renal population stems from the ESRD (dialysis and transplant) populations,[437–440] there is recognition that many if not all of the factors responsible for such outcomes will develop much earlier in this course of CKD. In fact, the current American Heart Association's guidelines for reduction of cardiovascular risk in pediatrics stratified the child with CKD to the highest risk category.[441]

Based on data from the CKiD trial, Wilson et al.[442] demonstrated extremely high prevalence rates for four traditional cardiovascular risk factors (hypertension, dyslipidemia, abnormal glucose metabolism, and obesity) in a subgroup of this cohort of 586 children with iohexol GFR proven mild to moderate CKD. In this cross-sectional analysis of 250 children who had data on all variables of interest, median GFR of 45.2 ml/min/1.73 m^2 (IQR 34.6-58.2), the prevalence of hypertension was 46%, dyslipidemia was 44%, abnormal glucose metabolism was present in 21%, and obesity in 15%. Hypertriglyceridemia was common, seen in 33%. In aggregate, only 26% of the cohort had no risk factors present, 39% had at least one and 22% had two, 11% had three and 2% had all four risk factors present. The prevalence of all these factors remained elevated even when the population was restricted to those defined as lean, BMI $<85^{th}$. In this group, the presence of 2 or 3 cardiovascular risk factors was still seen in 20% and 2%, respectively. Within the lean group 12% demonstrated abnormal glucose metabolism. Finally, multivariate regression analysis of their data demonstrated that glomerular disease as a cause of CKD and the presence of nephrotic range proteinuria were associated with much higher odds of having cardiovascular risk factors, 1.96 (95% CI 1.04-3.72) and 2.04 (95% CI 0.94-4.43), respectively.

It is also well-recognized that carotid intimal media thickness and pulse wave velocity changes, as potential surrogate measures for vascular damage in children, can be increased in in children with CKD.[443,444]

For further detailed discussions of the pathophysiology and complexity of CVD in the pediatric CKD population, two recent review papers from Mitsnefes[445] and Shroff et al.[446] are suggested. Both papers identify and discuss the pathophysiology of both traditional and CKD-specific cardiovascular risk factors as seen in this population.

4.1.2: We recommend that the level of care for ischemic heart disease offered to people with CKD should not be prejudiced by their CKD. (*1A*)

4.1.3: We suggest that adults with CKD at risk for atherosclerotic events be offered treatment with antiplatelet agents unless there is an increased bleeding risk that needs to be balanced against the possible cardiovascular benefits. (*2B*)

RATIONALE

These statements are worded in this way to reflect the growing body of evidence that suggests that treatment of traditional risk factors in CKD patients is of benefit, and that attempts to modify or preclude usual investigations and therapies are not necessary in CKD patients. Inasmuch as CKD populations have been understudied, but likely inadvertently included in larger population studies, the rationale for risk factor modification is similar to that in the general population. Modification of risk factors includes:

1. Smoking cessation
2. Exercise
3. Weight reduction to optimal targets
4. Lipid modification recognizing that the risk reduction associated with statin therapy in adults with CKD is

relatively constant across a broad range of baseline low-density lipoprotein cholesterol (LDL-C) levels
5. Optimal diabetes control HbA_{1C} <7% (53 mmol/mol)
6. Optimal BP control to <140/90 mm Hg or <130/80 mm Hg in those with CKD and depending on the degree of proteinuria (see Recommendations 3.1.4 and 3.1.5)
7. Aspirin is indicated for secondary prevention but not primary prevention
8. Correction of anemia to individualized targets (see *KDIGO Clinical Practice Guideline for Anemia in CKD*[11])

Evidence Base

The maintenance of cardiovascular health ultimately impacts 'kidney health' given the links between cardiac function, renal perfusion, atherosclerosis, and glomerulosclerois. The details of this complex biology are beyond the scope of these guidelines, but can be found in key references below.

There is evidence in the general population that smoking cessation is associated with a reduction in cardiovascular risk. In CKD there is evidence that smoking is associated with progression of renal disease, though no specific data exist that support cessation of smoking and delay of progression.[447]

People with CKD have reduced levels of muscle strength and aerobic activity. In those not on dialysis, exercise training is shown to improve functional capacity and BP.[448]

Weight loss in obese CKD patients can reduce rate of decline, proteinuria, and BP.[354]

The Study of Heart and Renal Protection (SHARP)[449] is the largest RCT in people with CKD to date. The results demonstrate that a lipid-lowering strategy which included fixed dose simvastatin and ezetimibe resulted in a 17% reduction in atherosclerotic events, as compared to placebo. The cohort enrolled included those with eGFR under 60 ml/min/1.73 m^2, age greater than 40 years, and was an international study including more than 9000 subjects from around the globe. The lipid-lowering strategy was effective and safe. Lipid targets have not been established specifically for people with CKD. Treatment strategies should be implemented in accordance with current recommendations for high-risk populations.

At the time of this writing, the *KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease* was under preparation for public review. In brief, the key aspects of the draft recommendations include treating those at high risk for atherosclerotic disease with lipid-lowering therapies, regardless of LDL levels, in those 50 years of age and above. Since this Guideline has not yet been finalized, interested readers should refer to the final document when it is formally released in 2013.

The benefits of aspirin in people with CKD and hypertension was demonstrated in a *post hoc* analysis of the Hypertension Optimal Treatment (HOT) trial.[450] Jardine et al. reported that among every 1000 persons with eGFR <45 ml/min/1.73 m^2 treated for 3.8 years, 76 major cardiovascular events and 54 all-cause deaths will be prevented while 27 excess major bleeds will occur. They concluded that an increased risk of major bleeding appears to be outweighed by the substantial benefits. Clopidogrel is used as an alternative to aspirin but CKD has been shown to be associated with an increase in platelet reactivity and there is resistance to clopidogrel in people with CKD, diabetes, and CVD.[451] The Clopidogrel for Reduction of Events During Observation (CREDO) trial concluded that clopidogrel in mild or moderate CKD may not have the same beneficial effect as it does in people without CKD. Subjects with normal renal function who received 1 year of clopidogrel had a marked reduction in death, MI, or stroke compared with those who received placebo (10.4% versus 4.4%, $P < 0.001$), whereas those with mild and moderate CKD did not have a significant difference in outcomes with clopidogrel therapy versus placebo (mild: 12.8% versus 10.3%, $P = 0.30$; moderate: 13.1% versus 17.8%, $P = 0.24$). Clopidogrel use was associated with an increased RR of major or minor bleeding, but this increased risk was not different based on renal function.[452]

International Relevance

Although it is clear and mentioned in many guidelines that CKD is associated with an increase in CVD risk, it is not included in many assessment tools and there is a deficiency in ethnicity and regional specific tools.

The assessment tool from US Third Report of the National Cholesterol Education Program (NCEP III) does not include CKD. The Fourth Joint Task Force of the European Society of Cardiology suggest that both an eGFR of less than 60 ml/min/1.73 m^2 and albuminuria increase risk but do not quantify the risk or include CKD in their Systematic COronary Risk Evaluation (SCORE) assessment tool.[453] In the UK, the QRISK®2 online tool includes CKD as 'yes' or 'no' and therefore does not allow for level of eGFR or proteinuria.[454] The Joint British Societies Guidelines regards proteinuria as a sign of target organ damage, which conveys a risk of at least 20% in 10 years.[455]

A study of cardiovascular risk estimation in Chinese adults in the USA–People's Republic of China Collaborative Study of Cardiovascular and Cardiopulmonary Epidemiology (USA-PRC Study) did not include CKD as a risk factor at all.[456] It is also important to remember that in this population stroke was the predominant CVD. A review of 25 risk assessment tools identified only 2 derived from an Asian population.[457] However, links between GFR categories and CVD events are evident in the Asian population, for example in the Japanese Gonryo study.[458] A prospective study in a general Japanese population demonstrated links between lower GFR, high creatinine levels, and proteinuria with cardiovascular mortality particularly stroke.[459] In Chinese patients who were at least 50 years old and either had existing CVD or were at high risk, 34% had an eGFR <60 ml/min/1.73 m^2 and eGFR <45 ml/min/1.73 m^2 was found to be an independent predictor of all-cause and cardiovascular death.[460] In a population-based study of 2353 people aged over 40 years in Beijing, an eGFR

<90 ml/min/1.73 m^2 was associated with increased CVD risk, and for each CKD category stroke was more prevalent than MI.[461]

In India the increasing prevalence of type 2 diabetes is driving an increase in CKD and both are associated with increased cardiovascular risk. In CKD patients attending one clinic in North India, 28% had diabetes, 27% were overweight, and 92% had hypertension. Metabolic syndrome as defined by the International Diabetes Federation (IDF) 2007 guidelines was present in 39% and more frequent in women.[462]

Implications for Clinical Practice and Public Policy

A full CVD risk assessment in a person with CKD should include an estimate of GFR and a quantitative assessment of albuminuria. Cystatin C may be helpful at risk stratifying those at intermediate risk.

The key aspect of these recommendations is to ensure that people with CKD are not deprived of treatment strategies known to be effective in general populations.

Areas of Controversy, Confusion, or Non-consensus

Many of the traditional cardiovascular risk assessment tools do not adjust for the presence of early CKD. Any tool should also adjust for level of eGFR because of increasing risk associated with lower levels of kidney function. The Framingham risk equation underestimates true events in a CKD population, but no validated different tools exist at present which better quantify cardiovascular or mortality risk in CKD populations.

Proteinuria is considered to be a sign of target organ damage and thus associated with high cardiovascular risk. However, assessment of risk should also include the presence of albuminuria. Few studies exist which demonstrate that targeting lowering of proteinuria results in reduced cardiovascular risk, though a number of studies which have targeted interruption of the RAAS (and in which lowering of urine protein has also been shown) have demonstrated a benefit.

An appropriate risk assessment tool should be available to assess risk in people with CKD. Addition of the presence of CKD to conventional risk factors in the Reykjavik population increased discrimination but did not increase risk to the same degree as smoking or diabetes.[463] In the Framingham Heart Study, GFR category 3b (GFR 30–44 ml/min/1.73 m^2) was associated with CVD but not equivalent to previous CVD.[464]

Lifestyle modification has not been studied in large trials in people with CKD but smoking cessation, achievement of optimum weight, regular exercise, and salt restriction should be seen as reasonable aims.

Pediatric Considerations

It is presently unclear whether children with CKD and elevated lipid levels will benefit from lipid-lowering strategies with no prospective trials ongoing in this area. It is hoped that data from both CKiD[55] and the 4C trials[78] may be able to address these shortcomings.

However, given that these children demonstrably have elevated risk of cardiovascular and atherosclerotic disease (see Recommendation 4.1.1), that there are data supporting the use of a number of statins in the pediatric population,[465] and that the adult evidence for benefit of statins in a subset of the SHARP trial[449] with a GFR <60 ml/min/1.73 m^2 exist, it would seem reasonable to consider the use of such drugs in children with CKD and elevated lipids.

Recommendations from 2006[441] for use of dietary modifications, followed by statins in children older than 8 years of age with persistent elevation in LDL-C levels, have been endorsed by the American Academy of Pediatrics. However, at the time of publication of these guidelines, the KDIGO Dyslipidemia Work Group has suggested that statin therapy may not be appropriate.

Age- and renal function-adjusted doses of such drugs should be carefully considered prior to any therapy being initiated (see Recommendation 4.4.1).

Regarding diabetes control, treatment in keeping with national and international diabetes recommendations is prudent. Note is made that there are specific caveats with respect to drugs and side effects that are important (see Recommendations 3.1.15-3.1.18).

There is no literature in the area of antiplatelet agents in atherosclerotic disease in the subset of children with CKD and the suggestion to offer antiplatelet agents does not apply to pediatric practice.

4.1.4: We suggest that the level of care for heart failure offered to people with CKD should be the same as is offered to those without CKD. (*2A*)

4.1.5: In people with CKD and heart failure, any escalation in therapy and/or clinical deterioration should prompt monitoring of eGFR and serum potassium concentration. (*Not Graded*)

RATIONALE

This statement is worded this way to make clinicians aware that people with CKD and heart failure should receive at least equal benefit from heart failure therapy as those without CKD, but that heart failure therapies (in particular increase of RAAS blockade and diuretic therapy) may lead to significant changes in GFR and serum potassium concentrations. This does not imply that such therapy should be avoided but only that clinicians are cognizant of this possibility, monitor it, and understand it in the context of individual risks and benefits.

Heart failure is a complex clinical syndrome which can be caused by any structural or functional cardiac disorder that impairs the pump function of the heart and has a high mortality. Within the general population, the commonest causes of heart failure are ischemic heart disease causing left ventricular systolic dysfunction, and hypertensive heart disease with left ventricular hypertrophy and diastolic dysfunction. Thus people with CKD are at increased risk of both. Evidence-based medication for heart failure impacts on

GFR and prescribers need to be alert to this. Changes in GFR are often transient and the downward trajectory GFR is not sustained if all other aspects of care and clinical status are stable. Monitoring and close follow-up are required.

Evidence Base

In an outpatient setting, normal GFR is unusual in heart failure. A study from the Alberta Heart Function Clinic found that in people with an ejection fraction of $\leq$35%, GFR categories G3a and G3b (GFR 30–59 ml/min/1.73 m^2) were present in 40% and 16% of people were GFR categories G4 or G5 (GFR $<$ 30 ml/min/1.73 m^2).[466] This study demonstrated a 1% increase in mortality associated with each 1 ml/min fall in CrCl demonstrating the clear link between kidney function and outcome for people with CKD and heart failure. Meta-analysis of 16 studies and over 80,000 people with heart failure by Smith et al. showed that renal impairment was present in 63% and was associated with increased mortality across the range of kidney function, with an adjusted HR of 1.56 (95% CI 1.53-1.60).[467] In the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) Program with candesartan in heart failure, 36% of subjects had eGFR $<$60 ml/min/1.73 m^2 which was associated with increased mortality and hospital admission regardless of ejection fraction.[468] The Digitalis Intervention Group (DIG) identified a GFR of 50 ml/min as a risk threshold for increased mortality risk in heart failure.[469] Smith et al. demonstrated that 1-year mortality after admission for heart failure was 29% in people with normal kidney function but 52% in those with moderate to severe renal impairment.[470] Anand et al. also demonstrated an independent association between the presence of positive reagent strip proteinuria present in 8% of subjects and increased mortality in heart failure.[471]

In the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) study of people with heart failure related to coronary artery disease (CAD), 39% had CrCl $<$60 ml/min ($<$1 ml/s). This study also demonstrated that the level of kidney function was a better indicator of poor outcome than cardiac anatomy.[472] In people admitted to hospital with heart failure, increasing SCr concentration is associated with a longer hospital stay and worse outcome.[473]

LVH is present in 40% of people with CKD,[474] progressively increasing as kidney function declines.[475] Ha et al. demonstrated LVH in 87% of people with predialysis CKD.[476] Parfrey et al. in a study of 432 people who were predialysis, found that only 16% had a normal echocardiogram while 41% had concentric LVH, 16% systolic dysfunction, and 28% left ventricular dilatation.[477] LVH is related to increased work load caused by arterial stiffness and hypertension, and at lower levels of GFR, volume overload. Alterations in electrolyte balance, anemia, bone metabolism, uremia, oxidative stress, inflammation, and other inflammatory mechanisms all play a role.[478]

In the majority of people with CKD, the myocardium develops concentric hypertrophy[476] with interstitial fibrosis and CKD-associated cardiomyopathy, leading to left ventricular stiffness.[474] This results in diastolic heart failure; people with CKD have higher mortality from diastolic heart failure than systolic heart failure.[479] Diastolic heart failure is more common in people with CKD who are older females with hypertension and/or diabetes.[480]

Left ventricular hypertrophy is particularly associated with anemia and a fall in Hb to less than 12.8 g/dl (128 g/l) is associated with left ventricular growth in people with early CKD.[481] Lower Hb levels are associated with increased risk of death and hospitalization in heart failure.[482] Other cardiovascular conditions, for example MI and atrial fibrillation, are more common in CKD and may exacerbate heart failure.

It is important to note that in a study of an older population (age $>$64 years), heart failure was an independent predictor of rapid kidney function decline.[483]

Standard therapy for the management of systolic heart failure includes an ACE-I or ARB and a beta-blocker licensed for heart failure such as bisoprolol or carvedilol. Meta-analysis of 25 trials of RAAS blockade (ACE-I or ARB) in people with CKD or proteinuria, demonstrated a reduction in the risk for heart failure and reduction in cardiovascular outcomes.[484] Subgroup analysis from the Valsartan Heart Failure Trial (Val-HeFT) demonstrated the beneficial effect of valsartan in people with CKD and that valsartan reduced the eGFR by the same amount in people with and without CKD.[471] Candesartan was also clinically effective in the CHARM study regardless of underlying kidney function[468] while irbesartan was associated with a 23% reduction in hospital admissions related to heart failure in people with nephropathy due to type 2 diabetes.[485] Analysis of data on bisoprolol from the Cardiac Insufficiency Bisoprolol Study II (CIBIS II)[486] identified 32% of subjects with eGFR $<$60 ml/min/1.73 m^2. These subjects were more likely to die or be admitted to hospital than those with eGFR $\geq$ 60 ml/min/1.73 m^2. However, they showed a similar benefit from bisoprolol treatment. A *post hoc* analysis of data on carvedilol from the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) and Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trials identified 60.8% of participants with eGFR $<$60 ml/min/1.73 m^2.[487] Carvedilol was well tolerated by subjects with CKD, and decreased all-cause, cardiovascular, and heart failure mortality. However, doubts were raised over the benefits when eGFR $<$45 ml/min/1.73 m^2.

Aldosterone antagonists are included in standard heart failure management, usually in addition to an ACE-I or ARB, leading to concerns relating to risk of hyperkalemia, particularly in people with lower GFRs. In a study of spironolactone therapy in severe heart failure, Pitt et al.[488] included subjects with SCr concentrations up to 2.5 mg/dl (221 μmol/l). There was a 30% reduction in mortality with spironolactone and the incidence of hyperkalemia was low. However, a review of real-world practice demonstrated a significant increase in hyperkalemia with the combination of RAAS blockade and an aldosterone antagonist, highlighting

the need for close monitoring with the introduction of combination therapy.[489]

In the APPROACH study on the specialist management of heart failure, subjects with CAD and CKD, despite being at high risk, were less likely to be taking ACE-Is, beta-blockers, statin, and aspirin. This study demonstrated that those subjects taking beta blockers had lower mortality, however ACE-Is were only of benefit when eGFR was >60 ml/min/1.73 m^2.[472]

International Relevance

The treatment of heart failure is similar around the globe. The ability to closely monitor kidney function or to offer conventional therapies may differ, however. Irrespective, this statement should hold true internationally. The National Heart Care Project of community subjects admitted to hospital with heart failure studied the differences between people of black and white ethnic groups. People with worse renal function were more likely to be black, older and female, and black people had a greater prevalence of hypertension and diabetes but less ischemic heart disease. Black people had a lower risk of mortality at every level of creatinine, for every 0.5 mg/dl (44.2 μmol/l) increase in creatinine, 1-year death risk increased 10% in black people and 15% in white people.[470]

Implications for Clinical Practice and Public Policy

Cardiorenal syndrome, an impairment of kidney function in the presence of heart disease, is a marker of worse prognosis. In addition to GFR, the presence and severity of albuminuria and anemia aid in prognostication and management.[490]

Where the link between LVH and heart failure in CKD is so strong and the outcome poor for people with LVH, efforts should be made to optimize care particularly BP. There is a lack of robust evidence for the optimal medical management of heart failure specifically in people with CKD; however, the prevalence of people with early CKD is so high in heart failure trials that we can apply standard treatment to these people. For those people with eGFR <45 ml/min/1.73 m^2, the situation is less clear.[487]

Areas of Controversy, Confusion, or Non-consensus

There are difficulties in making the diagnosis of heart failure in people with CKD, especially diastolic heart failure. Biomarkers such as B-type natriuretic peptide (BNP) may be abnormally elevated in CKD, but may or may not be as responsive to treatment or diagnostically accurate in people with CKD (see Chapter 4.2). There is little evidence to guide the management of left ventricular systolic dysfunction in people with CKD and evidence for the management of diastolic heart failure is generally lacking. However, there is evidence that medications to improve the outcome of people with heart failure are underused in people with CKD.

Appropriate management of the metabolic complications of kidney disease which can exacerbate heart failure needs to be clarified. Clinical studies are required on the role of device therapy in people with CKD (e.g., pacemakers, defibrillators, etc.).

4.2 CAVEATS WHEN INTERPRETING TESTS FOR CVD IN PEOPLE WITH CKD

BNP/N-terminal-proBNP (NT-proBNP)

As GFR diminishes, the prevalence and severity of cardiovascular abnormalities increase and are accepted as major causes of morbidity and mortality in people with CKD. The presence of congestive heart failure (CHF) in people with CKD conveys a worse prognosis than either condition alone. Therefore, early diagnosis and aggressive management of CHF are both highly desirable. A number of cardiac biomarkers (i.e., BNPs and cardiac troponins) appear to have both increasing clinical importance and increasing facility for detection and stratification of CHF. The stimulus for secretion of these biomarkers is the hemodynamic load (i.e., myocardial stretch) and their secretion is associated with the severity of CHF and the degree of left ventricular dysfunction. They are thus useful markers for diagnosis, management, and prognosis in people with normal renal function. However, when the eGFR is less than 60 ml/min/1.73 m^2, the accuracy of plasma BNP and NT-proBNP levels for detection and stratification of CHF becomes unreliable and the degree of responsiveness to treatment is not known.

4.2.1: In people with GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5), we recommend that serum concentrations of BNP/NT-proBNP be interpreted with caution and in relation to GFR with respect to diagnosis of heart failure and assessment of volume status. (*1B*)

RATIONALE

This statement is intended to remind clinicians that although the prevalence of fluid overload and heart failure increases with lower GFR categories, BNP becomes less reliable as a predictor of fluid overload and heart failure at lower GFRs. While it is associated with worse outcomes, cutoff values indicative of heart failure in general populations may or may not be appropriate and changes in values with treatment may or may not have the same meaning.

Evidence Base

Natriuretic peptides belong to a family of circulatory peptide hormones from either myocardial cell origin (atrial natriuretic peptide [ANP] and BNP) or endothelial cell origin (C-type).[491,492] They play an important role in regulating BP and body fluid volume by their natriuretic and diuretic actions, arterial dilatation, and inhibition of the RAAS.[493] Natriuretic peptides for the diagnosis of CHF have been a diagnostic breakthrough in cardiology where determination of their concentration in serum can help identify patients with left ventricular systolic dysfunction.[494,495]

Concentrations of natriuretic peptides increase in people with CHF and other CVDs as a consequence of

pressure and volume overload.[496,497] Among people with progressive LVH, concentrations of NT-proBNP are typically elevated in proportion to the degree of left ventricular mass increase.

Overall, BNP levels provide a better index of left ventricular mass and load than do ANP levels and BNP has emerged as a superior biomarker to ANP for clinical applications involving CHF and left ventricular dysfunction.[491,498] NT-proBNP may have analytical advantages over BNP because of greater stability due to a longer half-life. The cause of an elevated BNP level is multifactorial in origin and may reflect cardiac dysfunction, and/or changes in renal function.[499] Since renal dysfunction intrinsically was shown to affect BNP levels in some studies, the diagnostic value of BNP levels in the presence of CKD has been questioned.[500,501]

Earlier research hypothesized that measurement of natriuretic peptides could be of use in monitoring excess fluid volume and dry weight in people requiring dialysis,[502,503] but this remains unproven and the significance of plasma natriuretic peptides and their clinical role in dialysis remains unclear.[491]

Although several studies revealed higher BNP levels as GFR declined, outcomes of other studies suggest that the relationship between renal function and BNP levels may be most strongly dependent on cardiac and volume-related factors.[504–506] To test this hypothesis, Tagore et al. studied BNP levels in a cohort of 143 clinically euvolemic subjects with CKD in whom absence of heart disease was clinically validated and found that plasma BNP levels were independent of GFR.[504] Suresh and Farrington[507] studied people on dialysis and concluded that BNP levels were predictive of presence of left ventricular dysfunction, cardiac events, and survival in the presence of ESRD, suggesting that BNP levels may be informative across the full range of renal function and even in its absence. As previously established by several studies, the level of NT-proBNP is a strong prognostic marker in both the general population[508] and in various disease states, e.g., acute and CHF,[509,510] coronary heart disease,[511,512] and hypertension.[513]

International Relevance

The issue of how to differentially interpret BNP in the presence or absence of CHF and within the context of declining renal function has received considerable attention but remains incompletely resolved from a clinical perspective. Changes in either renal or cardiac function could potentially impact levels of natriuretic peptides and incomplete knowledge of an individual's clinical status relative to the degree of cardiac pathology or renal dysfunction could confound interpretation of BNP levels. Given the cost of biomarkers assays and the uncertainties related to interpretation of serum levels of BNP/NT-proBNP in people with CKD, competing priorities for health-care resource may dictate reliance on clinical evaluation and local practices of care in some areas of the world. Until better data are available, clinicians are asked to use this laboratory measurement with caution as a diagnostic test for heart failure in those with CKD.

Implications for Clinical Practice and Public Policy

Since people with ESRD with elevated levels of BNP have a higher RR of death, this biomarker could be used as an individual risk marker with the aim of identifying those at high risk. Clinical correlation is of utmost importance to ensure accurate diagnosis and appropriate therapy.

Studies to understand the variability of BNP by categories of eGFR and urine ACR, within and between individuals over time, and the response to therapy should be undertaken so as to better inform clinicians.

Areas of Controversy, Confusion, or Non-consensus

The relationship between renal function and BNP, the role of natriuretic peptides as markers of fluid overload and as predictors of mortality, and the utility of serial monitoring of BNP/NT-proBNP levels in people with CKD, and responsiveness to therapy remains unknown.

Clarification of issues and key points

Natriuretic peptides may be surrogate markers for prediction of mortality in people with CKD reflecting the association of mortality with left ventricular dysfunction and LVH. Before routine measurements of these biomarkers are recommended, their utility in guiding or changing clinical practice should be assessed.

Pediatric Considerations

There is robust literature in both children and neonates regarding both the normative values of BNP[514] and its value in predicting outcomes of pediatric heart failure.[515] To date no studies in children specifically address the issue of reduced GFR in this population. However, application of similar principles would likely apply.

Troponins

In recent years newer markers of myocardial injury have been introduced into clinical practice.[516,517] Among these, cardiac troponins have proven to be specific markers of myocardial damage.[518,519] Cardiac troponins have been considered the gold standard biochemical test for diagnosis of myocardial damage because they have nearly absolute myocardial tissue specificity, as well as high sensitivity, thereby reflecting even microscopic zones of myocardial necrosis.[517,520] Furthermore, increasing evidence indicates that abnormal troponin measurements identify a subgroup of patients who have an increased risk of major cardiac events[519,521–525] and that measurement of cardiac troponin T (cTnT) prior to commencing renal replacement is a significant independent predictor of survival.[526] However, these markers are renally excreted and are often found to be elevated in people with CKD irrespective of specific symptomatology. Thus, there is uncertainty as to the clinical importance of their different

magnitudes of elevation in CKD. There are no data on 'expected' values of these markers in the context of CKD, or at different categories of GFR and albuminuria.

4.2.2: In people with GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5), we recommend that serum concentrations of troponin be interpreted with caution with respect to diagnosis of acute coronary syndrome. (*1B*)

RATIONALE

This statement is intended to remind clinicians that isolated elevated serum concentrations of troponin (in the absence of symptoms or electrocardiographic changes) may not necessarily portend a diagnosis of ACS at lower GFR categories. While there are data linking troponin elevations with poor outcomes, the specific implications for an individual in clinical practice are not clear. Hence, this statement simply cautions the clinician with respect to interpretation but does not suggest that the laboratory values are not of significance. In a patient with clinical symptoms suggestive for ischemic heart disease, an elevated cardiac troponin I (cTnI) is suggestive for ACS.

Evidence Base

cTnT and cTnI are low-molecular-weight proteins that form part of the troponin complex and are integral components of the myofibrillar contractile apparatus of the heart.[527] Loss of integrity of cardiac myocyte membranes causes release of cardiac troponins into the circulation, which can be detected by highly sensitive assays developed for cTnT and cTnI to diagnose ACS.[521] A potent stimulus for the release or production of natriuretic peptides is mechanical stretching,[528] whereas plasma cTnT specifically and sensitively reflects myocardial injury and is considered to be an index of irreversible myocardial change.[521] In addition, cTnT levels can predict multi-vessel CAD in people requiring dialysis.[529] However, the significance of screening people with CKD for CAD using these cardiac biomarkers is questionable[530] since increases in serum cardiac troponin concentration can occur in the absence of an ACS.[531]

Most studies[517,532–545] have focused on people with ESRD where increases in serum cTnT concentrations have been observed in 20%–90% of subjects[540] but generally much lower when cTnI was measured. Information about cardiac troponins and their relationship with comorbidity is sparse in people with CKD who are not receiving dialysis treatment.[526,527,546,547] Increased cardiac troponin concentrations may occur early in CKD, including GFR categories 30-59 ml/min/1.73 m^2, and more commonly as CKD advances.

Powerful prognostic data emerging from the dialysis population demonstrate that increased concentrations of cardiac troponins reflect either subclinical myocardial damage caused by silent ischemia or myocardial remodeling in the development of LVH.[539,542]

Increased levels of cTnT measured with the highly sensitive assay, well below the detection range of standard assays, have been shown to be associated with cardiac structural abnormalities including LVH (both left ventricular wall thickening and dilation) and left ventricular systolic dysfunction,[548] and to have a graded association with all-cause and CVD mortality independent of traditional risk factors, renal function, and levels of other biomarkers such as high sensitivity CRP and NT-proBNP.

These findings suggest that chronic elevation of troponin levels may be mediated to a greater extent by indices of heart failure (such as higher left ventricular mass, left ventricular dysfunction, or increased NT-proBNP levels) than indices of atherosclerosis or ischemia.[548]

International Relevance

The costs of these tests, the differing sensitivity of the assays available, the paucity of data in people with CKD, and the poor correlation of serum troponin levels with ACS in people with CKD should be weighed against competing local health-care priorities and resource before their introduction into routine clinical practice. Emphasis should be placed on the clinical context and local standard practices of care.

Implications for Clinical Practice and Public Policy

Troponin elevation may result from repeated episodes of clinically silent MI,[522,549] although CAD frequently underlies troponin elevation and increased cTnT is also frequently encountered in patients at low risk for CAD. Troponin elevations are as frequent in subjects without CAD as in those with known CAD[517,550–552] and in people with CKD, serial increasing cTn levels may be of greater utility for diagnosis of ACS. In the context of symptoms and signs of ACS, elevations of troponins should not be ignored nor incorrectly attributed to simply 'CKD.' Thus the importance of ordering the test for specific indications for those with CKD should be emphasized.

Areas of Controversy, Confusion, or Non-consensus

Information about cardiac troponins and their relationship with comorbidity is sparse in people with CKD who are not receiving dialysis treatment. Although elevated values for TnT are common in people with low GFR in the absence of ACS or CHF, the prevelance of elevated TnI in the absence of ACS or CHF in people with low GFR may be only 0.4-6% depending on the cutoff value chosen.[532]

Clarification of Issues and Key Points

As pointed out by Roberts et al.,[553] although management strategies in people without CKD based on these biomarkers are quite clear, in people with CKD it is not the case despite the strong data on the prognostic implications. These biochemical markers can only be useful if they are interpreted in the context of the clinical history and examination with consideration given as to what management is appropriate for each individual, and if a cardiovascular therapy that is effective in this population is identified or developed.[553] The importance of understanding and contextualizing elevations

in troponin values in CKD populations cannot be overstated: under-treatment in symptomatic individuals should be avoided, and better understanding of treatment strategies in those asymptomatic individuals is the focus of ongoing study.

Pediatric Considerations

While normative values exist for troponin in children,[554] its utility as a general screening marker for myocardial ischemia in pediatrics has recently been called into question,[555] and no data exist relating reduced renal function and troponin levels in children.

Non-invasive testing

Most studies of cardiac evaluation in people with CKD have involved candidates for kidney transplantation in order to identify existing cardiac conditions amenable to risk modification and to exclude people with short expected survival due to cardiac morbidity. Among the tests for cardiovascular assessment, coronary angiography is considered invasive, expensive, and associated with risks such as contrast-induced nephropathy and cholesterol embolism. When trying to detect CAD or predict future cardiovascular events in people with CKD, nuclear imaging modalities using thallium tracers have shown conflicting results, especially in the context of small vessel disease. Clinicians should be aware of the limitations of radionuclear testing as a screening tool for significant CAD given the limitations of the test. Exercise-dependent techniques are limited by poor exercise tolerance of many subjects and people with CKD frequently have cardiac evaluation performed with pharmacological agents.[556,557]

4.2.3: We recommend that people with CKD presenting with chest pain should be investigated for underlying cardiac disease and other disorders according to the same local practice for people without CKD (and subsequent treatment should be initiated similarly). (*1B*)

4.2.4: We suggest that clinicians are familiar with the limitations of non-invasive cardiac tests (e.g., exercise electrocardiography [ECG], nuclear imaging, echocardiography, etc.) in adults with CKD and interpret the results accordingly. (*2B*)

RATIONALE

These statements are worded in this way firstly because although people with CKD are at increased risk from cardiovascular events, observational study has shown that they are frequently discriminated against in terms of investigation and management of such events. Secondly, non-invasive cardiac tests have known additional limitations in people with CKD and such limitations and their consequences need to be clearly understood by health professionals caring for people with CKD.

Evidence Base

Noninvasive stress testing appears to be the most common first approach to cardiac evaluation of asymptomatic patients, prompted by diabetes, age and risk-factor burden. These tests include myocardial perfusion studies, stress echocardiography, and most recently, cardiac computed tomographic angiography. However, people with CKD are underrepresented in studies evaluating the diagnostic sensitivities and specificities of noninvasive tests. Exercise ECG is limited by lack of specificity of the ST-segment response and by inability of many people with CKD to exercise to a diagnostic workload.

These tests have imperfect sensitivity and specificity in people with CKD or, in the case of tomographic angiography, evaluation in this population is as yet unpublished.[556] CAD has been detected in a high proportion of people on long–term dialysis therapy. Studies describing associations of angiographic coronary stenosis with subsequent clinical events in people with ESRD, including those undergoing transplant evaluations, have reached inconsistent conclusions.[558–562]

Abnormalities on myocardial perfusion studies correlate well with the presence of CAD in the general population, with mean weighted sensitivity of 88% and mean weighted specificity of 74%.[563] The performance of myocardial perfusion studies in identifying CAD in people with CKD is more variable, with reported sensitivities and specificities in people with ESRD ranging from 37% to 90% and 40% to 90%, respectively.[564–567] Nonetheless, results from myocardial perfusion studies have prognostic value for cardiac events and mortality.[568,569] In a meta-analysis of 12 studies involving thallium-201 scintigraphy and dobutamine stress echocardiography, people with ESRD with inducible ischemia had approximately 6 times the risk of MI and 4 times the risk of cardiac death as those without inducible defects.[570] Moreover, subjects with fixed defects also had nearly 5 times the risk of cardiac death.

The prognostic value of myocardial perfusion studies has been shown with other perfusion tracers. For example, in a study of 126 people with ESRD who underwent technetium-99m myocardial perfusion studies as part of their pre-transplant assessment, the presence of a reversible defect was associated with 3 times the risk of post-transplant cardiac events (HR 3.1; 95% CI 1.1-18.2) and nearly twice the risk of death (HR 1.92; 95% CI 1.1-4.4) compared with normal test results.[571]

De Lima et al.[572] prospectively studied 126 renal transplant candidates clinically classified as moderate (age >50 years) or high (diabetes, extra cardiac vascular disease, or known CAD) coronary risk with myocardial perfusion studies, dobutamine stress echocardiography, and coronary angiography. Significant CAD, defined as greater than 70% stenosis in 1 or more major epicardial artery on angiography was found in 42% of the sample. After a median follow-up of 46 months, clinical risk stratification and coronary angiography predicted major cardiac events, but myocardial perfusion studies and dobutamine stress echocardiography did not.

Newer imaging techniques are under current evaluation but a review here is beyond the scope of this guideline; these

techniques include: stress myocardial perfusion single photon emission computed tomography (SPECT);[557,573–576] ^{18}F-BMS, a novel fluorine-based myocardial perfusion tracer;[557,577] and gated imaging using radio-labelled ammonia ($^{13}NH_3$).

International Relevance

People with CKD who are being investigated prior to transplantation should be assessed according to the national and international cardiology guidelines and taking into account local practice and availability of resource.

Implications for Clinical Practice and Public Policy

There is still a need for a safe, noninvasive, diagnostic modality that will allow stratification of cardiovascular risk among people with CKD. With the development of new imaging markers, it becomes difficult for clinicians to choose the imaging tests that can best aid clinical decisions for a given patient. Imaging methods should provide accuracy and precision at acceptable cost. Until advanced imaging techniques (e.g., cardiac MRI, positron emission tomography, cardiac computed tomography) are standardized, clinicians should rely on the most reliable and familiar techniques in their environment.[578]

Areas of Controversy, Confusion, or Non-consensus

Clinical and cost-effectiveness could be improved; cardiac evaluation in people with CKD should be based on data from clinical trials.

Clarification of Issues and Key Points

If cardiac evaluation is at present predominantly used for risk stratification and prognosis, in the future it may guide optimal therapy and monitor clinical progress.[557]

4.3 CKD AND PERIPHERAL ARTERIAL DISEASE

There is a strong link between CKD and peripheral arterial disease (PAD). Symptoms of PAD may only be present in a minority of people who have clinical evidence of PAD.[579] It is therefore important to measure ankle-brachial index and perform regular systematic assessment of the lower limbs of people at high risk of PAD to identify bruits, loss of pulses, cool pale extremities, delay in venous filling, and skin ulceration.[580]

4.3.1: We recommend that adults with CKD be regularly examined for signs of peripheral arterial disease and be considered for usual approaches to therapy. (*1B*)

4.3.2: We suggest that adults with CKD and diabetes are offered regular podiatric assessment. (*2A*)

RATIONALE

These statements are worded in this way in order to highlight the increased risk of PAD in people with CKD, particularly those with CKD and diabetes.

Evidence Base

The prevalence of PAD is common in people with CKD and it increases with lower levels of GFR (Table 31). PAD can be

Table 31 | Peripheral arterial disease and CKD

Study	Population	PAD definition	Outcome of interest
O'Hare et al.[585]	NHANES age 40+	ABI <0.9	24% prevalence in people with CKD and a CrCl of <60 ml/min ($<$ 1 ml/s) versus 3.7% in those with normal kidney function
O'Hare et al.[587]	HERS study, postmenopausal women with known CHD	PAD event rates (amputation, revascularization, or lumbar sympathectomy)	Incident PAD event rates were 0.55%, 0.92%, and 2.73% per year with CrCl 60, 30-59, and 30 ml/min/1.73 m^2, respectively
O'Hare et al.[586]	Cardiovascular Health Study, adults age 65+	Lower-extremity PAD procedure (bypass surgery, angioplasty, or amputation)	HR for PAD procedure 2.5 (95% CI 1.2-5.1) for highest quintile of cystatin C ($\geq$1.28 mg/l) versus lowest ($\leq$0.9 mg/l)
De Vinuesa et al.[582]	102 adults in a CKD clinic, mean age 70 $\pm$ 11 years, GFR 15-60 ml/min/1.73 m^2	ABI <0.9	17% signs and symptoms of PAD, which had passed unnoticed; 32% had ABI <0.9 (mean 0.64 ± 0.25)
Liew et al.[584]	6-year follow up of 1027 subjects (ABI index recording and GFR measured within 90 d)	ABI <0.9	6-year mortality rate for CKD and PAD 45% versus 28% CKD alone, 26% PAD alone, and 18% for neither condition
Wattanakit et al.[588]	6760 subjects, aged 45–84 years in the Multi-Ethnic Study of Atherosclerosis	ABI <0.9	Albuminuria was associated with PAD in subjects with diabetes (odds ratio 1.90, 95% CI 1.19–3.04) but not in those without
Lash et al.[583]	3612 subjects age 58.2 ± 11.0 years in the Chronic Renal Insufficiency Cohort study	ABI <0.9	Overall, 16% prevalence of PAD in subjects with GFR$<$60 ml/min/1.73 m^2, increasing from 4% in those with GFR$>$60 to 22% in those with GFR$<$30 ml/min/1.73 m^2
Bello et al.[581]	920,985 subjects with GFR and proteinuria assessment, median follow-up 35 months (IQR 22-44)	Time to first hospitalization with PAD	1891 of subjects (0.2%) hospitalized at least once for PVD, adjusted rates increased with lower GFR

Abbreviations: ABI, ankle-brachial index; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; d, day; GFR, glomerular filtration rate; HERS, Heart and Estrogen/Progestin Replacement Study; HR, hazard ratio; IQR, interquartile range; NHANES, National Health and Nutrition Examination Survey; PAD, peripheral arterial disease; PVD, peripheral vascular disease.

attributed to the greater prevalence of traditional risk factors such as diabetes, hypertension, dyslipidemia, advanced age, and renal-specific factors.[581–588]

Diabetes is the leading cause of CKD globally and the risk of diabetic foot ulceration and lower extremity amputation in subjects with diabetes increases dramatically with lower GFR. In a cohort of 90,617 individuals with diabetes over a median observation time of 2.4 years, the HR for amputation increased from 2.08 (95% CI 1.68–2.58) for those with GFR 30-59 ml/min/1.73 m^2 to 7.71 (95% CI 5.29–11.26) for those with GFR <30 ml/min/1.73 m^2 compared to reference subjects with GFR >60 ml/min/1.73 m^2.[589]

Screening for PAD is recommended for adults in the general population based on age and number of risk factors.[590] Although an ankle-brachial index of <0.9 is generally considered evidence of PAD, the utility of this measure is unproven in CKD because of the greater prevalence of vessel calcification. Evidence-based medical therapies for PAD in people with CKD are similarly lacking. Smoking cessation is mandatory. Aspirin may be beneficial for prevention of cardiovascular events. Clopidogrel has not been studied in people with CKD and PAD. No RCTs evaluating percutaneous versus surgical revascularization techniques have been conducted in people with CKD and PAD but outcome studies all suggest that CKD confers an increased risk of adverse outcome, regardless of the revascularization technique employed.[591,592] These statements do not apply to pediatric practice.

International Relevance

There is no evidence to suggest that the international approach to identification and management of PAD in people with CKD should differ.

Implications for Clinical Practice and Public Policy

People with CKD are more at risk of PAD and need regular assessment and monitoring. The role of ankle-brachial index versus other diagnostic techniques may have implications for future practice. Prospective data on non-surgical therapies and data regarding percutaneous versus surgical revascularization are required to inform policy and recommended procedure.

Areas of Controversy, Confusion, or Non-consensus

There remains ongoing debate as to the timing and use of specific diagnostic criteria for identification of PAD in people with CKD and no studies have examined the utility of conventional methods in early detection of PAD in CKD. The use of specific medical and surgical management strategies in people with CKD and PAD has not been evaluated. There is no reason to believe that treatment strategies should differ, though risks of diagnostic testing (such as angiography) remain real.

4.4 MEDICATION MANAGEMENT AND PATIENT SAFETY IN CKD

Many drugs and investigative pharmaceuticals are renally excreted and their dosage may need to be reduced in patients with CKD in order to avoid toxicity. As many people with CKD are elderly, there should also be consideration of chronological age.

It is beyond the scope of this guideline to list all the agents that may need dose adjustment in CKD or which should be avoided due to potential nephrotoxicity. This information is widely available in documents which may exist at local, regional, or national bodies (e.g., British National Formulary: www.bnf.org), and other textbooks of pharmacology.[593,594] However key classes of commonly prescribed drugs in people with CKD will be mentioned together with suggestions for dose adjustment. Much of this guidance is based upon our understanding of pharmacology and pharmacokinetics rather than randomized control trial evidence.

The statements presented here are intended to inform clinicians caring for those with CKD or at risk for CKD with respect to common clinical situations or exposures which may put people at risk for AKI or progression of CKD.

4.4.1: We recommend that prescribers should take GFR into account when drug dosing. (*1A*)

4.4.2: Where precision is required for dosing (due to narrow therapeutic or toxic range) and/or estimates may be unreliable (e.g., due to low muscle mass), we recommend methods based upon cystatin C or direct measurement of GFR. (*1C*)

4.4.3: We recommend temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI. These agents include, but are not limited to: RAAS blockers (including ACE-Is, ARBs, aldosterone inhibitors, direct renin inhibitors), diuretics, NSAIDs, metformin, lithium, and digoxin. (*1C*)

4.4.4: We recommend that adults with CKD seek medical or pharmacist advice before using over-the-counter medicines or nutritional protein supplements. (*1B*)

4.4.5: We recommend not using herbal remedies in people with CKD. (*1B*)

4.4.6: We recommend that metformin be continued in people with GFR ≥ 45 ml/min/1.73 m^2 (GFR categories G1-G3a); its use should be reviewed in those with GFR 30–44 ml/min/1.73 m^2 (GFR category G3b); and it should be discontinued in people with GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5). (*1C*)

4.4.7: We recommend that all people taking potentially nephrotoxic agents such as lithium and calcineurin inhibitors should have their GFR, electrolytes and drug levels regularly monitored. (*1A*)

4.4.8: People with CKD should not be denied therapies for other conditions such as cancer but there should be appropriate dose adjustment of cytotoxic drugs according to knowledge of GFR. (*Not Graded*)

RATIONALE

These statements are worded in this way in order to inform appropriate prescribing and management of medical conditions in people with CKD. Recommendation 4.4.1 is specifically worded to ensure that clinicians remember that in those circumstances where accurate GFR is required (narrow therapeutic or toxic window), a direct measurement, not an estimate of GFR should be undertaken.

Evidence Base

Potential problems associated with use of medication in people with CKD include:

a) Reduced ability to excrete drugs and/or their metabolites
b) Increased sensitivity to medications (e.g., those bound to albumin in hypoalbuminemic states such as nephrotic syndrome)
c) Diminished tolerance of side effects, particularly in the elderly
d) Loss of efficacy[13]

Wherever possible, people with CKD should receive the same treatment as those with normal renal function. However, the dosages may need adjustment according to GFR.

There are medicines whose toxicity is worsened in acute illness particularly in a setting of dehydration such as diarrhea and vomiting. General advice about appropriate dosing and when to restart these agents should be given to people taking these drugs during intercurrent illness, together with a recommendation for consultation with a health-care professional as soon as possible.

Use of herbal and over-the-counter medicines is very common worldwide and some (such as those containing aristolochic acid)[595,596] are known to be nephrotoxic. There is no good quality safety or efficacy data for many of these compounds.

Table 32 details specific advice for various classes of drugs where CKD may be an issue. These include RAAS blocking agents,[262] beta-blockers, analgesics, antibiotics, lithium,[597] hypoglycemic agents,[598–600] lipid-lowering agents,[449,601–604] certain chemotherapeutic agents, and anticoagulants.[605]

International Relevance

This guidance is based upon knowledge of pharmacology that has universal relevance. The main international implication is centered on costs of some newer therapies compared to the older ones. Somewhat paradoxically, as the weight of evidence resides mainly with agents that have been available for longer, they have the advantage of being less costly, and have the side effects that are well documented; thus many of these older agents are preferred.

Pediatric Considerations

No specific recommendation for or against the use of a BSA adjusted eGFR in relation to drug dosing can be made in children with CKD as the majority of drug studies have been performed in adult males and extrapolated to children without consideration for BSA and/or pediatric renal function or clearance.

The exception to this rule would be that for any drug where pediatric pharmacokinetic or pharmacodynamic studies exist, the method used in calculating the effect of renal function should be used when estimating the need for dose adjustments or modifications for the individual patient.

Numerous resources for dose adjustments for pediatric CKD and ESRD patients exist, including those found in numerous textbooks[606,607] and online resources.[608]

An additional value of dedicated pediatric renal multidisciplinary teams, in terms of caring for children with CKD and ESRD, is their ability to provide anticipatory guidance for the patients and families. All such teams should at the least provide written or online information to their patients and families directing them to seek advice in situations where they may be prescribed medications from other providers or may be seeking over-the-counter drugs or supplements. The presence of trained pediatric pharmacists as part of such teams can be invaluable in achieving such support and education for both families as well as the CKD health-care providers and community resources such as local pharmacists.

LIMITATIONS

People with CKD are often excluded or not identified from trials of medications for non-renal disease. Recommendations are partly based upon knowledge of pharmacology rather than controlled trials in carefully defined populations.

RESEARCH RECOMMENDATIONS

National and international research groups, and those with CKD-focus organizations (International Society of Nephrology, International Federation of Kidney Foundations, and other national bodies) should ensure adequate representation of people with CKD in clinical trials, leading to an improved understanding of pharmacodynamics of those with CKD.

4.5: IMAGING STUDIES

4.5.1: Balance the risk of acute impairment in kidney function due to contrast agent use against the diagnostic value and therapeutic implications of the investigation. (*Not Graded*)

RATIONALE

Use of iodinated radiocontrast media has been associated with AKI with reported rates of 0-11% depending on the population under study, the type of agent that is used, and the definition of nephrotoxicity.[609] The following recommendations are concordant with those from the American College of Radiology (ACR),[610] the European Society of Urogenital Radiology (ESUR)[611] and the *KDIGO Clinical Practice Guideine for Acute Kidney Injury.*[7]

Table 32 | Cautionary notes for prescribing in people with CKD

Agents	Cautionary notes
1. Antihypertensives/cardiac medications	
RAAS antagonists (ACE-Is, ARBs, aldosterone antagonists, direct renin inhibitors)	• Avoid in people with suspected functional renal artery stenosis • Start at lower dose in people with GFR <45 ml/min/1.73 m^2 • Assess GFR and measure serum potassium within 1 week of starting or following any dose escalation • Temporarily suspend during intercurrent illness, planned IV radiocontrast administration, bowel preparation prior to colonoscopy, or prior to major surgery • Do not routinely discontinue in people with GFR <30 ml/min/1.73 m^2 as they remain nephroprotective
Beta-blockers	• Reduce dose by 50% in people with GFR <30 ml/min/1.73 m^2
Digoxin	• Reduce dose based on plasma concentrations
2. Analgesics	
NSAIDS	• Avoid in people with GFR <30 ml/min/1.73 m^2 • Prolonged therapy is not recommended in people with GFR <60 ml/min/1.73 m^2 • Should not be used in people taking lithium • Avoid in people taking RAAS blocking agents
Opioids	• Reduce dose when GFR <60 ml/min/1.73 m^2 • Use with caution in people with GFR <15 ml/min/1.73 m^2
3. Antimicrobials	
Penicillin	• Risk of crystalluria when GFR <15 ml/min/1.73 m^2 with high doses • Neurotoxicity with benzylpenicillin when GFR <15 ml/min/1.73 m^2 with high doses (maximum 6 g/day)
Aminoglycosides	• Reduce dose and/or increase dosage interval when GFR <60 ml/min/1.73 m^2 • Monitor serum levels (trough and peak) • Avoid concomitant ototoxic agents such as furosemide
Macrolides	• Reduce dose by 50% when GFR <30 ml/min/1.73 m^2
Fluoroquinolones	• Reduce dose by 50% when GFR <15 ml/min/1.73 m^2
Tetracyclines	• Reduce dose when GFR <45 ml/min/1.73 m^2; can exacerbate uremia
Antifungals	• Avoid amphotericin unless no alternative when GFR <60 ml/min/1.73 m^2 • Reduce maintenance dose of fluconazole by 50% when GFR <45 ml/min/1.73 m^2 • Reduce dose of flucytosine when GFR <60 ml/min/1.73 m^2
4. Hypoglycemics	
Sulfonylureas	• Avoid agents that are mainly renally excreted (e.g., glyburide/ glibenclamide) • Other agents that are mainly metabolized in the liver may need reduced dose when GFR <30 ml/min/1.73 m^2 (e.g., gliclazide, gliquidone)
Insulin	• Partly renally excreted and may need reduced dose when GFR <30 ml/min/1.73 m^2
Metformin	• Suggest avoid when GFR <30 ml/min/1.73 m^2, but consider risk-benefit if GFR is stable • Review use when GFR <45 ml/min/1.73 m^2 • Probably safe when GFR $\geqslant 45$ ml/min/1.73 m^2 • Suspend in people who become acutely unwell
5. Lipid-lowering	
Statins	• No increase in toxicity for simvastatin dosed at 20 mg per day or simvastatin 20 mg /ezetimide 10 mg combinations per day in people with GFR <30 ml/min/1.73 m^2 or on dialysis[449] • Other trials of statins in people with GFR <15 ml/min/1.73 m^2 or on dialysis also showed no excess toxicity
Fenofibrate	• Increases SCr by approximately 0.13 mg/dl (12 μmol/l)
6. Chemotherapeutic	
Cisplatin	• Reduce dose when GFR <60 ml/min/1.73 m^2 • Avoid when GFR <30 ml/min/1.73 m^2
Melphalan	• Reduce dose when GFR <60 ml/min/1.73 m^2
Methotrexate	• Reduce dose when GFR <60 ml/min/1.73 m^2 • Avoid if possible when GFR <15 ml/min/1.73 m^2
7. Anticoagulants	
Low-molecular-weight heparins	• Halve the dose when GFR <30 ml/min/1.73 m^2 • Consider switch to conventional heparin or alternatively monitor plasma anti-factor Xa in those at high risk for bleeding
Warfarin	• Increased risk of bleeding when GFR <30 ml/min/1.73 m^2 • Use lower doses and monitor closely when GFR <30 ml/min/1.73 m^2
8. Miscellaneous	
Lithium	• Nephrotoxic and may cause renal tubular dysfunction with prolonged use even at therapeutic levels • Monitor GFR, electrolytes, and lithium levels 6 monthly or more frequently if the dose changes or the patient is acutely unwell • Avoid using concomitant NSAIDs • Maintain hydration during intercurrent illness • Risk-benefit of drug in specific situation must be weighed

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CKD, chronic kidney disease; GFR, glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system; SCr, serum creatinine.

Radiocontrast

4.5.2: We recommend that all people with GFR <60 ml/min/1.73m^2 (GFR categories G3a-G5) undergoing elective investigation involving the intravascular administration of iodinated radiocontrast media should be managed according to the *KDIGO Clinical Practice Guideline for AKI* including:

- **Avoidance of high osmolar agents (*1B*);**
- **Use of lowest possible radiocontrast dose (*Not Graded*);**
- **Withdrawal of potentially nephrotoxic agents before and after the procedure (*1C*);**
- **Adequate hydration with saline before, during, and after the procedure (*1A*);**
- **Measurement of GFR 48–96 hours after the procedure (*1C*).**

RATIONALE

These statements have been worded in order to inform safe radiological investigation of people with CKD and to avoid potential nephrotoxcity that can be associated with radiological imaging.

Evidence Base

Radiocontrast media associated AKI is a largely preventable cause of morbidity and mortality. There is no internationally agreed definition but most studies use an increase in SCr of >0.5 mg/dl (44 μmol/l) and/or a 25% increase from baseline SCr within 3 days of the procedure.[7,609–611] Epidemiological studies and case series have identified the following risk factors for AKI:

a) GFR <60 ml/min/1.73 m^2 (particularly if <30 ml/min/1.73 m^2)
b) Diabetes
c) Concurrent dehydration
d) CHF
e) >70 years of age
f) Concurrent use of known nephrotoxic agents such as NSAIDs
g) Use of high osmolality agents (especially in those with GFR <60 ml/min/1.73 m^2)
h) Use of large doses of radiocontrast media
i) Intra-arterial injection
j) Gout (hyperuricemia)

Numerous studies of preventative strategies have been performed with the following conclusions:

a) High osmolar agents pose a greater risk of AKI in people with CKD.[609]
b) Iso-osmolar agents compared to low-osmolar agents are associated with lower rates of AKI in some but not all studies. Wherever possible iso-osmolar agents should be used in people with CKD at high risk for AKI (although these tend to be more expensive).[612]
c) Although risk for AKI increases with GFR <60 ml/min/1.73 m^2, the rates are particularly high (7.8% in one study) when GFR is <30 ml/min/1.73 m^2. Implementing preventative strategies for all with a GFR <60 ml/min/1.73 m^2 may not be practical but a graded risk assessment taking into account all factors may be more realistic. Some guidelines such as American College Radiology[610] and ESUR[611] provide a checklist as a means of identifying patients at risk of AKI before investigation.
d) Extracellular volume expansion is widely recommended although there are few good quality trials on which to base an ideal protocol.[609] 0.9% saline given by continuous infusion appears superior to 0.45% saline or bolus injection and there is no demonstration of consistent superiority of sodium bicarbonate over saline. Current guidance suggests either infusion of 1 ml/kg body weight/hour for 3-12 hours before and after the procedure or 100 ml/hr, beginning 6 to 12 hours before and continuing 4 to 12 hours after intravascular iodinated contrast medium administration.[609,610]
e) Use of N-acetylcysteine or ascorbic acid as preventative measures has not been shown to be a consistent benefit.

International Relevance

This guidance has universal relevance although there are cost implications as the iso-osmolar contrast media are more expensive.

LIMITATIONS

Some of the guidance is based upon limited evidence and there is a need for more research into simple preventative measure such as pre-investigation rehydration (see below). There has not previously been a universal definition for AKI following administration of contrast media. However, recommendations from the KDIGO AKI Guideline suggest that the same general AKI definition and staging be used for changes in kidney function, irrespective of etiology.

RESEARCH RECOMMENDATIONS

Prospective studies using direct measures of GFR before and after administration of radiological contrast media are required to help define the incidence of AKI. Such studies would also be able to validate creatinine or other estimates of GFR in people undergoing radiological investigation.

Prospective controlled trials of rehydration using different fluids (saline, bicarbonate, Hartmann's) and validated estimates of GFR are urgently required.

Definitive studies of N-acetylcysteine and other antioxidants would help determine their usefulness or otherwise.

Gadolinium-containing contrast media

Gadolinium is a rare earth element that is naturally highly toxic. When bound to proprietary chelating agents, it is essentially biologically inert in people with normal renal function and provides excellent contrast during MRI. These

chelates are excreted unchanged by the kidneys by glomerular filtration and have much lower direct nephrotoxicity than conventional radioiodine contrast media.[613] However over 200 cases of a scleroderma-like condition now termed nephrogenic systemic fibrosis (NSF) following gadolinium use in patients with CKD have been reported.[613, 614]

4.5.3: We recommend not using gadolinium-containing contrast media in people with GFR <15 ml/min/1.73 m^2 (GFR category G5) unless there is no alternative appropriate test. (*1B*)

4.5.4: We suggest that people with a GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5) who require gadolinium-containing contrast media are preferentially offered a macrocyclic chelate preparation. (*2B*)

RATIONALE

These statements have been worded in order to enable safe administration of gadolinium to people with CKD. As with all tests requested in the CKD population, clinicians should be aware of the risk-benefit ratio of the use of gadolinium in people with GFR 15-29 ml/min/1.73 m^2.

Evidence Base

NSF is an untreatable and sometimes fatal condition that complicates the use of gadolinium-containing contrast media in people with CKD. Prevention is therefore the best approach with avoidance of gadolinium exposure unless clinically indicated and to use the lowest risk agent at the lowest dose.[613,615]

Although the risk of AKI with iodinated contrast media is much greater than that for NSF with gadolinium, the former is treatable with dialysis whereas the latter is not. Thus, consideration of more conventional imaging techniques should be undertaken in all with a GFR <30 ml/min/1.73 m^2.[610,613–615]

A recent meta-analysis and review have highlighted those patients most at risk and quantified an OR for NSF of between 20-50 for those with a GFR <15 ml/min/1.73 m^2.[614]

While there is general agreement that patients with a GFR >15 ml/min/1.73 m^2 are at increased risk, it is not possible to derive a precise estimate. No patients with a GFR >30 ml/min/1.73 m^2 have developed NSF without concomitant liver failure.[614]

There is some suggestion that the type of gadolinium preparation plays a role:[614,615] Linear chelated preparations such as gadodiamide may be more likely to cause NSF and should be avoided when GFR is <30 ml/min/1.73 m^2. Gadoteridol, gadobutrol, or gadoterate should be considered if MRI with contrast is clinically essential.[610,613,615] Moreover, as gadolinium is freely dialysed,[616] most guidelines recommend dialysis in patients with a GFR <15 ml/min/1.73 m^2 or for those already on dialysis immediately after (and perhaps repeated 24 hours later) completion of the procedure.[610,615] The role of dialysis in people with GFR above 15 ml/min/1.73 m^2 is uncertain.

International Relevance

This guidance has universal relevance although there are cost implications as the non-linear chelated preparations are more expensive.

Pediatric Considerations

Regarding both Recommendations 4.5.3 and 4.5.4, a number of considerations specific to the use of gadolinium preparations in young children and neonates must also be considered in addition to the general admonishments against their use in situations of GFR <30 ml/min/1.73 m^2. In particular, the FDA currently does not license any gadolinium-based contrast agent (GBCA) product for use in children less than 2 years of age; and likewise the European Medicines Agency cautions against the use of any GBCA in a child less than 1 year of age.

In addition, the ability to accurately estimate the relative value of a neonate or young infant's GFR leads to great difficulty in terms of assigning risk of GBCA exposure if one bases this on renal clearance. In a recent paper by Meng and colleagues,[617] they surveyed a worldwide group of both cardiologists and radiologists with respect to their use of gadolinium in their pediatric MRI practice. While 93% of the respondents did evaluate renal function in some or all of their patients, only a slight majority (54%) used an estimating formula, most often the Schwartz equation, with the remainder relying on SCr alone (31%) or urine output (6%). Perhaps of most concern was that renal function was assessed in only 33% and 31%, respectively, of patients classified as 'all neonates' or 'all patients <1 week of age.' Equally concerning was the fact that 13% of the respondents would give gadolinium to some of these children in the face of a GFR <30 ml/min/1.73 m^2.

In recognition of our inability to accurately measure GFR in the neonate and, by extension, the clearance of compounds such as gadolinium, all nephrologists and radiologists must exercise caution in terms of use of GBCA in this potentially high-risk population, and all other imaging modalities should be considered prior to choosing one requiring gadolinium exposure.

LIMITATIONS

The evidence is largely based upon case series rather than prospective studies or RCTs.

RESEARCH RECOMMENDATIONS

As for iodinated contrast media, a prospective study of people with CKD undergoing nuclear MRI with gadolinium contrast would help define change in GFR and validate estimators. Because NSF is such a serious condition, an RCT of dialysis in people with GFR <30 ml/min/1.73 m^2 would help to determine risk-benefit in these patients, though recruitment may be difficult due to potential ethical concerns.

Bowel preparation

The increasing use of colonoscopy as a screening tool for bowel cancer has resulted in many people undergoing bowel

preparation with oral sodium phosphate-containing preparations. Case reports of acute and late irreversible renal failure with biopsy-proven phosphate deposition have led to a new disease entity termed acute phosphate nephropathy.[618,619] Less than 40 definite cases have been reported and these have been extensively reviewed.

4.5.5: We recommend not to use oral phosphate-containing bowel preparations in people with a GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5) or in those known to be at risk of phosphate nephropathy. (*1A*)

RATIONALE

This statement has been worded in order to enable safe bowel preparation in people with CKD who need to undergo investigation of bowel disease.

Evidence Base

Electrolyte disturbances that are sometimes severe and include hyperphosphatemia, hypocalcemia, hypo- and hypernatremia, and hypokalemia have been reported in normal volunteers undergoing oral phosphate bowel preparation.[620] Renal injury has been reported in a small number of people although the condition is likely to be underrecorded. A recent study from Iceland estimated the incidence to be around 1 per thousand doses[621] but others would suggest incidence rates of between 1% and 4%.[618,619]

Two broad patterns of renal injury have been described. An early symptomatic response associated with severe hyperphosphatemia and hypocalcemia and a later (days to months) irreversible kidney injury associated with a specific tubulointerstitial calcium phosphate deposition.[618,619]

The following people are said to be at particular risk although the link to kidney injury is associative in many cases and firm evidence is lacking:

a) GFR <60 ml/min/1.73 m^2
b) >60 years of age
c) Female
d) Hypertension
e) Diabetes
f) CHF
g) Dehydration
h) Active colitis
i) Concurrent use of RAAS blocking agents, diuretics, lithium, NSAIDs
j) Large and/or repeat dosing of oral phosphate preparations
k) Hypoparathyroidism

Although the FDA has banned oral phosphate solutions, there is no qualitative difference with tablet preparations. Both should be avoided in people at risk and this is the current recommendation of the American Society for Gastrointestinal Endoscopy.[622]

There is some debate as to whether the cause of the kidney injury is entirely due to dehydration rather than phosphate use *per se*.[623] However, it is hard to understand why calcium phosphate deposits occur and cause late renal impairment if dehydration was the only factor.

There is a single RCT of phosphate versus non-phosphate preparations but assessment of renal function was limited to change in SCr and GFR at baseline is not reported.[624] Notwithstanding these limitations, there were greater changes in serum potassium, calcium, and phosphate in those given sodium phosphate-containing preparations.

As there are non-phosphate-containing bowel preparations available, these should be used in all the above groups (and arguably in all people given the biochemical abnormalities observed in normal volunteers). As for radiocontrast media, rehydration with saline may be required in the frail and ill irrespective of the bowel preparation that is used.

International Relevance

This guidance has universal relevance but non-phosphate-containing bowel preparations are more expensive, so the use of these agents may differ around the world.

LIMITATIONS

The data are based upon case series with a limited number of affected individuals and retrospective population studies.

RESEARCH RECOMMENDATIONS

Prospective study in people with normal renal function and those with different severities of CKD are urgently required in order to define the acute biochemical and metabolic effects of phosphate-containing bowel preparations. There is also a need for a study of all people undergoing bowel preparation with whatever preparation in order to explore the effects on GFR on the incidence of this complication. More definitive exploration of rehydration therapy (type and volume) in people with CKD undergoing bowel preparation is urgently needed.

4.6 CKD AND RISKS FOR INFECTIONS, AKI, HOSPITALIZATIONS, AND MORTALITY

The following section gives guidance for the care of people with CKD given that they are at increased risk for a number of events such as infections, AKI, CVD, hospitalizations, and mortality. Appreciating that increased risk and implementing some of the recommendations below may result in improved outcomes for people. It will be important to develop policies and robust research agendas to address areas which do not have a substantial evidentiary base.

CKD and risk of infections

CKD is associated with significant major infectious complications, which occur at rates 3 to 4 times the general population. Infection is an important cause of morbidity and mortality among patients with kidney failure and is the

second leading cause of death following CVD. CKD may be a risk-multiplier for acute infectious disease-associated mortality, as it is for CVD. Despite a less effective response to vaccination, there are data suggesting benefit from immunization among people with CKD as in the general population.

4.6.1: We recommend that all adults with CKD are offered annual vaccination with influenza vaccine, unless contraindicated. (*1B*)

4.6.2: We recommend that all adults with eGFR <30 ml/min/1.73 m^2 (GFR categories G4-G5) and those at high risk of pneumococcal infection (e.g., nephrotic syndrome, diabetes, or those receiving immunosuppression) receive vaccination with polyvalent pneumococcal vaccine unless contraindicated. (*1B*)

4.6.3: We recommend that all adults with CKD who have received pneumococcal vaccination are offered revaccination within 5 years. (*1B*)

4.6.4: We recommend that all adults who are at high risk of progression of CKD and have GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5) be immunized against hepatitis B and the response confirmed by appropriate serological testing. (*1B*)

4.6.5: Consideration of live vaccine should include an appreciation of the patient's immune status and should be in line with recommendations from official or governmental bodies. (*Not Graded*)

4.6.6: Pediatric immunization schedules should be followed according to official international and regional recommedations for children with CKD. (*Not Graded*)

RATIONALE

CKD is associated with alterations in primary host defense mechanisms and increases the risk of bacterial infections (Table 33). Epidemiological study suggests that the 3 most commonly seen infectious complications in the CKD population are: urinary tract infection, pneumonia, and sepsis. In the general population, there is strong evidence that preventive measures are effective in adults and there are data suggesting benefit from immunization in people with CKD.

Evidence Base

Previous investigations have firmly established ESRD as a strong risk factor for infectious complications.[625–628] However, few epidemiologic reports have addressed the risk of infections in people with CKD not treated with dialysis.[629,630] Data from the US Renal Data System (USRDS) suggest that higher rates of hospital admission because of septicemia are noted in people with CKD compared with those without CKD.[631] Comprehensive studies of the absolute rates, risk factors, clinical course, and outcomes of different types of clinically relevant infections across the spectrum of CKD are not available.

Among people with CKD, very few studies have examined the incidence or prevalence of infections and no published data describe GFR category–specific infection rates. Among Medicare beneficiaries aged more than 66 yr, people with diagnosed CKD seem to have substantially higher rates of hospitalization for diagnoses of pneumonia and sepsis compared with people without diagnosed CKD.[628] In addition to an increased incidence of being hospitalized with infections, people with CKD have longer lengths of hospital stay during infection-related admissions compared with people without CKD.[632]

Table 33 | Risk factors for infection in people with CKD

Advanced age
High burden of coexisting illnesses such as diabetes
Hypoalbuminemia[625]
Immunosuppressive therapy[628]
Nephrotic syndrome[634]
Uremia
Anemia and malnutrition[635]
High prevalence of functional disabilities

Abbreviation: CKD, chronic kidney disese

Among USRDS data admission rates for all causes, CVD and infection, are 38–46% higher for those with CKD than for those without.[633] Rates for pneumonia in CKD were nearly three times higher than those for non-CKD. Hospitalizations for bacteremia/septicemia, were nearly four times higher for people with CKD compared to those without. Hospitalization rates for urinary tract infections were three-fold higher for people with CKD.

In people with ESRD, the function of polymorphonuclear white blood cells, lymphocytes, and monocytes is altered, resulting in an impaired host response to infection.[636–638] However, these issues have not been adequately investigated in people with CKD.

There is a growing body of evidence in the general population for reduction in infections, hospitalizations, and mortality as a result of immunizations. Current data suggest that vaccination is an underused prevention strategy in the CKD and ESRD populations.[639] Potential barriers to immunization that are specific to the CKD populations have not been systematically examined. Although lower vaccine responsiveness has been widely recognized in the ESRD population, to what extent moderate to advanced CKD modifies vaccine responsiveness remains unclear.[640–642] Studies that have examined vaccination in the setting of CKD or ESRD have been limited by small study size, variable follow-up, and ascertainment of surrogates for vaccine effectiveness such as antibody response and rate of antibody decline after vaccination as opposed to vaccine efficacy for preventing infection.[643]

Influenza A and B vaccine. Despite potentially impaired antibody responses, a 2-year analysis of US Medicare claims data found that people vaccinated against influenza A and B on dialysis had a substantially lower chance of any-cause hospital admission and any-cause death than those patients not vaccinated on dialysis.[644] This finding might indicate clinical effectiveness of vaccinating this population but its observational design might also reflect differences in the underlying clinical status among people vaccinated and not

vaccinated. No unique adverse events related to influenza vaccine have been identified in people on dialysis.

Pneumococcal vaccine. People with kidney disease vaccinated with the pneumococcal vaccine seem to develop different serotype-specific titers, develop lower levels of antibody titers, and have a more rapid loss of antibody titers as compared with healthy control subjects.[639,645,646] Practitioners should be aware of the impact of specific vaccines on responsiveness and duration of responsiveness. Revaccination practices will be dictated by that knowledge.

Hepatitis B vaccine. Widespread hepatitis B virus (HBV) vaccination at the onset of dialysis has led to a marked reduction of HBV infections in people with ESRD, although improved screening of blood products and dissemination of recommendations for reducing the spread of HBV infections in dialysis units have also likely contributed.[647] Among people with moderate to advanced CKD, hepatitis B vaccination responsiveness has been shown to range from approximately 60 to 80% depending on the dosage, number of administered vaccines, and study population. Although findings have been inconsistent as to whether the level of GFR affects vaccine responsiveness in people with CKD[640,642] those with higher GFR are more likely to respond with seroconversion, independent of other factors.[640]

S. aureus vaccine. StaphVAX has not been shown to be efficacious in reducing the risk for Staphylococcus aureus bacteremia in people on hemodialysis.[648,649] No data are published in people with CKD.

Live vaccines. Due to the fact that people with CKD are often immunocompromised, live vaccines should only be used with caution on an individual basis.

In summary, although some vaccines (like influenza) in usual doses provide protection, other vaccines (HBV and pneumococcal) require more frequent dosing or larger doses to achieve and maintain protective antibody titers. Frequency and type of vaccination will vary according to local circumstances and prevalence of disease.

International Relevance

The availability of different vaccinations may vary worldwide, as does the prevalence of specific bacterial, viral, and other infections. It is reasonable to offer individuals appropriate immunization according to local practices.

Implications for Clinical Practice and Public Policy

Vaccines for influenza, hepatitis B, and pneumococcus are currently recommended for people with CKD by the local, regional, or national advisory committees on immunization practices from most countries.

Current recommendations are to:

- Provide influenza vaccination annually to people with CKD.
- Provide pneumococcal vaccine with a single booster dose 5 years after the initial dose.
- Provide HBV vaccine to people with CKD who are likely to require RRT. Although the recommendation is to give the HBV vaccine during more severe CKD (GFR <15 ml/min/1.73 m^2), it may be preferable to give this earlier to maximize the chances of achieving immunity; there are data to support this practice.[640] This would also ensure that all patients are immunized against HBV before receiving a transplant. As protective antibody levels may fall, this should be checked (possibly annually) with booster doses given if appropriate.

Areas of Controversy, Confusion, or Non-consensus

Much remains to be understood concerning impaired host response to infection in patients with CKD.

- Studies should be undertaken to determine the absolute rates, risk factors, and clinical course of different types of clinically relevant infections across the spectrum of CKD, by GFR and albuminuria category, and by cause.
- The outcomes across the range of acute infections in CKD population need to be ascertained.
- Studies should be undertaken to assess the rate of decline of antibody titers post-vaccination and the efficacy of immunization in people with CKD.

Pediatric Considerations

Current immunization schedules for children are regularly updated by both the US Centers for Disease Control and Prevention[650] and American Academy of Pediatrics.[651]

Current and comprehensive immunization recommendations for children with CKD have been published by Neu in 2012.[652] The paper addresses key issues regarding the use of vaccines in CKD pediatric populations who are receiving concomitant immunosuppression and in those awaiting transplantation. The need for, and interpretation of, protective antibody levels for those vaccines where this is indicated is described.

An oversimplified summary of the recommendations would be to provide all recommended childhood vaccines to every child with CKD with the exception of any live viral vaccine in a child receiving immunosuppressive medications. Likewise children on dialysis should not receive the live attenuated influenza vaccine although the inactivated version can and should be given to all children with CKD on an annual basis otherwise. Pneumococcal vaccination is particularly important in children with nephrotic syndrome and those with CKD, and current vaccination schedules and products should be carefully reviewed to ensure proper serotype coverage is being provided. Hepatitis B status and vaccination are of extreme importance in all children who may go onto dialysis – and specific recommendations for ongoing monitoring and interpretation of antibody levels should be carefully reviewed.

CKD and risk of AKI

Due to the epidemiological association between CKD and AKI and the number of observational studies reporting an association between pre-existing CKD and AKI, CKD is

considered the most consistent pre-existing condition associated with a high risk of AKI. However the potential linkage between patients with AKI, CKD, and ESRD has been inadequately studied to date and remains ill defined. This section describes AKI as a complication which needs to be managed in those with CKD. Given its association with progression, it is also described in that section.

4.6.7: We recommend that all people with CKD are considered to be at increased risk of AKI. (*1A*)

4.6.7.1: In people with CKD, the recommendations detailed in the KDIGO AKI Guideline should be followed for management of those at risk of AKI during intercurrent illness, or when undergoing investigation and procedures that are likely to increase the risk of AKI. (*Not Graded*)

RATIONALE

Observational data suggest a strong association between pre-existing CKD and AKI. The appreciation that CKD patients may be more susceptible to AKI is the purpose of the above set of statements. However, methodological issues such as how CKD and AKI are defined in clinical studies and the statistical adjustments for non-uniformity of comorbidities among various studies may affect the validity of observed associations.

Evidence Base

CKD is designated as a risk factor for AKI because of the epidemiological association between the two.[263,264] A number of studies in a variety of settings report an association between pre-existing CKD and AKI. [265-271] CKD is a potent predictor of acute decline in kidney function following exposure to radiocontrast,[272] major surgery,[273] and other medical conditions.[274]

Hsu et al.[14] compared the pre-hospitalization MDRD GFR of 1764 adult members of the Kaiser Permanente Northern California health-care system who developed dialysis-requiring AKI during hospitalization with 600,820 individuals who did not. Compared with a reference baseline GFR of $\geq$60 ml/min/1.73 m^2, a baseline GFR of 45–59 ml/min/1.73 m^2 was associated with an adjusted OR of in-hospital AKI of 1.66 (95% CI 1.40–1.97). For GFR values of 15–29 ml/min/1.73 m^2, the adjusted OR for in-hospital AKI was 20.42 (95% CI 17.40–23.96). The presence of diabetes, hypertension, and proteinuria increased the likelihood of developing in-hospital AKI, with adjusted ORs of 1.99 (95% CI 1.78–2.23), 1.55 (95% CI 1.37–1.76) and 2.84 (95% CI 2.52–3.19), respectively. The authors concluded that CKD is the main risk factor for AKI during hospitalization. A contrasting approach by Singh et al. defined AKI as dialysis-requiring acute renal failure.[275] Because the clinical decision to dialyze a patient is frequently influenced by a higher overall SCr, presence of hemodialysis access, or consideration of inevitable progression to ESRD, this definition of AKI could bias toward capturing more AKI cases in CKD patients. Moreover, in patients with advanced CKD, the progression of CKD to ESRD may sometimes be difficult to separate from acute-on-chronic renal failure. A cohort study by Lafrance et al. followed a referred CKD population in British Columbia for a median of 19.4 months after achieving a GFR of $\leq$30 ml/min/1.73 m^2. Forty-five percent had at least one episode of AKI.[276] In another cohort study of 920,985 adults in Alberta, Canada with at least one outpatient measurement of SCr and proteinuria and not requiring chronic dialysis, risk of admission with AKI increased with heavier proteinuria and reduced GFR.[16]

International Relevance

These guidelines about AKI have relevance around the world. While the causes of AKI may differ by region, country, socio-economic status, and age, the consequences remain the similar. Where there are no facilitities to support AKI or CKD, people will die.

Areas of Controversy, Confusion, or Non-consensus

Interpretation of published data examining the influence of pre-existing CKD on the increased likelihood of AKI is potentially confounded by a number of issues. These include the comorbidities associated with CKD, influenced by repeated exposure to various nephrotoxic insults or in-hospital errors,[57,277] or primarily due to the altered physiology in CKD. There are also methodological issues such as how CKD and AKI are defined in clinical studies and the varying statistical adjustments for comorbidities which may affect the validity of observed associations.

A further important issue to clarify is whether pre-existing CKD influences the outcome of AKI. Currently, there is no single biomarker that can differentiate 'acute' from 'chronic' kidney disease and help to address this issue. Several large observational and database studies report, surprisingly, lower in-hospital mortality in patients with AKI superimposed on CKD compared with controls.[278-283] Data from PICARD reveal lower in-patient mortality and median length of stay in ICU subjects with acute-on-chronic renal injury compared with non-CKD subjects with AKI, though the post-discharge dialysis rates were higher in subjects with pre-existing CKD.[284]

Pediatric Considerations

The relative paucity of pediatric specific guidelines (due to lack of high-quality studies) in the KDIGO AKI guideline would suggest that the use of pediatric data and review papers as well as relevant pediatric nephrology texts would be of benefit to the practitioner interested in reviewing this topic in greater detail and applying pediatric data to their practice.[653–658]

RESEARCH RECOMMENDATIONS

Prospectively designed clinical studies with a clear and uniform definition of CKD and AKI and adjusted for comorbidities are needed to determine:

- the frequency of AKI events in a CKD population
- the outcome of AKI in patients with CKD condition

- the importance of proteinuria in addition to low GFR in the risk of AKI

CKD and risk of hospitalization and mortality

Regardless of the method used to estimate GFR, hospitalization and mortality rates are higher in people with CKD. Exact rates vary with comorbidity and severity of CKD, and are not well-defined. Selection of interventions that could reduce hospitalizations, morbidity, mortality, and costs in people with CKD is not well-studied.

4.6.8: CKD disease management programs should be developed in order to optimize the community management of people with CKD and reduce the risk of hospital admission. (*Not Graded*)

4.6.9: Interventions to reduce hospitalization and mortality for people with CKD should pay close attention to the management of associated comorbid conditions and cardiovascular disease in particular. (*Not Graded*)

RATIONALE

There are observational and database studies reporting an association between pre-existing CKD and hospitalizations and mortality. A better understanding of the rates, causes, and risk factors for hospitalization among people with CKD would allow estimates of the economic burden of CKD and identification of those at risk for increased resource utilization. People with CKD are an ideal target for interventions aimed at reduction of morbidity, hospitalization, mortality, and costs. These statements suggest that a coordinated approach to the identification and management would result in better outcomes and are intended as 'best practices' statements, recognizing the difficulty in developing an evidence base while addressing issues related to resource allocations (Table 34).

Evidence Base

Mortality rates remain high (16-22%) with the use of dialysis, with more than half of all deaths related to CVD. Less is known about mortality and CVD rates, and resource use among persons with a reduced GFR who are not yet receiving maintenance dialysis. Few studies have investigated the association between CKD and the risk of hospitalization.

Data from the USRDS reveal that hospitalization rates vary with comorbidity and interact with degrees of CKD. Adjusted rates are 38% higher in people with CKD and 19% greater in people with CKD and GFR under 60 ml/min/1.73 m^2 than in those with GFR >60 ml/min/1.73 m^2, who in turn are 20% higher than in people without CKD-illustrating the graded impact of advancing kidney disease. Not surprisingly, rates of cardiovascular hospitalization are greater for people with CKD, particularly those with increasing severity of CKD.[659] In both the CKD and non-CKD populations, adjusted rates of hospitalization increase with greater comorbidity. In 2008, for example, the rate for people with CKD with both diabetes and CHF was 726 per 1000 person-years at risk — 85% greater than the rate of 393 among people with neither diagnosis. Rates of admission for CVD increase even more in the higher categories of GFR. Among Medicare subjects, the rate of 141 admissions per 1000 person-years for those with GFR <60 ml/min/1.73 m^2 is 26% higher than the rate of 112 reported for those with CKD and GFR ≥ 60 ml/min/1.73 m^2. The admission rates of 101 and 90 reported for MarketScan and Ingenix i3 subjects with GFR <60 ml/min/1.73 m^2 are 48 and 16% greater, respectively, than those occurring in people with higher GFRs.[633] Adjusted rates of mortality in USRDS 2008 increased with age, and were highest in people with advanced categories of GFR: 31–72% higher, for example, in people with GFR <60 ml/min/1.73 m^2 compared to those with no CKD. By gender, rates in men with CKD were 91.8 per 1000 person-years at risk compared to 85.6 in women. Rates for people with CKD overall were similar in whites and African Americans, but in people with GFR <60 ml/min/1.73 m^2, rates for African Americans were 18% higher than those for whites, at 95.0 and 80.5 per 1000 person-years, respectively.[633]

Khan et al.[660] confirmed that hospital utilization among people with CKD is high. During a median follow-up of 11.4 months, 47% of subjects had at least one hospitalization and there were on average 0.96 hospitalizations, 6.6 hospital days, and 4.0 outpatient nephrology visits per person-year at risk. Cardiac disease/hypertension was the most common primary diagnosis of hospitalizations and progression of CKD/acute kidney failure was the most common secondary cause of hospitalization. The authors had previously shown that the dialysis population at their institution had 2.2 hospitalizations and 14.8 hospital days per person-year at risk,[659] which was similar to that among US hemodialysis patients between 1996 and 1998, who had 1.9 hospitalizations and 14 hospital days per person-year at risk.[661] In the general population, there were 0.31 hospitalizations and 1.9 hospital days per person in 1998.[662]

Go et al.[58] reported an independent, graded association between GFR and the risk of death, cardiovascular events, and hospitalization in 1,120,295 adults within a large, integrated system of health-care delivery in whom SCr had been measured between 1996 and 2000 and who had not

Table 34 | Components of community CKD management programs

Disease monitoring
Integration with other chronic disease management programs including diabetes, hypertension and heart failure
Medication management and dietary advice
Anemia management programs
Vaccination programs
Information and psychosocial support
Renal replacement therapy (dialysis and transplant) education
Advanced care planning and end-of-life care (where appropriate)

Abbreviation: CKD, chronic kidney disease.

undergone dialysis or kidney transplantation. These risks were evident at GFR <60 ml/min/1.73 m^2 and substantially increased at GFR <45 ml/min/1.73 m^2.

The higher hospital utilization among people with CKD compared to the general population, and the similarity in the comorbid conditions and the causes of hospitalization between people with CKD and ESRD, confirm the hypothesis that the complications and comorbidity observed in ESRD are manifest earlier in the disease process. Previous studies have demonstrated an association between age, gender, race, cardiac disease, peripheral vascular disease, serum albumin and hematocrit levels, and resource utilization among people on dialysis.[659,663,664] Holland et al.[665] identified baseline predictors of first non-elective hospitalization among a retrospective cohort of 362 predialysis subjects. Multivariate analysis, adjusted for baseline creatinine concentration, selected advanced age (RR 1.02; 95% CI 1.01–1.03), angina (RR 1.9; CI 1.37–2.61), peripheral vascular disease (RR 1.55, CI 1.05–2.27), and Hb concentration (RR 0.99, CI 0.94–0.98) as independent predictors of hospitalization. These comorbid conditions progressively worsen with advancing kidney disease and result in a substantial proportion of people having severe complications by the time they come to RRT.

Interventions to reduce hospitalizations and mortality for people with CKD should pay close attention to the management of associated comorbid conditions and CVD.[666] Closer attention to the management of heart disease in this population could substantially improve outcomes.[667]

The influence of correction of anemia on hospitalization is controversial. Drüeke et al.[668] randomly assigned 603 subjects with GFR 15-35 ml/min/1.73 m^2 and mild-to-moderate anemia (Hb level: 11.0-12.5 g/dl [110-125 g/l]) to a target Hb value in the normal range (13.0-15.0 g/dl [130-150 g/l]) or the subnormal range (10.5-11.5 g/dl [105-115 g/l]). There were no significant differences between the two groups in the incidence of hospital admission (61% and 59%, respectively) or mean duration of hospitalization for cardiovascular reasons (33.0 and 28.2 days, respectively). Singh et al.[669] studied 1432 people with CKD, 715 of whom were randomly assigned to receive a dose of epoetin alfa targeted to achieve a Hb level of 13.5 g/dl (135 g/l) and 717 of whom were assigned to receive a dose targeted to achieve a level of 11.3 g/dl (113 g/l). The median study duration was 16 months. The primary end point was a composite of death, MI, hospitalization for CHF (without RRT), and stroke. They observed an increased risk of the primary composite end point in the high Hb group as compared with the low Hb group. Death and hospitalization for CHF accounted for 74.8% of the composite events. The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)[375] study involved 4038 people with diabetes, CKD, and anemia. Subjects were randomly assigned to treatment with darbepoetin alfa to achieve a Hb level of approximately 13 g/dl (130 g/l) or to placebo, with rescue darbepoetin alfa when the Hb level was less than 9.0 g/dl (90 g/l). The primary end points were the composite outcomes of death or a cardiovascular event (nonfatal MI, CHF, stroke, or hospitalization for myocardial ischemia) and of death or ESRD. Again there were no significant between-group differences in the outcomes of interest.

International Relevance

It is of benefit for all jurisdictions to appreciate the increase in resource utilization by CKD populations. Identification of people at risk for increased resource utilization and economic burden of CKD should result in strategies to attenuate that risk or address the resource implications. Selection of interventions that could reduce hospitalizations, morbidity, mortality, and costs in these populations should be evaluated.

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Chapter 5: Referral to specialists and models of care

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Early identification and referral of people with CKD has the potential to reverse, delay, or prevent progression of disease and is a key focus of international initiatives in the area of kidney disease. The goals of early identification and referral are several-fold and include:

1. Provision of specific therapy based on diagnosis
2. Slowing/arresting CKD progression
3. Evaluation and management of comorbid conditions
4. Prevention and management of CVD
5. Identification, prevention, and management of CKD-specific complications (e.g., malnutrition, anemia, bone disease, acidosis)
6. Planning and preparation for RRT (e.g., choice of modality, access-placement and care, preemptive transplantation)
7. Psychosocial support and provision of conservative care and palliative care options where required

5.1: REFERRAL TO SPECIALIST SERVICES

5.1.1: We recommend referral to specialist kidney care services for people with CKD in the following circumstances (*1B*):

- **AKI or abrupt sustained fall in GFR;**
- **GFR <30 ml/min/1.73 m^2 (GFR categories G4-G5)*;**
- **a consistent finding of significant albuminuria (ACR ≥ 300 mg/g [≥ 30 mg/mmol] or AER ≥ 300 mg/24 hours, approximately equivalent to PCR ≥ 500 mg/g [≥ 50 mg/mmol] or PER ≥ 500 mg/24 hours);**
- **progression of CKD (see Recommendation 2.1.3 for definition);**
- **urinary red cell casts, RBC >20 per high power field sustained and not readily explained;**
- **CKD and hypertension refractory to treatment with 4 or more antihypertensive agents;**
- **persistent abnormalities of serum potassium;**
- **recurrent or extensive nephrolithiasis;**
- **hereditary kidney disease.**

5.1.2: We recommend timely referral for planning renal replacement therapy (RRT) in people with progressive CKD in whom the risk of kidney failure within 1 year is 10-20% or higher†, as determined by validated risk prediction tools. *(1B)*

RATIONALE

This statement reminds the practitioner that there is a need for timely referral for RRT planning in order to ensure good decision making and outcomes. The use of the word 'timely' is vague as this is not yet determined, and is based on patient and system factors. The actual amount of time required at a minimum is at least 1 year to ensure appropriate education, understanding and referrals to other practitioners (e.g., vascular access surgeons, transplant teams, etc). The second part of the statement refers to the fact that those who are progressing (versus those who are stable) are the ones who will benefit from this referral. Hence, there is a need to apply prediction tools to help identify the risk of progression. We have not stated which prediction tool is preferred as these may differ depending on information available in any individual or local experience. Examples of prediction tools can be found in recent publications.[257,260,261]

The scope of nephrology practice includes a wide variety of conditions including not only ESRD but also acute and chronic primary and systemic diseases involving individual elements of the kidney, resistant hypertension, and biochemical derangements. There are thus more potential benefits of nephrology referral than those widely recognized such as identification of reversible causes of CKD, provision of treatment that may slow progression of CKD, management of the metabolic complications of advanced CKD, and preparation for dialysis and transplantation.

In certain people, such as those with diabetes, transition to a severe reduction in GFR and kidney failure may progress rapidly. In such individuals early nephrology referral is the watchword but when an individual's kidney function is relatively stable (rate of decline in GFR <5 ml/min/1.73 m^2/year), we suggest using the grid as a guide (Figure 21). Where refer is marked by an asterisk, referring clinicians may wish to discuss with their nephrology service depending on local arrangements.

Evidence Base

Although referral recommendations in the literature are inconsistent, criteria for nephrology referral include SCr or GFR, proteinuria, hematuria, BP, and electrolyte derange-

*If this is a stable isolated finding, formal referral (i.e., formal consultation and ongoing care management) may not be necessary and advice from specialist services may be all that is required to facilitate best care for the patients. This will be health-care system dependent.

†The aim is to avoid late referral, defined here as referral to specialist services less than 1 year before start of RRT.

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90		Monitor	Refer*
	G2	Mildly decreased	60–89		Monitor	Refer*
	G3a	Mildly to moderately decreased	45–59	Monitor	Monitor	Refer
	G3b	Moderately to severely decreased	30–44	Monitor	Monitor	Refer
	G4	Severely decreased	15–29	Refer*	Refer*	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

Figure 21 | Referral decision making by GFR and albuminuria. *Referring clinicians may wish to discuss with their nephrology service depending on local arrangements regarding monitoring or referring. GFR, glomerular filtration rate. Modified with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, *et al.*[30] The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17-28; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

ment.[670] Data relating to referral for those with glomerular disease, hypertension, AKI, and diabetes may be found in the relevant guidelines.[7,8,10,262]

In this section we will briefly consider summaries of the evidence relating to timely referral for planning RRT in people with progressive CKD. In this aspect the literature concerning late referral in the last quarter of a century has been remarkably consistent; both studies and narrative reviews identifying a number of adverse consequences of late referral and related benefits of early referral (Table 35).

Patients who are aged >75 years, female, non-Caucasian, uninsured, of lower socioeconomic or educational status, or have multiple comorbidities are most at risk for non-referral for CKD care.[671,672] Patients with kidney disease have never been randomized to early or late referral to nephrology services and the definition of late referral in the published studies varies; three months is probably less than the absolute minimum amount of time required for assessment, education, preparation for RRT and creation of access but is the most frequently employed definition. Overall there are more than 50 studies in the published literature and a meta-analysis of 22 of these studies from 10 different countries serves to underline some of the key messages (Table 36), giving an indication of the size of the differences in mortality and hospital length of stay and also highlighting the significantly lower serum albumin level in late referred patients.[673]

A systematic review considered twenty-seven longitudinal cohort studies providing data on 17,646 participants of whom 11,734 were referred early and 5912 (33%) were referred late.[674] OR for mortality reductions in patients referred early were evident at 3 months (OR 0.51; 95% CI 0.44-0.59; $P<0.0001$) and remained significant at 5 years (OR 0.45; 95% CI 0.38-0.53; $P<0.0001$). Initial hospitalization was 8.8 days shorter with early referral (95% CI -10.7 to -7.0 days; $P<0.0001$). Differences in mortality and hospitalization data between the 2 groups were not explained by differences in prevalence of diabetes mellitus, previous CAD, BP control, serum phosphate, and serum albumin. Early referral was associated with better preparation and earlier placement of dialysis access and better uptake of peritoneal dialysis.

Over a decade ago McLaughlin et al. evaluated the cost implications of early versus late referral.[675] Outcomes of interest were total cost of patient care, patient life-years, patient life-years free of RRT and hospital length of stay. Mean total costs per patient over five years were US$87,711 and US$110,056 for early and late referrals, respectively. The mean patient life-years were 3.53 and 3.36 years, respectively, and the patient life-years free of RRT were 2.18 and 1.76 years, respectively. Those patients referred early spent significantly less time in hospital (length of stay 25 days versus 41 days). Klebe et al. subsequently investigated the annualized cost of implementation of referral guidelines for CKD.[676] Although CKD guideline implementation resulted in significant increases in nephrology referral and additional investigation, they estimated that the associated costs could

Table 35 | Early versus late referral: consequences and benefits

Consequences of late referral	Benefits of early referral
Anemia and bone disease	Delay need to initiate RRT
Severe hypertension and fluid overload	Increased proportion with permanent access
Low prevalence of permanent access	Greater choice of treatment options
Delayed referral for transplant	Reduced need for urgent dialysis
Higher initial hospitalization rate	Reduced hospital length of stay and costs
Higher 1-year mortality rate	Improved nutritional status
Less patient choice of RRT modality	Better management of CVD and comorbid conditions
Worse psychosocial adjustment	Improved patient survival

Abbreviations: CVD, cardiovascular disease; RRT, renal replacement therapy.

Table 36 | Outcomes of early versus late referral

Variable	Early referral mean (SD)	Late referral mean (SD)	P value
Overall mortality, %	11 (3)	23 (4)	<0.0001
1-year mortality, %	13 (4)	29 (5)	0.028
Hospital length of stay, days	13.5 (2.2)	25.3 (3.8)	0.0007
Serum albumin at RRT start, g/dl [g/l]	3.62 (0.05) [36.2 (0.5)]	3.40 (0.03) [34.0 (0.3)]	0.001
Hematocrit at RRT start, %	30.54 (0.18)	29.71 (0.10)	0.013

Abbreviation: RRT, renal replacement therapy.
Adapted from Am J Med, Chan MR, Dall AT, Fletcher KE, *et al.*[673] Outcomes in patients with chronic kidney disease referred late to nephrologists: a meta-analysis. 120: 1063-1070, 2007, with permission from Elsevier; accessed http://download.journals.elsevierhealth.com/pdfs/journals/0002-9343/PIIS000293430700664X.pdf

be recouped by delaying dialysis requirement by 1 year in one individual per 10,000 patients managed according to guidelines.

International Relevance

Local practice and resource will dictate local referral practice but regardless of the health-care system, delay or prevention of progression of both CKD and complications associated with CKD will add value. Local organizations will determine the best methods of communication and interaction between patients, specialists, and primary care physicians.

Implications for Clinical Practice and Public Policy

Implementation of referral guidelines will inevitably lead to an increased workload for specialist nephrology services. However, introduction of local initiatives in conjunction with primary care providers can improve the appropriateness and quality of the referral. Local initiatives combined with national policy and practice changes can lead to an improvement in the outcomes of CKD patients regardless of the level of resource available.

Pediatric Considerations

Current pediatric practice in most areas of the world would suggest a higher level of kidney function for referral than that for adults, though the principles remain the same. Much of the pediatric nephrologist's consultation occurs from infants, or even antenatal sources, where the identification of the child as being 'at-risk' may be apparent from radiographic studies performed *in utero*. The relatively non-specific signs and symptoms of most forms of renal disease in the young child mandates a higher level of suspicion in the referring physician, and a lower threshold of acceptance of the consult in the subspecialty clinic accepting these referrals.

Attempts to develop universal guidelines for referral of children to pediatric nephrology services would be dependent on local resources (as is the case for adults) and it is of value to consider in broad categories the types of conditions for which referral to a pediatric nephrologist would be expected to provide benefit to the referring physician and patient/family.

In a recent review Barakat[677] attempts to address a number of these issues by outlining the most common presentations of a child with significant renal disorders. Barakat and Chesney also suggest a number of specific areas in terms of initial investigations, management, and follow-up where the primary care physician can legitimately play a role in the care of the child with renal disease and provides a list of suggested referral triggers.[678]

While there will be variation in referral triggers, referral would be recommended for the following: acute or chronic reduction in renal function, poorly treated or severe hypertension, severe electrolyte abnormalities, the finding of significant abnormalities in urinary tract structure, or the presence of systemic diseases likely to produce renal effects. Similarly, the need for education in progressive conditions, performance of and interpretation of renal biopsies, and allaying parental/patient anxiety would also be acceptable reasons for referral.

There is no 'minimum acceptable value' of renal dysfunction below which one can be certain to see significant abnormalities in clearance, electrolyte, or other side effects associated with progressive renal disease in children such as growth failure or neurocognitive issues. However, the

KDOQI CKD Guidelines[1] stated that while a child with a eGFR <30 ml/min/1.73 m^2 warranted referral to a pediatric nephrologist in all cases, that in fact it was also reasonable to consider any child with evidence of CKD– and in particular those with eGFR <60 ml/min/1.73 m^2 – for referral to a pediatric nephrologist regarding evaluation and management.[43]

It is reasonable to presume that, as in adults, the concept of referral 'early' or 'above' some minimum level of function should allow for numerous benefits to the patient and family, but again there are few data for this in children. The most informative information on both of these issues can be derived from two papers examining the issue of late referrals of children who eventually required ESRD care. Kennedy et al.[679] demonstrated that at the time of referral to their center, the children >1 year of age had a median Schwartz eGFR of only 27 (IQR 9-52) ml/min/1.73 m^2, and in fact 55% of these children over the age of 1 year were referred with an eGFR <30 ml/min/1.73 m^2, meeting one of two definitions of a late referral. When they considered their second definition of initiation of RRT within 90 days of referral, commonly used in the literature for this particular topic, 30% of the eligible cohort required RRT within that 90-day window and hence were considered late referrals on this basis. The potential effect on the child's health could be ascribed to such a delay in referral: those children had lower mean Hb (8.7 $\pm$ 0.6 g/dl [87 $\pm$ 6 g/l]) versus (12.8 $\pm$ 0.6 g/dl [128 $\pm$ 6 g/l]) and higher median urea (34 (IQR 5-14) mmol/l [203 (IQR 30-84) mg/dl] versus 6 (IQR 5-14) mmol/l [36 (IQR 30-84) mg/dl], $P<0.001$) than those who presented with eGFR >30 ml/min/1.73 m^2. Secondary analysis confirmed this was also true in the groups if one looked at those above or below an eGFR of 60 ml/min/1.73 m^2. The second paper by Boehm and colleagues[680] was a retrospective single pediatric center report that demonstrated that over $\sim$30 years of referrals (N = 111), 24% of them could be considered as late referrals, as defined by need for RRT within 90 days of referral. In this late referral group, the eGFR (Schwartz) was significantly lower than those presenting later, (14.9 versus 34.2 ml/min/1.73 m^2, $P<0.001$) as was the Hb at presentation (8.0 g/dl [80 g/l] versus 10.5 $\pm$ 2.3 g/dl [105 $\pm$ 23 g/l]; $P<0.001$). Importantly the Hb deficit persisted at the time of RRT initiation, with the Hb in the late referral group being 8.5 g/dl [85 g/l] versus 9.8 $\pm$ 1.9 g/dl [98 $\pm$ 19 g/l] in the earlier referred patients, $P<0.01$. The other metric of interest chosen by these authors to evaluate the possible detrimental effect of late referral was the likelihood of a given child having a pre-emptive transplant, i.e., prior to dialysis initiation. While this association was not confirmed in Kennedy's paper, Boehm and his group demonstrated that in their patient population children who were referred late only 11% were preemptively transplanted as compared to 40% of children who presented to care more than 90 days prior to the need for some form of RRT. Of further interest, although somewhat counterintuitive, the proportion of patients in the Boehm study who initiated hemodialysis was not statistically different between those in the late versus early referral groups, 62% versus 67%, $P<0.05$ respectively.

The underlying concept of referral to a pediatric nephrologist in the face of rapid progression of renal failure is of course applicable in full. However, no current validated risk of progression tool exists in pediatric nephrology. As to what level of functional decline might be considered 'concerning,' the best evidence is derived from the longitudinal iohexol GFR data as accrued in the CKiD trial. Data from that study related to the annualized rate of decline in renal function for children with glomerular conditions is -10.5% as compared to those with a non-glomerular causes in whom the annualized rate of change is only -3.9%.[71] Any child whose rate of decline exceeded these two values would at least warrant much closer follow-up and/or investigation for modifiable factors to slow progression. Note this is not to say these rates of decline should be considered to be 'normal' for either category. All efforts to slow decline in renal function would still be of vital importance in every individual.

5.2: CARE OF THE PATIENT WITH PROGRESSIVE CKD

The following section describes recommended structures and key milestones for people with progressive CKD. The recommendations are intended to model best practices but it is appreciated that different health-care systems, geographical issues, and economic considerations will have variable abilities to implement these recommendations.

Key aspects of caring for people with progressive CKD, as they approach end of life or RRT options are addressed in this section.

5.2.1: We suggest that people with progressive CKD should be managed in a multidisciplinary care setting. (*2B*)

5.2.2: The multidisciplinary team should include or have access to dietary counseling, education and counseling about different RRT modalities, transplant options, vascular access surgery, and ethical, psychological, and social care. (*Not Graded*)

RATIONALE

Optimal care is that care which leads to the best outcomes for the individual, the population, and society. The model of care varies according to CKD severity, which will determine the target population and goals. These statements are worded to predominantly encompass those people likely to progress to ESRD. CKD models of care follow the same principles embodied in the chronic disease model of care (Figure 22). The specific components for CKD models of care include: protocols for laboratory and clinic visits; attention to cardiovascular comorbidities and CKD-associated comorbidities such as anemia; a vaccination program (see Recommendation 4.6.1-4.6.6); an education program which includes both general CKD and RRT education (including conservative management where appropriate); self-management; lifestyle modification including diet, exercise, and smoking

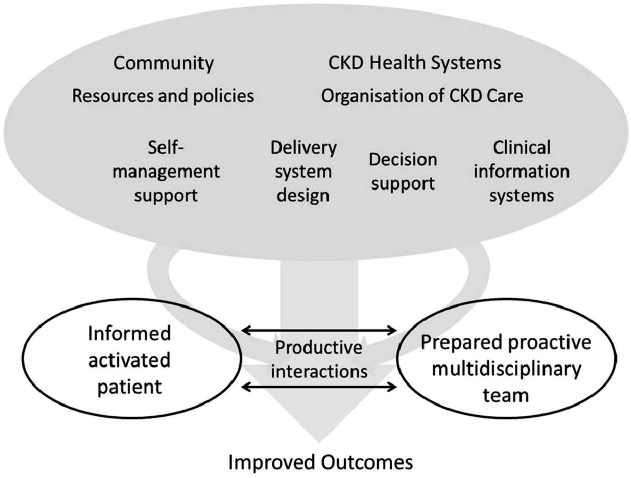


Figure 22 | The CKD chronic care model. CKD, chronic kidney disease. Adapted by permission from BMJ Publishing Group Limited. Improving the quality of health-care for chronic conditions. Epping-Jordan JE, Pruitt SD, Bengoa R, *et al.*[681] Qual Saf Health Care. 13: 299-305, 2004; accessed http://qualitysafety.bmj.com/content/13/4/299.full.pdf+html

cessation; and counseling and support for factors such as social bereavement, depression, and anxiety.

International Relevance

Standardized and culturally appropriate protocols should be considered. While it is recognized that resources may vary across and within jurisdictions, recommendations here are based on principles of care, which should be relevant across the globe.

Implications for Clinical Practice and Public Policy

CKD is a complex condition and co-exists with many other conditions. Therefore models of care should be developed that integrate the complexity of the clinical conditions involved, patient-centered philosophies, and the health-care environment. The principles of care are universal but implementation may be customized to specific circumstances.

Pediatric Considerations

Papers addressing the need for and effectiveness in the utility of multidisciplinary clinics for management of pediatric CKD patients have been published. In 2012, Ajarmeh et al.[682] described a retrospective comparison of two cohorts of children aged 0-18 years of age and followed at a single Canadian tertiary care referral center over a 1-year time period either before or following the full implementation of a multidisciplinary CKD clinic which included the services of dedicated pediatric nephrologists, renal nursing, pharmacy, dietitians, social workers, and a renal database manager. In 2009, Menon et al.[683] published data from a large American pediatric referral center and compared the outcomes of children from one of two 5-year cohorts in the period immediately preceding or following the initiation of a specific Chronic Renal Insufficiency clinic which was staffed by pediatric nephrologists, nurse clinicians, transplant coordinators, dietitians, social workers, and a psychologist.

Ajarmeh et al.[682] compared the two cohorts in a number of areas during their year of follow-up whereas Menon et al.[683] chose to look at each individual patient in the 12 months immediately prior to initiating RRT. While the studies had different variables of interest and used slightly different approaches for comparison of results between their groups, both demonstrated a reduction in the rate of decline in estimated renal function, improved Hb levels, and improvement in at least some aspect of bone mineral metabolism control in their respective cohorts cared for in the multidisciplinary era. In addition, both studies also demonstrated a decrease in resource utilization by patients in the multidisciplinary clinic as measured by median length of stay[682] and number of unplanned admissions per patient per year.[683] Also of note, Menon *et al*. demonstrated that in the patients who initiated dialysis (which was how the cohort was chosen), more patients who started hemodialysis did so with a functioning arteriovenous fistula or arteriovenous graft at the time of initiation compared to those from the general nephrology clinic era (85.7 versus 20%, $P = 0.02$).

5.3: TIMING THE INITIATION OF RRT

5.3.1: We suggest that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment. This often but not invariably occurs in the GFR range between 5 and 10 ml/min/1.73 m^2. (*2B*)

5.3.2: Living donor preemptive renal transplantation in adults should be considered when the GFR is $<$20 ml/min/1.73 m^2, and there is evidence of progressive and irreversible CKD over the preceding 6-12 months. (*Not Graded*)

RATIONALE

The statement is worded very precisely to highlight the need for RRT to address symptoms and to avoid the institution of dialysis therapy at an arbitrary number representing the degree of residual renal function. Given the risks and benefits of RRT, as well as the potential imprecision of measurements, patients need to be treated according to symptoms and signs, not simply based on a laboratory value.

Data from national registries has shown a consistent rise in GFR at initiation of RRT. This rise has been driven partly by a desire to improve nutritional status and also by earlier observational data suggesting adverse outcomes associated with RRT initiation at lower GFR. These early data were subject to much confounding. RCT data, supported by large registry-based studies corrected for confounding, show no survival advantage to early start dialysis (Initiating Dialysis

Early and Late [IDEAL] study, see Evidence Base Below). Thus, the statement as written should help the clinician to balance symptoms with laboratory values in decision making.

The statement regarding living donor transplantation is intended to ensure that practitioners think about this option in the context of the totality of RRT options. It is worded to be concordant with local living donation transplant policies. It aims to reflect the need for risk-benefit assessment of preemptive renal transplantation in all individuals. Note that the statement asks clinicians to consider this option, but does not state at which level of GFR the preemptive transplant would occur as this is a matter of local practice and patient-specific considerations.

Evidence Base

The perceived survival advantage of early start of dialysis was questioned by a study from the Netherlands Cooperative Study on the Adequacy of Dialysis Study Group (NECOSAD).[684] Of 253 patients with new ESRD, 94 (37%) started dialysis late (GFR 4.9 ± 1.7 ml/min/1.73 m^2) and 157 started in a timely fashion (GFR 7.1 ± 2.4 ml/min/1.73 m^2). Although there was a small gain in survival time over 3 years after start of dialysis for the timely start group (2.5 months) there was no significant difference in survival between the 2 groups and the gain in survival time was offset by an estimated lead-time bias of between 4.1 and 8.3 months. In a study eliminating the effect of lead-time bias Traynor et al. found no benefit in survival in those initiating dialysis early.[685] Subjects starting dialysis early (N = 119) had a median IQR CrCl of 10.4 (9.1-11.9) ml/min versus 6.7 (5.6-7.5) ml/min in 116 subjects starting dialysis late. After correction for multiple confounders, they found an 11% greater hazard for mortality with each 1 ml/min increase in CrCl at start of dialysis (HR 1.11; 95% CI 1.01-1.21; P = 0.024). Subsequent observational studies, including large dialysis registry studies from around the globe, have all suggested increased mortality when dialysis is started early.[686–696] These studies encountered multiple difficulties in drawing conclusions from this observational approach including lead-time bias, problems with estimating GFR from SCr in people with low muscle mass and/or fluid overload, the fact that people with symptoms and/or increased comorbidity are more likely to start dialysis early, and finally survivor bias in studies including people only when they start dialysis (and therefore excluding those who die prior to starting diaysis). These confounders were largely addressed by a multicenter controlled trial in which 828 adults with progressive CKD and CrCl 10-15 ml/min/1.73 m^2 were randomly assigned to early (CrCl 10-14 ml/min [0.17-0.23 ml/s]) or late (CrCl 5-7 ml/min [0.08-0.12 ml/s]) initiation of dialysis.[697] The study protocol allowed an earlier start where deemed clinically necessary by investigators and although the difference in GFR at dialysis initiation between the 2 groups was significant (early start CrCl 12.0 versus late start 9.8 ml/min, MDRD GFR 9.0 versus 7.2 ml/min/1.73 m^2), it was less than planned because 19% of early starters started late and 76% of late starters started early. There was no difference in mortality between the early and late start groups and no difference in the study's secondary outcomes (cardiovascular events, infectious events and complications of dialysis) between the 2 groups. Finally, a further observational study sought to examine the effect of early initiation of dialysis on survival in a 'healthy' group of 81,176 subjects with ESRD aged 20-64 years, without diabetes, and with no comorbidity other than hypertension.[698] The unadjusted 1-year mortality by MDRD GFR at dialysis initiation ranged from 6.8% in the reference group (GFR < 5.0 ml/min/1.73 m^2) to 20.1% in the highest GFR group (≥ 15.0 ml/min/1.73 m^2). In an even healthier subset of 35,665 subjects with serum albumin concentrations of 3.5 g/dl or higher prior to hemodialysis initiation, the 1-year mortality was 4.7%. In this group the adjusted HR for mortality was 1.27 for GFR 5.0-9.9 ml/min/1.73 m^2, 1.53 for GFR 10.0-14.9 ml/min/1.73 m^2, and 2.18 for GFR ≥ 15.0 ml/min/1.73 m^2 compared with the reference group of GFR < 5.0 ml/min/1.73 m^2.

International Relevance

The availability of resources for formal multidisciplinary teams, educational materials, and access to specialized counseling for diet, advance directives, access planning, and pre-emptive transplantation varies around the world. These statements are proposed so that 'best practices' can be documented or aspired to. The need for education, planning, and appropriate expertise for the management of this patient group is internationally relevant. The methods, frequency, and tools with which this can be accomplished will be region specific.

Implications for Clinical Practice and Public Policy

There is a need to focus on regular symptom assessment as part of CKD review in those with lower eGFR values. Individual assessment and availability of resources will dictate specific timing of therapies.

Clinicians should be aware of the impact of early dialysis start on QOL[699] before recommending this strategy to patients.

Pediatric Consideration

Timing of initiation of dialysis. As might be expected, information as to the proper timing for initiation of dialysis does not exist for children. Thus, it would seem reasonable to follow the guidelines as set out for the adults. A review by Greenbaum and Schaefer[700] provides the reader with generally agreed upon absolute and relative indications for initiation of dialysis in the child. The absolute indications listed are those of neurologic consequences attributable to uremia; hypertension that fails to respond to antihypertensive therapy; pulmonary edema unresponsive to diuretics; pericarditis; bleeding tendency; and refractory nausea or vomiting. However, the authors clearly state that there is no current consensus as to the validity of the relative indications and specifically the level at which each engenders the need for

dialysis. Relative indications to commence dialysis include less severe uremic symptoms, hyperkalemia, hyperphosphatemia, malnutrition, and growth failure. The authors point out as well that the answer to 'early' versus 'late' dialysis initiation cannot be addressed in any meaningful way in children as there is currently lack of data; and the unique factors to consider in a child such as growth, psychosocial development, likely renal transplant, and need for extended time on both dialysis and in transplant make the probability of a clinical trial to address this issue nearly impossible.

Timing of living donor transplant. There is no direct evidence to guide the pediatric nephrologist as to the 'best' timing for a living donor transplant in children. In each individual case the relative likelihood of improvement in presumed uremic symptoms and burden of disease as related to management of CKD will need to be balanced against the risks of transplant surgery itself and the attendant medication risks with prolonged immunosuppression. While there is little doubt as to the benefit in overall lifespan accrued by a child who is transplanted as opposed to one maintained on standard dialysis therapies during their childhood (average life expectancy of 63 versus 38 years respectively),[701] the issue as to what level of residual function is sufficient to justify delay or conversely proceeding to transplant is simply not readily available.

It should also be noted that reliance on GFR as the sole marker of disease intensity is unlikely to be sufficient for making such a decision, and patient symptoms and/or unique family factors may play a significant role in the decision as to timing of a living donor transplant (e.g., a young grandparent available and healthy to donate at age 60 years may not be eligible at age 63 years and so an earlier transplant would be favored).

5.4: STRUCTURE AND PROCESS OF COMPREHENSIVE CONSERVATIVE MANAGEMENT

5.4.1: Conservative management should be an option in people who choose not to pursue RRT and this should be supported by a comprehensive management program. (*Not Graded*)

5.4.2: All CKD programs and care providers should be able to deliver advance care planning for people with a recognized need for end-of-life care, including those people undergoing conservative kidney care. (*Not Graded*)

5.4.3: Coordinated end-of-life care should be available to people and families through either primary care or specialist care as local circumstances dictate. (*Not Graded*)

5.4.4: The comprehensive conservative management program should include protocols for symptom and pain management, psychological care, spiritual care, and culturally sensitive care for the dying patient and their family (whether at home, in a hospice or a hospital setting), followed by the provision of culturally appropriate bereavement support. (*Not Graded*)

RATIONALE

These statements are intended to highlight the need for comprehensive conservative care processes and resources in the care of this complex patient group. There is increasing recognition that provision of organized care to those who are dying or choose to not pursue dialysis and transplant care is of value to the patients and their families. Clinicians involved in caring for these patients should be alerted to this need. These statements are positioned so as to overtly state this need.

In different societies or cultural areas, the form and structure of this care may vary tremendously and families or religious organizations may be able to deliver expert and sensitive care. The details here are listed not to be prescriptive but rather to articulate the 'best practices' in communities where resources may be available and to serve a construct to review in those locations where resources are more limited.

Evidence Base

The evidence base for these statements is limited to documents describing the burden of illness and unmet needs in patients with CKD as they decide either not to pursue dialysis or to withdraw from RRT. As the readers will appreciate, there are neither RCTs nor even large cohort studies to inform these statements within the CKD populations. Analogies with oncology have been drawn and literature from there has been used to justify the concepts above.

Patients with advanced CKD have extensive palliative care needs for years before death. Throughout their illness trajectory, symptom burden is high.[702–707] The number and severity of physical and emotional symptoms are similar to those of cancer patients hospitalized in palliative care settings.[703,708] Advanced CKD patients managed without dialysis are equally symptomatic.[706] An increasing number of dialysis patients die after withdrawal of dialysis (10-15% in 1990, 20% in 2004), primarily due to poor QOL, representing the second leading cause of death after CVD.

Conservative care focuses on slowing the decline in renal function, actively managing symptoms, advance care planning, and the provision of appropriate palliative care. In oncology, receiving early palliative care is associated with better QOL, fewer emergency department visits and hospitalizations, less aggressive care at the end of life, and surprisingly, longer survival.[709] These observations suggest that development of clinical models that integrate appropriate palliative care, including the creation of conservative care pathways, are likely to be hugely beneficial and would help avoid harmful dialysis to those patients unlikely to realize benefit. Such conservative care programs are slowly being developed, primarily in the UK and Canada.

The literature describing experiences of specific programs and symptom burden in CKD, as well as advocating for better care, has only become more prevalent since 2005.[709–716]

Poor quality, hospitalized deaths began to improve for patients dying with cancer as a result of an increasing emphasis on palliative care teams providing attention to symptom control, psychosocial needs, and options for location of care. The literature suggests that current models of palliative care for cancer patients that deinstitutionalized health-care services have not only improved patient outcomes and quality of care[717–720] but have been cost-neutral.[721]

International Relevance

All countries have people with CKD who withdraw either voluntarily or involuntarily from dialysis services. Best care for those patients will obviously need to respect cultural and religious values, but would necessarily be based on the same philosophical grounds of maintaining dignity of the individual. Appreciating the need for and articulating conservative care pathways overtly would be internationally applicable.

Implications for Clinical Practice and Public Policy

There is a need to ensure appropriate access to services and education surrounding quality care during terminal stages of a chronic condition. There is increasing attention to this in many societies but not in all. Appreciating the variability in the resources required and their availability to different groups of patients is important for implementation. Furthermore, involvement of religious and cultural leaders in recognition of these care practices can be enhanced if they are overtly recognized as part of the care continuum.

There is a need for robust assessment of best practices in CKD and other chronic conditions so that we may provide best care throughout the continuum of life. Researchers around the world are actively pursuing this so that we may have better tools, programs, and ultimately, better outcomes for our patients.

Pediatric Consideration

Despite the lack of published evidence, there is no reason to believe that children and families faced with the need to consider conservative care or a palliative approach to their impending ESRD would not benefit from all of the above recommendations. It would seem reasonable for pediatric nephrology centers to liaise with their pediatric oncology or palliative care teams, ethicists, and pastoral care providers to assist them in developing, defining, and/or identifying locally available resources for situations where a child is not deemed a candidate for RRT prior to their occurrence.

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Methods for guideline development

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AIM

The overall aim of this project was to develop an evidence-based clinical practice guideline for evaluation and management of CKD. The guideline consists of recommendation statements, rationales, and a summary of systematically generated evidence on relevant pre-defined clinical topics. To a large extent the guideline builds on the output of the KDIGO Controversies Conference in 2009,[30] which generated epidemiological data to support a revision of the classification and staging system. The vision for this KDIGO guideline is that it would endorse the current CKD definition as an imperfect convention for describing a state of function, revise classification based on risk, revise risk states, and revise and update action plans in view of the revised classifications. Additional systematic evidence review focused on specific topics.

OVERVIEW PROCESS

The guideline development process included the following steps:

- Appointing Work Group members and the ERT
- Discussing process, methods, and results
- Developing and refining topics
- Identifying populations, interventions or predictors, and outcomes of interest
- Selecting topics for systematic evidence review
- Standardizing quality assessment methodology
- Developing and implementing literature-search strategies
- Screening abstracts and retrieving full text articles on the basis of predefined eligibility criteria
- Creating data extraction forms
- Extracting data and performing critical appraisal of the literature
- Grading the methodology and outcomes in individual studies
- Tabulating data from individual studies into summary tables
- Grading the strength of recommendations on the basis of the quality of evidence and other considerations
- Finalizing guideline recommendations and supporting rationales
- Sending the guideline draft for peer review to the KDIGO Board of Directors in January 2012 and for public review in May 2012
- Publishing the final version of the guideline

Collaboration Among Participants

The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group of domain experts, including individuals with expertise in internal medicine, adult and pediatric nephrology, diabetology/endocrinology, clinical chemistry, and epidemiology. The Tufts Center for Kidney Disease Guideline Development and Implementation at Tufts Medical Center in Boston, Massachusetts, USA, was contracted to conduct systematic evidence review and provide expertise in guideline development methodology. The ERT consisted of physician–methodologists with expertise in nephrology, a project coordinator, a research assistant, and a medical writer–editor. The ERT instructed and advised Work Group members in all steps of literature review, critical literature appraisal, and guideline development. The Work Group and the ERT collaborated closely throughout the project.

The Work Group and its Chairs, KDIGO Co-chairs, ERT, and KDIGO support staff met for three 2-day meetings for training in the guideline development process, topic discussion, and consensus development.

Throughout the project, the ERT offered suggestions for guideline development and led discussions on systematic review, literature searches, data extraction, assessment of quality and applicability of articles, evidence synthesis, grading of evidence and guideline recommendations, and consensus development. The Work Group took the primary role of writing the recommendation statements and rationales and retained final responsibility for their content.

Defining Scope and Topics

This KDIGO CKD guideline was set out to update the *KDOQI Clinical Practice Guidelines for CKD: Evaluation, Classification, and Stratification*[1] in 2002, which spans many topics related to the diagnosis, classification, stratification, and management of CKD.[1]

The Work Group Co-Chairs prepared the first draft of the scope of work document as a series of open-ended questions to be considered by Work Group members. At their first 2-day meeting, members added further questions until the initial working document included all topics of interest to the Work Group. The inclusive, combined set of questions formed the basis for the deliberation and discussion that followed. The Work Group strove to ensure that all topics deemed clinically relevant and worthy of review were identified and addressed.

Updating the topics of definitions and classification was based on the output from the KDIGO Controversies Conference and the CKD Prognosis Consortium.[4,30]

Additional topics that relate to explicit selection of diagnostic tests or interventions were chosen to undergo systematic review of the best available evidence. Systematic

evidence review entails *a priori* question formulation, specification of important outcomes for the review, systematic searches, data extraction, tabulation, analysis, and synthesis of evidence and is described in detail for each of the specific questions. The process followed for each evidence review topic (a total of four non-treatment topics and four treatment topics) is detailed below.

The eight topics for which the ERT conducted searches and evidence review are shown in Table 37. For the systematic review topics, the Work Group and ERT further developed and refined each topic and specified screening criteria, literature search strategies, and data extraction forms.

Many other topics were not suitable to be addressed by in-depth evidence review. When the anticipated outcome of an extensive literature search was unlikely to yield evidence that directly informs practice choices, the approach chosen was that of a narrative review.

APPROACH TO EVIDENCE REVIEW TOPICS

Formulating Questions of Interest

Questions of interest were formulated according to the PICODD (Population, Intervention or Predictor, Comparator, Outcome, study Design, and Duration of follow-up) criteria. Details of the PICODD criteria are presented in Table 37.

Literature Searches and Article Selection for Evidence Review Topics

Search strategies were developed by the ERT, with input from the Work Group, for each topic of interest (whether treatment or non-treatment topics). The ERT performed literature searches and conducted abstract and article screening. The ERT also coordinated the methodological and analytic processes, data extraction, and summarizing of the evidence. Before initiating our own *de novo* systematic review, we searched for existing systematic reviews that could be used. The searches and search terms are provided in Supplemental Table 1 and the search dates and yields for all topics are presented in Table 38.

Selection of Outcomes of Interest

The Work Group selected outcomes of interest on the basis of their importance for informing clinical decision making. Importance of mortality and ESRD was considered to be critical; the importance of progression of CKD and categorical or continuous measures of kidney function was considered to be high; and the importance of QOL, BP, gout attacks, and proteinuria was considered to be moderate.

Data Extraction

Text articles were extracted by the ERT onto forms customized to capture data on design, methodology, baseline characteristics, interventions or predictors, comparators, outcomes, results, and limitations of individual studies. Study methodology and risk of bias were also systematically graded for each outcome and recorded.

Summary Tables

Pertinent information for systematic review topics was tabulated in summary tables. Summary tables list outcomes of interest as well as relevant population characteristics, descriptions of interventions and comparators, results, and quality grades for each outcome. Categorical and continuous outcomes were summarized separately. Work Group members reviewed all summary table data and quality grades.

Evidence Profiles

Evidence profiles are usually constructed as a means to assess the quality and record quality grades and descriptions of effect for each outcome across studies, as well as the quality grades and description of net benefits or harms of the intervention or comparator across studies. These profiles aim to make the evidence synthesis process transparent. However, since no treatment or non-treatment topic had more than one study in a summary table for which the quality was graded, no evidence profiles were generated, and the information in the summary table shows the highest level of synthesis.

Grading of Quality of Evidence for Outcomes of Individual Studies

Methodological quality. Methodological quality (internal validity) refers to the design, conduct, and reporting of outcomes of a clinical study. A previously devised three-level classification system for quality assessment was used to grade the overall study quality and quality of all relevant outcomes in the study (Table 39). Variations of this system have been used in most KDOQI and all KDIGO guidelines and have been recommended for the US Agency for Healthcare Research and Quality Evidence-based Practice Center program.[722]

Each study was given an overall quality grade on the basis of its design, methodology (randomization, allocation, blinding, definition of outcomes, appropriate use of statistical methods, etc.), conduct (drop-out percentage, outcome assessment methodologies, etc.), and reporting (internal consistency, clarity, thoroughness, and precision, etc.). Each reported outcome was then evaluated and given an individual grade depending on the quality of reporting and methodological issues specific to that outcome. However, the quality grade of an individual outcome could not exceed the quality grade for the overall study.

Grading the Quality of Evidence and the Strength of Guideline Recommendations

A structured approach, based on the GRADE approach,[723–725] was used to grade the quality of the overall evidence and the strength of recommendations for each topic. This grading scheme-with two levels for the strength of a recommendation together with four levels of grading for the quality of the evidence, as well as the option of an ungraded statement for general guidance-was adopted by the KDIGO Board in December 2008.

Table 37 | Topics of interest for the management of CKD guideline

Topic	Question	Population	Treatment, predictor or index test	Comparator or alternative test or gold standard	Outcome (ranked by importance)	Study design	Inclusion criteria	Methodological approach	No. of reports or articles yielded
Non-Treatment									
Prediction equations for GFR	How do SCr- or SCysC-based prediction equations perform compared to gold standard measurement of GFR?	Patients in steady state with or without CKD and other special populations (DM, HTN, KTR or donors, various age groups, races, or ethnic groups)	GFR prediction based on SCr or SCysC must be directly traceable to (*not just indirectly calibrated to*) IDMS standards	Gold standard measure of GFR (e.g., iothalamate, EDTA, iohexal, inulin clearance) Not 24-hr urine collection	Bias precision, accuracy expressed as P_{30} †	Cross-sectional or diagnostic test study	Overall N >100 N >50 for subgroups	SR Equation must be validated in an external dataset	15
Prediction equations for risk of kidney failure	What prediction equations exist to predict kidney failure?	GFR <60 ml/min/ 1.73 m^2 and/or kidney transplant	Candidate predictors had to include at least age, sex, SCr, and DM status	NA	ESRD, mortality	Longtudinal cohort study	Equation must be validated in an external dataset N >100	Studies identified by WG	2
Gadolinium exposure and nephrogenic fibrosing dermopathy	What is the incidence of NFD after exposure to gadolinium?	GFR <60 ml/min/ 1.73 m^2 and/or kidney transplant	Gadolinium exposure	No gadolinium exposure	Nephrogenic fibrosing dermopathy	SR of case-control and cohort studies	None	Search for SRs	1
AKI and phosphate-containing bowel preparations	What is the incidence of AKI after taking a phosphate-containing bowel preparation?	Any GFR category; individuals without CKD	Exposure to phosphate-containing bowel preparation	No exposure to phosphate-containing bowel preparation	Categorical kidney outcomes	Narrative review of case-control studies; observational cohort studies	None	Search for recent guidelines, SRs, RCTs, observational studies, or narrative reviews	2
Treatment									
Treatment with bicarbonate	Does treatment with bicarbonate in CKD improve clinical outcomes?	GFR <60 ml/min/ 1.73 m^2 and/or kidney transplant	Bicarbonate or citrate	No bicarbonate or citrate	ESRD, categorical or continuous kidney function; QOL and BP control as adverse events	RCT	N >100	Review of Cochrane SRs plus systematic search for RCTs published after search dates in most recent Cochrane SR	1 SR + 1 RCT
Treatment with allopurinol	Does treatment with allopurinol in CKD improve clinical outcomes?	GFR <60 ml/min/ 1.73 m^2 and/or kidney transplant with or without hyperuricemia	Allopurinol	No allopurinol	Mortality, cardiovascular events, ESRD, CKD progression, gout attacks; QOL and BP control as adverse events; proteinuria	RCT	N >100	SR	1
Timing of initiation of RRT in CKD	When should dialysis be started: early or late?	GFR <30 ml/min/ 1.73 m^2	Early start of dialysis	Late start of dialysis	Mortality, ESRD	RCT	N >100	Review of studies identified by WG	1
Protein restriction	Should patients with CKD be on a protein-restricted diet?	GFR <60 ml/min/ 1.73 m^2 and/or kidney transplant	Reduced protein intake	Usual protein intake	ESRD, mortality, categorical or continuous kidney function	RCT	N >100	Review of Cochrane SRs plus systematic search for RCTs published after search dates in most recent Cochrane SR	3 SR+ 1 RCT

Abbreviations: AKI, acute kidney injury; BP, blood pressure; CKD, chronic kidney disease; cys C, cystatin C; DM, diabetes mellitus; EDTA, ethylenediamine tetraacetic acid; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HTN, hypertension; IDMS, isotope dilution mass spectrometry; KTR, kidney-transplant recipient; NA, not applicable; NFD, nephrogenic fibrosing dermopathy; QOL, quality of life; RCT, randomized controlled trial; RRT renal-replacement therapy; SCr, serum creatinine; SCysC, serum cystatin C; SR, systematic review; WG, Work Group.

†Accuracy specifically measured as the percentage of GFR estimates within 30% (P_{30}) of the measured GFR. Higher P_{30} values reflect greater accuracy; values are decreased by both greater bias and worse precision.

Table 38 | Literature yield of primary articles for all topics

Topic	Systematic review performed	Search dates	Search terms	Articles retrieved	Articles with full text screened	Articles used in tables
Non-treatment topics						
Prediction equations for eGFR	Y	MEDLINE search from 2006 until 2011, with an update in June 2011	"kidney," and "prediction," "equation," "formula," or "regression analysis"	2921	86	15
Prediction equations for risk of kidney failure or death	N	nd	nd	10*	10	2
Risk from gadolinium for nephrogenic fibrosing dermopathy	Y	MEDLINE search from 1996 until 2011 was run in March 2011	"kidney," and "gadolinium," "nephrogenic fibrosing dermopathy," or "nephrogenic systemic fibrosis," and systematic review	1†	0	0
Risk for nephropathy from phosphate-containing bowel preparations	N	MEDLINE search for recent (2008-2011) narrative reviews was run in March 2011	"Phosphate nephropathy"	2	2	2
Treatment topics						
Treatment with bicarbonate	Y	MEDLINE search from 2005 until 2011, with an update in May 2011	"randomized controlled trial," and "kidney," or "metabolic acidosis," and "bicarbonate"	3981	6	1
Treatment with allopurinol	Y	MEDLINE search from 1996 until 2011, with an update in May 2011	"randomized controlled trial," and "kidney," and "allopurinol"	393	4	1
Earlier versus later initiation of RRT in CKD	N	nd	nd	8‡	8	1
Treatment with protein restriction	Y	Three Cochrane systematic reviews were identified and used instead of a *de novo* systematic review. MEDLINE search from 1996-2011, with an update in March 2011	"randomized controlled trial," and "kidney," and "diet, protein-restricted"	561	1	1

Abbreviations: CKD, chronic kidney disease; eGFR, estimated GFR; nd, not done; RRT, renal replacement therapy.
*References were provided by Work Group members.
†Systematic review provided to Work Group members.
‡References were provided by Work Group members.

The strength of a recommendation indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The quality of a body of evidence refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation.[724] The process of transparently grading evidence and recommendations for treatment topics is described below in further detail. However, the approach had to be adapted for the main topics of the KDIGO CKD guideline because they were not treatment-related topics.

Table 39 | Classification of study quality

Good quality	Low risk of bias and no obvious reporting errors, complete reporting of data. Must be prospective. If study of intervention, must be randomized controlled study.
Fair quality	Moderate risk of bias, but problems with study or paper are unlikely to cause major bias. If study of intervention, must be prospective.
Poor quality	High risk of bias or cannot exclude possible significant biases. Poor methods, incomplete data, reporting errors. Prospective or retrospective.

Grading the Quality of Evidence for Each Outcome Across Studies

Following the GRADE approach, the quality of a body of evidence pertaining to a particular outcome of interest was initially categorized on the basis of study design (Table 40). For questions of interventions, the initial quality grade was high if the body of evidence consisted of RCTs, low if it consisted of observational studies, and very low if it consisted of studies of other designs. For questions of interventions, the Work Group decided to use only RCTs. The grade for the quality of evidence for each intervention–outcome pair was then lowered if there were serious limitations to the methodological quality of the aggregate of studies, if there was thought to be a high likelihood of bias, if there were important inconsistencies in the results across studies, if there was uncertainty about the directness of evidence (including limited applicability of the findings to the population of interest), if the data were sparse (for example if there was only one study or if the results include just a few events or observations and were uninformative) or imprecise (for example the CI spans a range greater than 1 or confidence limits are <0.5 to >2.0). The final grade for the quality of the evidence for an intervention–outcome pair was then assigned as high, moderate, low, or very low (Table 40).

Grading the Overall Quality of Evidence

The quality of the overall body of evidence was then determined on the basis of the quality grades for all

Table 40 | GRADE system for grading quality of evidence

Step 1: Starting grade for quality of evidence based on study design	Step 2: Reduce grade	Step 3: Raise grade	Final grade for quality of evidence and definition
Randomized trials = High	*Study quality* -1 level if serious limitations -2 levels if very serious limitations *Consistency* -1 level if important inconsistency	*Strength of association* +1 level is strong[a], no plausible confounders +2 levels if very strong[b], no major threats to validity *Other* +1 level if evidence of a dose-response gradient +1 level if all residual plausible confounders would have reduced the observed effect	High = Further research is unlikely to change confidence in the estimate of the effect Moderate = Further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate Low = Further research is very likely to have an important impact on confidence in the estimate and may change the estimate Very low = Any estimate of effect is very uncertain
Observational study = Low	*Directness* -1 level if some uncertainty -2 levels if major uncertainty		
Any other evidence = Very low	*Other:* -1 level if sparse or imprecise data[c] -1 level if high probability of reporting bias		

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
[a]Strong evidence of association is defined as 'significant relative risk of >2 (<0.5)' based on consistent evidence from two or more observational studies, with no plausible confounders.
[b]Very strong evidence of association is defined as 'significant relative risk of >5 (<0.2)' based on direct evidence with no major threats to validity.
[c]Sparse if there was only one study or if the results include just a few events or observations and were uninformative. Imprecise if the confidence interval spans a range greater than 1 or confidence limits are <0.5 to >2.0
Adapted by permission from Macmillan Publishers Ltd: *Kidney International*. Uhlig K, Macleod A, Craig J et al.[725] Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; 70: 2058–2065; accessed http://www.nature.com/ki/journal/v70/n12/pdf/5001875a.pdf

Table 41 | Final grade for overall quality of evidence

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

Table 42 | Balance of benefits and harm

When there was evidence to determine the balance of medical benefits and harm of an intervention to a patient, conclusions were categorized as follows:

- For statistically significant benefit/harm, report as 'benefit [or harm] of drug X'.
- For non-statistically significant benefit/harm, report as 'possible benefit [or harm] of drug X'.
- In instances where studies are inconsistent, report as 'possible benefit [or harm] of drug X'.
- 'No difference' can only be reported if a study is not imprecise.
- 'Insufficient evidence' is reported if imprecision is a factor.

outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting four final categories for the quality of overall evidence were A, B, C, and D (Table 41).

Assessment of the Net Health Benefit Across All Important Clinical Outcomes

The net health benefit was determined on the basis of the anticipated balance of benefits and harms across all clinically important outcomes (Table 42). The assessment of net benefit also involved the judgment of the Work Group and the ERT.

Grading the Strength of the Recommendations

The strength of a recommendation is graded as level 1 or level 2. Table 43 shows the KDIGO nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians, and policy makers. Recommendations can be for or against doing something. Table 44 shows that the strength of a recommendation is determined not only by the quality of the evidence, but also by other, often complex judgments regarding the size of the net medical benefit, values and preferences, and costs. Formal decision analyses including cost analysis were not conducted.

Ungraded Statements

This category was designed to allow the Work Group to issue general advice. Typically an ungraded statement meets the following criteria: it provides guidance that is based on common sense, it provides reminders of the obvious, and it is not sufficiently specific to allow for application of evidence to the issue and therefore it is not based on systematic evidence review. The GRADE system is best suited to evaluate evidence on comparative effectiveness. Some of our most important guideline topics involve diagnosis and staging within CKD, about which the Work Group chose to provide ungraded statements. These statements are indirectly supported by evidence on risk relationships and are the consensus of the Work Group. Thus, we believe that ungraded statements should not be viewed as weaker than graded recommendations.

Table 43 | KDIGO nomenclature and description for grading recommendations

	Implications		
Grade*	Patients	Clinicians	Policy
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Abbreviation: KDIGO, Kidney Disease: Improving Global Outcomes.
*The additional category ''Not Graded'' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Table 44 | Determinants of strength of recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is warranted. The narrower the gradient, the more likely a weak recommendation is warranted.
Quality of the evidence	The higher the quality of evidence, the more likely a strong recommendation is warranted.
Values and preferences	The more variability in values and preferences, or more uncertainty in values and preferences, the more likely a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

Reproduced from Going from evidence to recommendations. Guyatt GH, Oxman AD, Kunz R, *et al*.[724] BMJ 336: 1049-1051, 2008 with permission from BMJ Publishing Group Ltd.; accessed http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2376019/pdf/bmj-336-7652-analysis-01049.pdf

Table 45 | The Conference on Guideline Standardization[727] checklist for reporting clinical practice guidelines

Topic	Description	Discussed in KDIGO CKD Guideline
1. Overview material	Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.	*Abstract* and *Methods for Guideline Development*.
2. Focus	Describe the primary disease/condition and intervention/service/technology that the guideline addresses. Indicate any alternative preventative, diagnostic, or therapeutic interventions that were considered during development.	Evaluation and management of adults and children with CKD.
3. Goal	Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.	This clinical practice guideline is intended to assist the practitioner caring for patients with CKD and to prevent deaths, cardiovascular disease events and progression to kidney failure while optimizing patients' quality of life.
4. User/setting	Describe the intended users of the guideline (e.g., provider types, patients) and the settings in which the guideline is intended to be used.	Providers: Nephrologists (adult and pediatric), Dialysis providers (including nurses), Internists, and Pediatricians. Patients: Adult and pediatric individuals at risk for or with CKD. Policy Makers: Those in related health fields.
5. Target population	Describe the patient population eligible for guideline recommendations and list any exclusion criteria.	Individuals at risk for or with CKD.
6. Developer	Identify the organization(s) responsible for guideline development and the names/ credentials/potential conflicts of interest of individuals involved in the guideline's development.	Organization: KDIGO. Refer to *Biographic and Disclosure Information* section.
7. Funding source/sponsor	Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest.	KDIGO is supported by the following consortium of sponsors: Abbott, Amgen, Bayer Schering Pharma, Belo Foundation, Bristol-Myers Squibb, Chugai Pharmaceutical, Coca-Cola Company, Dole Food Company, Fresenius Medical Care, Genzyme, Hoffmann-LaRoche, JC Penney, Kyowa Hakko Kirin, NATCO—The Organization for Transplant Professionals, NKF-Board of Directors, Novartis, Pharmacosmos, PUMC Pharmaceutical, Robert and Jane Cizik

Table 45 | Continued

Topic	Description	Discussed in KDIGO CKD Guideline
		Foundation, Shire, Takeda Pharmaceutical, Transwestern Commercial Services, Vifor Pharma, and Wyeth. No funding is accepted for the development or reporting of specific guidelines. All stakeholders could participate in open review.
8. Evidence collection	Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.	Screening criteria are outlined in the methods chapter. The search was updated through June 2011 and supplemented by articles identified by Work Group members through November 2012. We also searched for pertinent existing guidelines and systematic reviews.
9. Recommendation grading criteria	Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance of adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harms.	Quality of individual studies was graded in a three-tiered grading system (see Table 39). Quality of evidence (Table 40) was graded following the GRADE approach. Strength of the recommendation was graded in a two-level grading system which was adapted from GRADE for KDIGO with the quality of overall evidence graded on a four-tiered system (Tables 41 and 43). The Work Group could provide general guidance in ungraded statements.
10. Method for synthesizing evidence	Describe how evidence was used to create recommendations, e.g., evidence tables, meta-analysis, decision analysis.	For systematic review topics, summary tables and evidence profiles were generated. For recommendations on treatment interventions, the steps outlined by GRADE were followed.
11. Prerelease review	Describe how the guideline developer reviewed and/or tested the guidelines prior to release.	The guideline had undergone internal review by the KDIGO Board of Directors in January 2012 and external review in May 2012. Public review comments were compiled and fed back to the Work Group, which considered comments in its revision of the guideline.
12. Update plan	State whether or not there is a plan to update the guideline and, if applicable, expiration date for this version of the guideline.	There is no date set for updating this entire guideline. The need for updating of the guideline will depend on the publication of new evidence that would change the quality of the evidence or the estimates for the benefits and harms. Results from registered ongoing studies and other publications will be reviewed periodically to evaluate their potential to impact on the recommendations in this guideline. Specific sections may be updated separately from the entire guideline within the next 3–5 years depending on the evidence base.
13. Definitions	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation.	*Acronyms and Abbreviations*.
14. Recommendations and rationale	State the recommended action precisely and the specific circumstances under which to perform it. Justify each recommendation by describing the linkage between the recommendation and its supporting evidence. Indicate the quality of evidence and the recommendation strength, based on the criteria described in Topic 9.	Each guideline chapter contains recommendations for evaluation and management of CKD patients. Each recommendation builds on a supporting rationale with evidence tables if available. The strength of the recommendation and the quality of evidence are provided in parenthesis within each recommendation.
15. Potential benefits and harm	Describe anticipated benefits and potential risks associated with implementation of guideline recommendations.	The benefits and harm for each comparison of interventions is provided in summary tables and summarized in evidence profiles. The estimated balance between potential benefits and harm was considered when formulating the recommendations.
16. Patient preferences	Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values.	Many recommendations are ungraded which indicates a greater need to help each patient arrive at a management decision consistent with her or his values and preferences.
17. Algorithm	Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline.	Algorithm for proteinuria/albuminuria testing in Chapter 1.
18. Implementation considerations	Describe anticipated barriers to application of the recommendations. Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation. Suggest review criteria for measuring changes in care when the guideline is implemented.	These recommendations are global and the Work Group acknowledges the importance of local application. Review criteria were not suggested because implementation with prioritization and development of review criteria must proceed locally. Furthermore, most recommendations are discretionary, requiring substantial discussion among stakeholders before they can be considered for adoptions as review criteria. Suggestions were provided for future research.

Abbreviations: CKD, chronic kidney disease; COGS, Conference on Guideline Standardization; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; KDIGO, Kidney Disease: Improving Global Outcomes; NKF, National Kidney Foundation.
Adapted with permission from Shiffman RN, Shekelle P, Overhage JM, et al.[727] Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. Ann Intern Med 2003; 139(6): 493-498; accessed http://annals.org/data/Journals/AIM/20049/0000605-200309160-00013.pdf

The Work Group took on the primary role of writing the recommendations and rationale statements and retained final responsibility for the content of the guideline statements and the accompanying narrative. The ERT reviewed draft recommendations and grades for consistency with the conclusions of the evidence review.

Format for Guideline Recommendations

Each chapter contains one or more specific recommendations. Within each recommendation, the strength of recommendation is indicated as level 1 or level 2 and the quality of the supporting evidence is shown as A, B, C or D. The recommendation statements and grades are followed by the rationale and clarification of the wording of the statement, a brief background with relevant definitions of terms, and then a chain of logic which summarizes the key points of the evidence base and the judgments supporting the recommendation. Some sections also contain research recommendations in variable degrees of detail, suggesting future research to resolve current uncertainties.

Limitations of Approach

Although the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was the only database searched. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to domain experts that were missed by the electronic literature searches were added to the retrieved articles and reviewed by the Work Group.

Summary of the Review Process

Several tools and checklists have been developed to assess the quality of the methodological process for systematic review and guideline development. These include the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria,[726] the Conference on Guideline Standardization (COGS) checklist,[727] and the Institute of Medicine's recent *Standards for Systematic Reviews*[728] and *Clinical Practice Guidelines We Can Trust*.[729] Table 45 and Appendix 1 demonstrate the level of concurrence to the COGS criteria and the Institute of Medicine standards, respectively.

SUPPLEMENTARY MATERIAL

Supplemental Table 1: Search strategy.
Appendix 1: Concurrence with Institute of Medicine standards for systematic reviews and for guidelines.
Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/ckd.php

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Biographic and Disclosure Information

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Adeera Levin, MD, FRCPC (Work Group Co-Chair), is Professor of Medicine, Division Head of Nephrology at the University of British Columbia, and Consultant Nephrologist at Providence Health Care/St Paul's Hospital, in Vancouver Canada.

Dr Levin is the Executive Director of the BC Renal Agency, which oversees the care, planning, and budgets for kidney services in the province of British Columbia. In this capacity, she has leveraged her epidemiological training, clinical knowledge, and health outcomes research to develop an evidence-based transparent system which enhances the care of patients across the continuum of care (from identification of CKD to dialysis, transplant, and death).

She is active in international activities across the spectrum of kidney activities including her appointment as Secretary General of the International Society of Nephrology (ISN), founding executive committee member of KDIGO, and as co-Chair of the Declaration of Istanbul Custodian group (DICG). Dr Levin has a long-standing clinical and research interest in CKD and CVD, and is Founding Director of the Kidney Function Clinic at St Paul's Hospital.

As an active researcher and mentor, she is involved in a national curriculum development for clinician scientists interested in kidney disease (KRESCENT), and mentors students, residents, and nephrology fellows in Vancouver as well. She has over 210 peer-reviewed publications, numerous book chapters, and is co-editor of a textbook *Chronic Kidney Disease: A Practical Guide to Understanding and Management*. Her major research areas of interest include non-traditional risk factors for CVD in CKD patients, with particular focus on anemia, phosphate and vitamin D, and progression of CKD variability.

Advisor/Consultant: Merck; Otsuka

Grant/Research Support: Abbott; Amgen; Canadian Institutes of Health Research; Genzyme, Kidney Foundation of Canada; Merck; Ortho

Paul E Stevens, MB, FRCP (Work Group Co-Chair), is Consultant Nephrologist and Associate Medical Director, East Kent Hospitals University NHS Foundation Trust, Kent and Canterbury Hospital in the UK. He is a member of the Department of Health's Renal Advisory Group and Renal Pathology Group and immediate past-President of the British Renal Society. Dr Stevens established the Kent Kidney Care Centre, one of the largest general hospital renal units in the UK and served as a clinical advisor on NICE publications *Anaemia Management in People with Chronic Kidney Disease* and *Chronic Kidney Disease: National Clinical Guideline for Early Identification and Management in Adults in Primary and Secondary Care*. He is also Chair of NICE Quality Standards in Chronic Kidney Disease.

His main interests include the epidemiology of CKD and AKI, prospective evaluation of a new method of assessing adequacy in peritoneal dialysis, evaluation of anemia in unreferred patients with CKD and in patients with diabetes, collaborative research with the elderly CKD care team, and the development of information technology-based solutions in the referral and follow-up of patients with kidney disease. Over the last several years, his program has also developed a clinical decision support system to aid management of CKD in primary care and this system is currently running live in a population of over 300,000 primary care patients. Dr Stevens has authored over 90 publications in peer-reviewed journals and textbooks, and has given over 100 presentations and 65 guest lectures in national and international society meetings.

Dr Stevens reported no relevant financial relationships

Rudy W Bilous, MD, is Professor of Clinical Medicine at Newcastle University and Honorary Consultant Physician at the James Cook University Hospital, Middlesbrough, UK. He studied medicine at Guy's Hospital and completed his clinical training at various hospitals in London. He was an National Institutes of Health (NIH) Fellow at the Unit for Metabolic Medicine at Guy's from 1980-1982 working for Professor Harry Keen and with Drs John Pickup and Giancarlo Viberti examining the effects of metabolic control on microvascular complications. From 1985-1987 he was Juvenile Diabetes Research Foundation fellow at the University of Minnesota working for Drs Mike Steffes and Mike Mauer. He was awarded his MD from the University of London in 1987 and elected Fellow of the Royal College of Physicians of London in 1991. He served as Secretary and Chair of the Specialty Advisory Committee for Endocrinology and Diabetes and Chairman of the Professional section of Diabetes UK. He is currently Chairman of the workgroup reviewing the NICE guideline for Diabetes in Pregnancy and President of the European Diabetic Nephropathy Study Group of the European Association for the Study of Diabetes.

Advisor/Consultant: Abbott; Boehringer Ingelheim; Novartis; Roche

Speaker: Boehringer Ingelheim; Novo Nordisk; Roche

Josef Coresh, MD, PhD, MHS, is Professor, Department of Epidemiology, Medicine, and Biostatistics at Johns Hopkins Bloomberg School of Public Health and School of Medicine where he also received his medical degree and PhD in epidemiology, and a master's in biostatistics. He is also presently the Director of the George W Comstock Center for Public Health Research and Prevention, and the Cardiovascular Epidemiology Program and Training Grant at Johns Hopkins Bloomberg School of Public Health.

Dr Coresh's primary research interest has been the investigation of risk factors for CVD in CKD and their role in mediating the excess risk among patients with various degrees of CKD severity. With the use of innovative epidemiologic methods and statistical analyses, his recent work uncovered several novel genetic susceptibility loci for gout as well as a susceptibility locus (*MYH9*/*APOL1*) which accounts for much of the excess risk of non-diabetic kidney disease among African-Americans. Since 2000, he has focused his attention on enhancing CKD classification, management and prognostication by improving the estimation of kidney function. In 2002, he served as Co-Chair on the KDOQI Clinical Practice Guidelines for CKD which produced the CKD definition and classification system that have been adopted widely today. More recently, his research led to the development of the 2009 CKD-EPI equation for estimating kidney function which is rapidly become the new standard for GFR estimation globally. In 2010, he became Steering Committee Chair of Chronic Kidney Disease Prognosis Consortium (CKD-PC) which analyzes data from two million study participants in order to provide better estimation on CKD prognosis. Dr Coresh has authored close to 300 publications and has mentored over 60 students. In recognition of his contributions, he was awarded the NKF's Garabed Eknoyan Award (2010), American Heart Association's 2010 Epidemiology and Prevention Mentoring Award and served as plenary speaker at the American Association for Clinical Chemistry 2011 Annual Meeting.

Advisor/Consultant: Merck

Grant/Research Support: Amgen; National Institutes of Health; National Kidney Foundation

Speaker: Abbott; Amgen

Angel LM de Francisco, MD, PhD, is Head of Dialysis Unit and Nephrology Section, Hospital Universitario Valdecilla, Santander (Spain), and Full Professor of Nephrology at Faculty of Medicine in Cantabria University. He completed his medical residency and nephrology fellowship at Hospital Puerta de Hierro in Madrid, and received his Doctor of Medicine degree from University of Cantabria (Spain). Prof de Francisco is an active member of several professional societies, an Executive member of the KDIGO Board, and was President of the Spanish Society of Nephrology from 2002 to 2008. He has been a frequently invited lecturer, speaking extensively on advancements in treatment of chronic kidney diseases and comorbid conditions such as metabolic bone disease, anemia, dialysis, and kidney transplantation. Prof de Francisco has authored or coauthored over 150 publications, including original peer-reviewed articles and book chapters. His primary focus has been on improving outcomes in patients receiving hemodialysis, and on issues surrounding organ transplantation and the impact of treatment guidelines on clinical practice.

Advisor/Consultant: Amgen

Speaker: Abbott; Fresenius

Paul E de Jong, MD, PhD, was Professor of Nephrology and Head, Division of Nephrology of the Groningen University Medical Center in Groningen, the Netherlands from 1992 to 2011. His main research interest is prevention of CKD. From 1980 to 2000, he focused most of his attention on the mechanisms of urinary protein loss in CKD patients and options to lower proteinuria with ACE-I. His studies had indeed shown that such treatment prevented ESRD progression. In 1996, he initiated the PREVEND study which consisted of a large cohort of 8592 subjects followed for the development of kidney disease and CVD. This prospective longitudinal study demonstrated the impact of albuminuria, even in the ranges of microalbuminuria and below, in predicting future cardiovascular and renal events. As former Director of the Groningen Institute of Kidney Diseases, his research program encompasses the studying of underlying susceptibility to kidney damage in health subjects and the identification of common pathophysiological pathways between CKD and CVD. Currently, he serves on the board of KDIGO, CKD-PC, and European Kidney Health Alliance. In 2010, he was the recipient of International Distinguished Medal from the US National Kidney Foundation and was awarded the Officer in the Order of Orange-Nassau for his lifetime achievement by Her Majesty Queen Beatrix of the Netherlands in 2011.

Dr de Jong reported no relevant financial relationships

Kathryn E Griffith, BM, BS, MSc, MRCP, MRCGP, is a general practitioner affiliated with The University Health Centre, York University and York Hospital Foundation Trust. Dr Griffith has a long-standing interest in the relationship between CVD and renal disease from a primary care physician's perspective. In this vein, she has served as a panel member for the Royal College of Physicians (RCP) Edinburgh Consensus Conference on CKD and was involved in the development of the 18-week Commissioning Pathway to CKD with the Department of Health. She is presently a member of the Renal Advisory Group at the Department of Health and a member of both UK Renal Association and British Renal Society. Dr Griffith has also been involved in the education of general practitioners and practice nurses, and most recently she has lectured extensively on various topics such as atrial fibrillation, heart failure, coronary heart

disease, hypertension, and stroke. For the past two years, she has worked with Yorkshire Cardiac and Stroke Networks on a guide to stroke prevention in atrial fibrillation, and contributed to the RCP Edinburgh Consensus on atrial fibrillation management and European Society of Cardiology's clinical practice guideline on management of dyslipidemias.

Advisor/Consultant: Boehringer Ingelheim
Honoraria: Pfizer
Travel Stipend: Merck Sharp & Dohme
Grant/Research Support: Roche
Speaker: Boehringer Ingelheim

Brenda R Hemmelgarn, MD, PhD, FRCP(C), is Associate Professor in the Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, Alberta. She is a clinician scientist with clinical training in nephrology as well as a PhD in Epidemiology and Biostatistics. Dr Hemmelgarn's research interests are in the study of chronic medical conditions including CKD, diabetes, hypertension and CVD, as well as health services research aimed at improving management of these chronic conditions. Dr Hemmelgarn holds provincial and national salary awards and operating grants, and is the recipient of the Roy and Vi Baay Chair in Kidney Research. She is also actively involved in Clinical Practice Guideline development both nationally through the Canadian Society of Nephrology and internationally through KDIGO, and has over 180 peer-reviewed publications.

Grant/Research Support: Roche

Kunitoshi Iseki, MD, is currently affiliated with University Hospital of the Ryukyus in Okinawa, Japan. Dr Iseki received his medical training at Kyushu University in Fukuoka, Japan and completed his fellowship at University of Southern California under Professors Shaul Massry and Vito Campese. He was Senior Assistant Professor of Medicine at Ryukyu University Hospital and later became its Director of Dialysis Unit. Dr Iseki is a member of numerous professional organizations including the Japanese Society of Nephrology and Japanese Society for Dialysis Therapy. He is also an organizing member for Asian Forum of Chronic Kidney Disease Initiatives (AFCKDI) since 2007 and an ISN-COMGAN Educational Ambassador since 2009. Dr. Iseki has also participated and contributed data to the CKD-PC whose collaborative meta-analyses were conducted to study CKD prognosis. He has previously served as Editorial board member for *American Journal Kidney Disease* and is presently an editorial board member of *Nephrology*, *Nephron Clinical Practice* and *Nephrology Dialysis Transplantation*.

Dr Iseki reported no relevant financial relationships

Edmund J Lamb, PhD, FRCPath, is a Consultant Clinical Scientist and Head of Clinical Biochemistry at East Kent Hospitals University NHS Foundation Trust, Canterbury, Kent, UK. He has a special interest in kidney disease and undertook his PhD in the Renal Research Laboratory at St Bartholomew's Hospital, London. He has 30 years experience as a clinical biochemist and his research interests relate to the use of biochemical markers to diagnose and monitor kidney disease, including the assessment of kidney function using eGFR, the evaluation of renal bone disease, the use and role of cystatin C, and the significance and use of cardiac biomarkers in kidney disease. Dr Lamb has authored or co-authored more than 60 full peer-reviewed papers in this area. He is a member of the UK Kidney Research Consortium Clinical Study Group on CKD-MBD and he is the lead investigator on two National Institute for Health Research-Research for Patient Benefit funded studies investigating aspects of kidney function testing. He has been involved in national and international committees and guidelines (e.g., Royal College of Physicians UK CKD Guidelines Group, NICE CKD Guideline Development Group, KDIGO Chronic Kidney Disease Guideline Work Group) and was recently involved in the Department of Health initiative to roll-out eGFR across England. He is Editor-in-Chief of *Annals of Clinical Biochemistry*.

Grant/Research Support: Siemens

Andrew S Levey, MD, is Dr Gerald J and Dorothy R Friedman Professor of Medicine at Tufts University School of Medicine, Chief of the William B Schwartz, MD Division of Nephrology at Tufts Medical Center, Senior Scientist at the US Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, and Professor, Clinical Research at the Sackler School of Graduate Biomedical Sciences at Tufts University. His research is mainly in the areas of epidemiology of CKD and CVD in CKD, controlled trials to slow the progression of CKD, clinical assessment of kidney function, assessment and improvement of outcomes in dialysis and transplantation, and clinical practice guideline development and implementation. Dr Levey is currently Program Director for an NIDDK-funded clinical research training program, "Clinical Trials, Epidemiology and Outcomes Research in Nephrology." He is also the Director of the Tufts Center for Guideline Development and Implementation and Editor of *American Journal of Kidney Disease*. Dr Levey is past Chair of the NKF's Task Force on Cardiovascular Disease in Chronic Renal Disease and served on KDOQI Work Group on Chronic Kidney Disease: Evaluation, Classification and Stratification, KDOQI Work Group on Hypertension and Antihypertensive Agents in Chronic Kidney Disease, and KDIGO Work Group on Acute Kidney Injury Guideline.

Dr Levey reported no relevant financial relationships

Miguel C Riella, MD, PhD, FACP, is a graduate of Federal University of Parana in Curitiba, Brazil and has undertaken his post-graduate training in the United States, first in Internal Medicine Residency at Mount Sinai Hospital in New York City and then Research Renal Fellowship at the University of Washington in Seattle, USA under the leadership of Prof Belding H Scribner, pioneer of chronic hemodialysis. Dr Riella's main interest has been on dialysis, particularly peritoneal dialysis and nutrition in uremia. More recently his research work has concentrated on the relationship of inflammation, uremia, nutrition and cardiovascular complications, and interventional nephrology. As part of his new Renal, Diabetes and Hypertension Research Center, he has recently established the Islet Cell Laboratory at Catholic University of Parana in Curitiba, Brazil for cell transplant in diabetic patients. Dr Riella has published several books in Portuguese and Spanish language in the area of nephrology and nutrition. His book *Principles of Nephrology and Electrolyte Disturbances* (Guanabara Koogan Group Gen, 2010) is on its 5th Edition. He has more than 150 publications and has given more than 600 lectures locally and internationally. He is a past Board member and executive committee member of the ISN and is currently the Chairman of the ISN-Interventional Nephrology Committee. Dr Riella is a member of the editorial board of several medical journals, including as Associate Editor of *Hemodialysis International* and International Editor of *Seminar in Dialysis* for Interventional Nephrology. He is also President and founder of Pro-Renal Foundation of Brazil (www.pro-renal.org.br), a non-for-profit organization dedicated to patient assistance, CKD prevention and education, and supporting research in kidney and metabolic diseases. The Foundation provides free medical care to more than 1800 renal patients through a multidisciplinary team of physicians, nurses, psychologists, social workers, and dietitians. The Foundation is maintained by donations of the community and receives no public funds. Dr Riella is the past-President of the International Federation of Kidney Foundations (IFKF) 2009-2011. He is also the co-chairman of World Kidney Day, a joint project of IFKF and and ISN. He is a member of the Executive Committee of KDIGO, National Academy of Medicine in Brazil, and the Academy of Medicine of Parana, Brazil. He has received many awards such as the International Distinguished Medal from the US NKF and Honorary Citizenship of the city of Curitiba and of the State of Parana in Brazil.

Advisor/Consultant: Abbott

Michael G Shlipak, MD, MPH, is Professor of Medicine, Epidemiology, and Biostatistics at University of California, San Francisco. Dr Shlipak obtained his MD degree from Harvard Medical School and his MPH from Harvard School of Public Health. His research program has been dedicated to understanding the causes and consequences of age-related kidney disease and to utilize novel biomarkers for the early detection of kidney damage and reduced kidney function. Along with his colleagues from the Cardiovascular Health Study and Health Aging and Body Composition study, Professor Shlipak has conducted the pioneering work to demonstrate with cystatin C the remarkable prognostic importance of impaired kidney function in elders. He coined the entity of "preclinical kidney disease" to describe the large population of elders with elevated cystatin C levels, but normal creatinine-based estimates of kidney function, who are at high risk for death and CVD.

The recent work from his research group has been dedicated to finding early markers of kidney injury in the urine that will precede any detectable loss in kidney function. They will study these urine biomarkers in several populations, including the ambulatory elderly, HIV-infected men and women, and in population-based studies. The group believes that these injury markers hold promise both for understanding how various exposures impact the kidney, and also to forecast future declines in kidney failure.

Dr Shlipak reported no relevant financial relationships

Haiyan Wang, MD, is Professor of Medicine at Peking University First Hospital. She is the current President of Peking University Institute of Nephrology and the Vice Director, Academic Committee, Peking University Health Science Center and Member, Academic Degree Committee, Peking University Health Science Center.

Professor Wang is very active in the academic area of national and international nephrology and internal medicine. She was the Vice President of Chinese Medical Association (1999-2009) and the President of Chinese Society of Internal Medicine (2000-2008), as well as the President of Chinese Society of Nephrology (1992-1998). She has also served as the ISN Councilor member (2004-2008), Executive Councilor of ISN (2006-2008) and is now Chair, East Asia committee of ISN GO (2004-present).

Dr Wang reported no relevant financial relationships

Colin T White, MD, FRCPC, completed his medical degree at the University of Ottawa, Canada and Pediatric Residency at the University of Western Ontario, Canada. His pediatric nephrology training took place at the University of Western Ontario and University of British Columbia. He is a Clinical Associate Professor in Pediatrics/Nephrology at the University of British Columbia and has a clinical appointment at BC Children's Hospital where in addition to an interest and participation in the CKD clinic, he is the Director of the Dialysis Program and is the Fellowship Program Director. Dr White was a work group member for the 2006 and 2007 Updated KDOQI Anemia Guidelines, and for the Canadian Society of Nephrology's Clinical Practice Guidelines for Anemia Management in 2007-2008; he is currently on the 2011-2012 CSN Workgroup revisiting these guidelines. He is the site Principal Investigator for the North American multicenter NIH-sponsored CKiDs trial and has particular research interests in hemodialysis and peritoneal dialysis as well as CKD management. His particular

areas of research interest include estimation of clearance, anemia protocol development, and translation of evidence into functional guidelines. He is active at the undergraduate medical school level and has coordinated the UBC Renal and Genitourinary Course for 1st year medical students for nearly a decade. He is currently the President of the Western Society of Pediatric Research and an invited member of the Renal Work Group for the World Health Organization's ICD-11 Code Revision.

Advisor/Consultant: Baxter Healthcare

Christopher G Winearls, MB, DPhil, FRCP, graduated in 1973 from University of Cape Town and as a Rhodes Scholar completed a PhD from University of Oxford in transplant immunology. Dr Winearls later pursued training in nephrology at the Hammersmith Hospital where he was part of the team that investigated the first clinical use of erythropoietin. Dr Winearls was appointed consultant in Oxford in 1988 and was Clinical Director 1995 to 2009. He has been Secretary and later Clinical Vice President of The Renal Association and an Editor of the *Oxford Textbook of Clinical Nephrology*. His research interests include myeloma kidney and autosomal dominant polycystic kidney disease, and has recently taken an interest in the new classification of CKD.

Dr Winearls reported no relevant financial relationships

KDIGO CHAIRS

Bertram L Kasiske, MD, is Professor of Medicine at the University of Minnesota, USA. He received his medical degree from the University of Iowa and completed his Internal Medicine residency and fellowship training in Nephrology at Hennepin County Medical Center where he is currently Director of Nephrology.

Dr Kasiske is former Deputy Director of the United States Renal Data System and former Editor-in-Chief of *American Journal of Kidney Diseases*. He has served as Secretary/Treasurer and on the Board of Directors of the American Society of Transplantation, and on the Organ Procurement and Transplantation Network/United Network of Organ Sharing Board of Directors, and the Scientific Advisory Board of the US NKF. He is currently serving on the Board of Councilors of the ISN and he is the Principal Investigator for a National Institutes of Health-sponsored, multicenter study of long term outcomes after kidney donation. Dr Kasiske is the Director of the Scientific Registry of Transplant Recipients and has over 160 scientific publications in major peer-reviewed journals, and 230 review articles, editorials and textbook chapters. Dr Kasiske is also a recipient of the US NKF's Garabed Eknoyan Award in 2003.

Advisor/Consultant: Litholink

Grant/Research Support: Bristol-Myers Squibb; Merck (Schering Plough)

David C Wheeler, MD, FRCP, holds an academic position in Nephrology (Reader) at University College London, UK and is an Honorary Consultant Nephrologist at the Royal Free Hospital. His research is focused on the cardiovascular complications of CKD and the role of vascular risk factors in progression of kidney damage. Dr Wheeler is a member of the International Steering Committee of the Study of Heart and Renal Protection (SHARP) and was UK National Coordinator for the trial. He is involved in several other randomized trials and observational studies involving patients with CKD.

Dr Wheeler is Co-Chair of KDIGO, having served previously on its Executive Committee and Board. He received an International Distinguished Medal from the US NKF in recognition of his contribution to guideline development. In the UK, he has been elected President of the Renal Association for the term 2012-2014.

Dr Wheeler has served on the editorial boards of *American Journal of Kidney Diseases* and *Journal of the American Society of Nephrology* and is presently Co-Editor for *Nephrology Dialysis Transplantation*.

Advisor/Consultant: Amgen

Honoraria: Abbott; Amgen; Fresenius; Otsuka; Shire

Travel Stipend: Amgen; Merck Sharp & Dohme; Shire

Grant/Research Support: Abbott; Genzyme

EVIDENCE REVIEW TEAM

Katrin Uhlig, MD, MS, is the Director, Guideline Development at the Tufts Center for Kidney Disease Guideline Development and Implementation, Boston, MA, USA, Associate Professor of Medicine at Tufts University School of Medicine, and a staff nephrologist at Tufts Medical Center. Dr Uhlig completed her training in internal medicine, nephrology, and rheumatology in Germany (Aachen University Hospital and Munich University Hospital) and the USA (Georgetown University Medical Center and Tufts Medical Center). Since 2001, she has been participating in or directing the evidence review for KDOQI and KDIGO guidelines. As Director of Guideline Development, Dr Uhlig has a substantial role in coordinating the ERT. She orchestrates and supervises the guideline development process and didactic curriculum that provides Work Group members with formal instruction on topics related to guideline development. As project director on individual guidelines, she directs and supervises the collection, evaluation, grading, and synthesis of evidence and the drafting and revisions of the final evidence report. She provides methodological guidance and training to Work Group members at meetings regarding topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. She provides nephrology expertise in the interpretation and review of guideline recommendations and evidence reports. In this capacity,

Dr Uhlig possesses unique knowledge as a methods expert in evidence synthesis and critical literature appraisal in the domain of nephrology.

In 2005, she co-chaired the KDIGO Evidence Rating Group to develop a consensus on grading of KDIGO guidelines and also co-chaired the KDIGO Consensus Conference on Guideline Methodology in October 2007. From 2006 to 2007, she served as Co-Editor of *American Journal of Kidney Diseases*. Her teaching and research focus includes evidence-based medicine, systematic review, clinical practice guideline development, and critical literature appraisal. Dr Uhlig lectures on guideline topics and is a co-instructor of an annual course on meta-analysis in the Master of Science Program at the Sackler School of Graduate Biomedical Sciences at Tufts University.

Dr Uhlig reported no relevant financial relationships

Dana C Miskulin, MD, MS, is Assistant Professor of Medicine at Tufts University School of Medicine, Boston, MA, USA. She completed a fellowship in Clinical Care Research and participated in the conduct of systematic reviews and critical literature appraisals for this guideline. Her primary research interests are in comparative effectiveness research in dialysis patients, BP treatment in dialysis patients, and autosomal dominant polycystic kidney disease.

Dr Miskulin reported no relevant financial relationships

Amy Earley, BS, is a project coordinator at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA, USA. She is key in coordinating the guideline development activities within the ERT, especially in the development of the evidence reports for all guidelines. Ms Earley also heads the actual evidence review, which includes running searches, screening, data extraction, drafting of tables and methods sections, proofing of guideline drafts, and critical literature appraisals. She participates in the conduct of research projects at the Center and actively collaborates with other members of the Center on independent research topics and manuscript submissions.

Ms. Earley reported no relevant financial relationships

Shana Haynes, MS, DHSc, is a research assistant at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA, USA. She participates in all aspects of evidence review and guideline development. She screens abstracts and articles, extracts data, and assists in the drafting and editing of evidence tables. Dr Haynes also assists in the development of clinical practice guidelines and conducts systematic reviews and critical literature appraisals.

Dr Haynes reported no relevant financial relationships

Jenny Lamont, MS, is a project manager and medical writer at the Tufts Center for Kidney Disease Guideline Development and Implementation in Boston, MA, USA. She participates in all aspects of evidence review and guideline development, assists in the preparation of talks and manuscripts, and edits KDIGO draft guidelines currently in progress.

Ms. Lamont reported no relevant financial relationships

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Adeera Levin, MD, FRCPC, Work Group Co-Chair
Paul E Stevens, MB, FRCP, Work Group Co-Chair

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Irina Nikolova, Valentina Petkova, Jasmina Tencheva, Niko Benbasat, Julian Voinikov & Nikolai Danchev

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PHARMACEUTICAL BIOTECHNOLOGY

METAMIZOLE: A REVIEW PROFILE OF A WELL-KNOWN "FORGOTTEN" DRUG. PART II: CLINICAL PROFILE

Irina Nikolova, Valentina Petkova, Jasmina Tencheva, Niko Benbasat, Julian Voinikov, Nikolai Danchev
Medical University of Sofia, Faculty of Pharmacy, Sofia, Bulgaria
Correspondence to: Irina Nikolova
E-mail: nikolova60@gmail.com

ABSTRACT

Part I of this review provided the pharmaceutical and non-clinical profile of metamizole, a non-narcotic analgesic with excellent analgesic and antipyretic effects. Metamizole is banned drug in many countries (United States, Japan, Australia, part of the European Union and nearly 30 other countries) for more than 40 years, where it is completely unknown or forgotten, while it is still freely available over-the-counter drug in many other countries, including Bulgaria. The drug's availability in oral and parenteral preparations has allowed its use in a range of clinical situations as monotherapy or in combination. It is known with different generic names, like metamizole, dipyrone, noramidopyrine, sulpyrine, novaminsulfon, methylmelubrin, etc. and marketed under hundreds of brand names worldwide. The objective of Part II of this review is to provide up-to-date scientific evidence for clinical safety and efficacy of the drug, as well as the place of metamizole in Bulgarian pharmaceutical market.

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Keywords: metamizole, NSAIDs, agranulocytosis, clinical trials, safety, efficacy

Overview of safety

The safety of metamizole has been subject of many contradictory debates provoked by the fact that metamizole is a widely used OTC medicine in some countries, while in others it is forbidden because of the risk of agranulocytosis. The publication of individual cases of agranulocytosis in the medical literature and the lack of a full overview of non-clinical and clinical characteristics of the drug provoked our team to provide this review. Metamizole sodium possesses the seldom, but life-threatening risk of agranulocytosis and anaphylactic shock. The onset of agranulocytosis is unpredictable, and fatal cases have occurred following short-term or intermittent use as well as after long-term administration; a hypersensitivity mechanism is speculated (7, 46, 93). Hemolytic anemia and aplastic anemia have been reported during metamizole administration. Virtually all adverse reactions to pyrazolones are non-dose-related (70). Metamizole does not cause significant adverse gastrointestinal effects and does not impair renal function in otherwise healthy subjects, effects typical for other NSAIDs (79); however, prolonged use may prove to be toxic to the kidneys. Furthermore, skin rashes and asthma can also be caused due to allergy (51).

Agranulocytosis

Agranulocytosis is a rare and serious disease often caused by drugs. Agranulocytosis is a hematologic syndrome of acute onset in which the numbers of circulating neutrophils decrease, often abruptly and to undetectable levels, leading to a markedly increased susceptibility to bacterial infection, serious local infection or sepsis, and a risk of mortality estimated at approximately 5 %. Typical signs of agranulocytosis are inflammation of the mucosa, sore throat, fever (including an unexpected, persistent, or recurrent course), increased erythrocyte sedimentation without or with only slight lymph node enlargement, or an unexpected but unspecific deterioration of the general health state. In patients currently receiving antibiotics symptoms may be minimal. In Europe, the annual incidence of drug-induced agranulocytosis is between 3.4 and 5.3 cases per million population, while in the USA the rates range from 2.4 to 15.4 per million per year (6).

The most serious side effect of metamizole is the negative effect on the bone marrow. There are various studies from different countries and populations that have evaluated a possible association between metamizole and blood dyscrasia. Some genetic mechanisms might be involved in metamizole-related agranulocytosis. Metamizole sodium has to be withdrawn immediately when signs of agranulocytosis or thrombocytopenia occur.

Studies with high incidence. The removal of metamizole from the USA market in 1977 was based on two studies that found an incidence of metamizole-induced agranulocytosis in the range of 0.79 %–0.86 %, with a mortality rate of 0.57 % (28, 44). In Sweden, all metamizole-containing products were first withdrawn in March 1974 due to an estimated incidence of agranulocytosis of 1 in 3000 patients. After registration of metamizole in Sweden, an incidence of 700 per 1 million users was claimed to be found. Therefore, in September 1995, metamizole was re-approved based on the results from the International Agranulocytosis and Aplastic Anaemia Study (IAAAS) (45) and then later, again suspended in April 1999 based on pharmacy sales data and spontaneous reporting of blood dyscrasias in Sweden. Hedenmalm and Spigset (43) estimated that the risk of agranulocytosis related to metamizole

appears to be at least 1:1439 prescriptions, a much higher figure than previously estimated. Ninety-two percent of the cases of blood dyscrasias occurred during the first 2 months of treatment. Additional risk factors were identified in 36 % of the patients. In addition, they reported that agranulocytosis was not the only manifestation of metamizole-induced blood dyscrasias; in some of the cases all three haematopoiesis were affected according to bone marrow sample findings. In these cases, the outcome was significantly poorer. In particular, the Swedish study has reignited the question of a genetic diversity with regard to this adverse effect. Backstrom et al. (10) making certain assumptions, calculated that the risk of metamizole-induced agranulocytosis would be approximately 1:31000 metamizole-treated inpatients and 1:1400 metamizole-treated outpatients.

Studies with low incidence. The IAAAS (45) found a reported overall incidence increase by metamizole use of 1 case per million users; however, it showed a wide regional variability of the incidence. As a part of this study, data collection from Sofia (population 1142000), Bulgaria, was extended from 1982 until 1987, due to very few cases. During that period 18 cases of agranulocytosis were compared with 106 controls; 9 cases and 27 controls were exposed to metamizole, for a multivariate RR estimate of 1.7 (95 % confidence interval 0-4-7-3). Sales of products containing metamizole rose steadily between 1982 and 1987, but the annual incidence of agranulocytosis was stable (3–4 per million). Authors concluded that there is no evidence of an increased risk of agranulocytosis related to the use of metamizole in Bulgaria and certainly not one as great as that found in Germany and Spain (95).

In a pharmacovigilance, prospective 12-month study in Poland involving 24 of 25 haematology centres that provide specialist care for the 30 million adults in Poland, revealed 21 cases of agranulocytosis, 48 of aplastic anaemia, 15 of neutropenia, and 11 of pancytopenia. Of these cases, three (2 agranulocytosis; 1 aplastic anaemia) were judged as being possibly related to metamizole. Crude estimates of the rate of agranulocytosis and aplastic anaemia associated with metamizole were 0.16 and 0.08 cases/million person-days of use, respectively. Ongoing national safety surveillance in Poland showed that, despite the possibility of drug-induced blood dyscrasias with metamizole, the risk is very low (12). Another study from Poland found no case of agranulocytosis related to metamizole use despite a consumption of over 110 million tablets per year (59).

A study performed in Bangkok, indicated that the incidence of agranulocytosis in the ambulatory population is exceedingly low, at 0.7 per million per year (84).

In a case control study from Spain, Ibanez et al. (46) calculated a rate of 0.56 cases of metamizole-induced agranulocytosis per 1 million inhabitants per year, with a lower risk if metamizole was used for a short period of time and at low doses of 1 g/day to 2 g/day. No association between aplastic anemia and the use of metamizole was found.

Hamerschlak et al. (42) and Maluf et al. (60) reported overall agranulocytosis and AA incidence rate of 0.38 and 1.64 cases per 1 million inhabitant–years, respectively in the LATIN study. Despite that the authors reported no statistically significant association, metamizole was the drug most commonly inducing agranulocytosis or AA in this multinational case–control study, designed to identify risk factors for agranulocytosis and AA and to estimate the incidence rate in Brazil, Argentina and Mexico.

In Bulgaria the risk of agranulocytosis is accounted to be 0.037 to 1 million persons (94).

In conclusion, the incidence of metamizole-induced agranulocytosis has varied geographically and from study to study. In our point of view, it is mostly due to differences in study methodology, patterns of use, terms of dose, duration and concomitant medications; however, some genetic predisposition could not be excluded, since metamizole appears to be strongly associated with agranulocytosis in certain regions of the world, but for reasons that are not understood, much less so in others. In 1996, a paper published by Vlahov et al. (96) revealed significant differences between the agranulocytosis patients and the healthy population in the human lymphocyte antigen (HLA) allele frequencies, and in the degree and the frequency of chromosome aberrations. Five patients with metamizole-induced agranulocytosis were included in the study. A higher frequency of the HLA24 antigen and a lower frequency of the DQA1*0501 allele were evident for the ex-agranulocytosis patients as compared to the controls (11 % versus 57 %, respectively). In the patients exposed to metamizol, an A24-B7 haplotype was found with a frequency higher than that in the non-exposed patients and the reference group. The HLA-DQwl antigen and metamizol-related agranulocytosis were evidently associated in all cases (5/5; 100 %) in contrast to the patients not exposed to metamizol and the controls. The HL-A2 antigen was absent in four of the five metamizol-associated agranulocytosis cases (20 %), while in the control group it was present in 56 % of the patients. The degree of structural rearrangements (0.62 % ± 0.2 %) and the frequency of chromosome breakages (7.75 % ± 0.68 %) in agranulocytosis patients were higher than those in the healthy population (0.3 % ± 0.12 %, $P < 0.05$ and 1.42 % ± 0.27 %). The abnormalities affected predominantly Chromosomes 1(1p13), 2(2p12) and 5(5p12). No differences were found between the agranulocytosis patients and the healthy population when considering the haemoglobin subtypes, ABO-and RH-blood groups, glucose-6-phosphate dehydrogenase activity, and the rates of slow and rapid acetylators.

There is no doubt that metamizole can induce agranulocytosis and other serious blood dyscrasias that justifies the ban on the drug in some countries, but in many others, including Bulgaria, enormously high consumption of metamizole-containing products does not correlate with steady and low incidence of agranulocytosis.

Anaphylaxis

Anaphylactic shock which has resulted in fatalities has been reported with metamizole (incidence of 1 in 5000 administrations) (14, 30). Anaphylactic reactions may develop immediately following intake/injection or hours later (49). Immediate hypersensitivity reactions are presumably IgE-mediated and clinically characterised by laryngeal and angioneurotic oedema, generalised urticaria, bronchospasm, vasomotor collapse, and death. In a study of a population of 14.5 million in Holland, for two years an incidence of drug induced anaphylaxis of 3.7 per million annually was found. The excess mortality estimate associated with metamizole use was 0.22 per 100 million (93). Risk factors for severe metamizole-induced allergy are: allergies/intolerability to metamizole and other non-opioids and bronchial asthma.

Severe anaphylactic reaction without any cutaneous symptoms after IV infusion of metamizole has been reported (87, 100). Allergic reaction after previous intake of metamizole without side effects has also been described (50, 52).

Cutaneous reactions

A variety of cutaneous reactions have been attributed to metamizole, including nonspecific skin rash, urticaria, morbilliform, scarlatiniform, erythematous, bullous, purpuric, exudative, fixed drug eruption, and toxic epidermal necrolysis (7, 68). Diaphoresis has been reported following oral and parenteral metamizole. Brenner et al. (22) reported three cases of pemphigus vulgaris believed to be induced or exacerbated by metamizole. All three of these patients had histologic evidence of suprabasal acantholysis and intercellular deposits of IgG. Gonzalo-Garijo et al. (39) reported an acute generalized exanthematous pustulosis in a 58-year-old man. The patient had been operated 48 h earlier for a ruptured tendon with mepivacaine and bupivacaine, and concurrent medications included cefazoline, metamizole, and enoxaparin. He had no known allergies, no history of drug or food reactions, nor contact hypersensitivity. Cefazoline and metamizole were discontinued, and the eruption resolved without sequelae after 1 week of treatment with oral dexclorpheniramine and prednisone, with emollients. Three months after the adverse reaction, only metamizole was positive in patch tests.

In 1973 the Boston Collaborative Drug Surveillance Program noticed that drug rash occurred more frequently in Israeli than in US patients. At that time 41.6 % of Israeli patients received metamizole, whereas in the USA metamizole was not in use. The risk of metamizole rash was estimated to be 2.4 % of the exposed patients. However, it was recognised as being caused by the drug in only one-third of the affected cases. In most cases metamizole rash was mild. Rarely, it may also be part of a generalised drug reaction. Pyrazolone-induced urticaria/angio-oedema can also be a manifestation of a pseudoallergic reaction, probably occurring via COX inhibition (57). Asero (9) has shown that three out of 34 patients (9 %) with a history of pyrazolone-induced urticaria/angio-oedema had such reactions after ASA administration.

The more serious life-threatening cutaneous complication is that of Stevens–Johnson's syndrome and toxic epidermal necrolysis (Lyell's syndrome). Cases have been reported following the use of pyrazolones. A large population-based case-control study covering about 120 million inhabitants of France, Germany, Italy, and Portugal was conducted between the years 1989 and 1992 to quantify the risks associated with the use of specific drugs within the week preceding the first manifestation of the disease. Seven of the 245 cases (3 %) and 1 % of the controls used pyrazolones. The association between both pyrazolones as a group and metamizole and these conditions, according to the multivariate relative risk, is statistically not significant (77).

Respiratory effects

Patients with analgesic intolerance commonly exhibit asthma attacks in case of allergic reactions to metamizole. Bronchospasm has been described following administration of metamizole (7, 51). Current evidence indicates that COX inhibition and increased production of cysteinyl leukotriene plays an important part in these obstructive reactions. A cross-reaction has been shown between NSAIDs, including metamizole, in the precipitation of asthmatic attacks. The incidence and risk estimates of the asthma syndrome induced by pyrazolones are unknown.

In a one-centered, non-randomized, non-comparative, open-labeled study, 15 normal healthy volunteers and 15 COPD patients were treated with metamizole as an oral suspension at a dose of 20 mg/kg. All of the normal healthy volunteers and COPD patients, except one in the COPD group, completed the study without any adverse events during the study. An adverse event, characterized by dyspnea, wheezing and cough, occurred in one COPD patient 45 min after metamizole intake. The patient recovered totally after treatment with bronchodilators. The relation between drug exposure and the bronchospasm was estimated as ''possible''. The authors conclude that metamizole can be safely used in such patients when indicated (41).

Gastrointestinal effects

Metamizole has favorable gastric tolerability (81). Nausea, vomiting, gastric irritation, and xerostomia have been described only with high doses oral and parenteral metamizole administration.

Cardiovascular findings

Hypotension has been reported following parenteral and oral administration of metamizole (40). This is not necessarily a symptom of drug intolerance, since it is observed as a procedure-related (not drug-related) side effect.

Renal findings

Deterioration of the renal function (proteinuria, oliguria, anuria) were rarely observed. The occurrence of acute interstitial nephritis is mostly a consequence of drug abuse and rare enough to still be subject of single case reports (16).

A summary of adverse events associated with metamizole, by organ systems, is given in **Table 1**. According to the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, the number of adverse effects registered in the years 1978–2009 (March) was 14441 for metamizol and 67581 for paracetamol (101).

In conclusion, life threatening reactions, including Stevens–Johnson's syndrome, toxic epidermal necrolysis, anaphylaxis, and agranulocytosis are extremely rare. Mild allergic reactions may deteriorate or generalize and may be associated with urticaria, severe angio-oedema, bronchospasm, arrhythmia, hypotension, and cardiovascular shock.

Overdose

The incidence of acute toxicity of metamizole is very low. Clinical manifestations are not immediately evident and an observation period of 8 h is warranted.

A retrospective review of prospectively collected poison center data on acute exposure to metamizole over a three-year period was published by Bentur and Cohen (15). A total of 243 records (204 asymptomatic and 39 symptomatic) met the inclusion and exclusion criteria. Median age was 17 y (4 m–83 y), median amount 5 g (250 mg–45 g), and median time to consultation was 2 h (5 min–48 h). Toxic events (49) occurred in 39 (16 %) patients; 57 % of these were gastrointestinal and all were mild. Suicidal patients (n = 99) ingested significantly larger amounts, as did patients with gastrointestinal symptomatology. No agranulocytosis was reported. Metamizole overdose was associated with mild, mainly gastrointestinal toxicity.

Peces and Pedrajas (73) reported a case of non-oliguric acute renal failure and abortion following the ingestion of an overdose of 11.5 g metamizole in an otherwise healthy 14-year-old girl. The mechanism of abortion in this case is unknown, however due to high dose, part of the drug probably entered the fetal tissues, and might have induced the abortion by direct toxic effect. Renal damage probably occurred as a result of toxic tubular necrosis, since it was not reversible despite volume repletion. In addition, she also presented microhaematuria and proteinuria, and renal function was rapidly reversible following steroid therapy. Therefore, on the basis of the time course of the disease, the authors speculated that the renal damage in this patient might be due to a toxic effect producing a tubular lesion and interstitial nephritis. Berruti et al. (16) reported a case of acute renal failure due to acute interstitial nephritis, following the ingestion of a self-prescribed megadose (30 g over 2 days) of metamizole in an otherwise healthy 45-year-old man. Mild gastrointestinal distress was the most commonly occurring adverse effect (57 %), in a series of 39 patients who were symptomatic following metamizole overdose ingestions, and included vomiting (n = 16), nausea (n = 3), and abdominal pain (n = 9). The median amount of metamizole ingested was 7.5 g (range of1 g to 25 g) (15).

De Giovanni and d'Aloja (27) reporetd a fatal suicidal intoxication in a 56-year-old man after ingestion of an unknown amount of baclofen and metamizole. The toxicological analyses revealed high concentration of 4-methyl-aminoantipyrine in blood and urine. Circumstantial evidence suggests the deceased had probably ingested acetylsalicylic acid, laxatives, terazosin and about 8 g of defibrotide, too. Therefore, they were not considered a factor in the cause of death.

Sinus tachycardia has been reported in 8 % of metamizole overdoses (70). Ataxia, lethargy, stupor, vertigo, seizures, agitation, coma, hallucinations, and paresthesias may occur with severe overdose. CNS depression is less frequent with metamizole overdose. Headaches and weakness were reported in 7 and 11 patients (n = 39), respectively, following metamizole overdose ingestions. Toxic gastroenteritis, with nausea, vomiting, and epigastric pain, is common, reported in 45 % of metamizole overdose cases. Gastric ulceration may occur as well.

Forrester (35) repoted no death cases in a survey of 81 metamizole exposures reported to poison centers in Texas during a period from 1998 to 2004. Of 81 metamizole exposures, 52 (64 %) were isolated and 29 (36 %) were non-isolated. Twenty-two percent (11/51) of isolated cases were intentional, while 59 % (17/29) of non-isolated cases were intentional. Of those cases with a known medical outcome, the medical outcome was no adverse clinical effect for 76 % (16/21) of isolated exposures and 42 % (8/19) of non-isolated exposures. The specific adverse clinical effects reported for isolated exposures were primarily neurological (n = 6), gastrointestinal (n = 4), and dermal (n = 3). The most frequently reported treatment for isolated exposures was some form of decontamination (n = 11). Although the majority of isolated and non-isolated metamizole exposures were adults, a higher proportion of isolated exposures involved children less than 6 years of age, while a higher proportion of non-isolated exposures involved older children. Non-isolated exposures were significantly more likely to be intentional, particularly, suspected suicide attempts.

Metamizole has been shown to be a very effective antipyretic and is capable of causing hypothermia when an overdose is given (61).

Treatment. Treatment should include symptomatic and supportive measures for respiratory and cardiovascular function. Gastrointestinal decontamination (i.e., activated charcoal) can be considered if 5 g or more have been ingested and if the patient presents within 1 h after exposure. Routine hematological follow-up does not seem to be warranted (15). In 81 reported metamizole exposures in Texas (from 1998 to 2004) surveyed by Forrester (35), specific adverse clinical effects were recorded for 12 (30.8 %) of the cases. The highest proportion of cases had neurological effects, followed by gastrointestinal and dermal effects. The most frequently reported specific adverse clinical effect was vomiting. No specific treatment was listed for the majority of cases. The most frequently reported type of treatment was decontamination, most frequently by administration of charcoal. Treatment other

TABLE 1

Summary of adverse events associated with metamizole, by organ systems

System	Adverse effects
Immunological	Hypersensitivity, anaphylaxis
Blood	Aplastic anemia, agranulocytosis
Skin	Nonspecific skin rash, urticaria, morbilliform, scarlatiniform, erythematous, bullous, purpuric, exudative, fixed drug eruption, diaphoresis, toxic epidermal necrolysis, Stevens–Johnson's syndrome
Respiratory	Bronchospasm
Gastrointestinal	Nausea, vomiting, gastric irritation, xerostomia
Cardiovascular	Hypotension
Renal	Deterioration of the renal function

TABLE 2

Registered metamizole-containing products in Bulgaria (13)

Trade name	Status/MAH	Strength
Products containing metamizole sodium as an active ingredient as ATC code: N02BB02		
Algozone	OTC/Ozone Laboratories	500 mg tabl. (adults and children over 15)
Analgin	OTC/Sopharma	500 mg tabl. (adults and children over 10)
Analgin Chin	OTC/Sopharma	250 mg film coated tabl. (adults and children over 10)
Dialgin	OTC/Himax	1000 mg powder for oral solution (adults and children over 16)
Dialgin	OTC/Himax	500 mg powder for oral solution (adults and children over 14)
Dialgin Junior	OTC/Himax	250 mg powder for oral solution (children over 7)
Hexalgin	OTC/Hexal	500 mg/mL oral solution (adults and children over 3 months)
Medphalgin	OTC/Sevex	500 mg tabl. (adults and children over 16 kg)
Angetop	OTC(*Rx*)/Inbiotech	500 mg tabl. (OTC – adults and children over 12; Rx – children over 7)
Freshalgin	OTC(*Rx*)/Adipharm	500 mf tabl. (OTC – adults and children over 15; Rx – children over 7)
Proalgin	OTC(*Rx*)/Chaikapharma	500 mg tabl. (OTC – adults and children over 15; Rx – children under 15)
Analgin	*Rx*/Sopharma	500 mg/mL solution for injection (adults and children over 15)
Metamizole sodium-Vetprom	*Rx*/Vetprom	500 mg/mL solution for injection (adults and children over 15)

Metamizole combinations				
Trade name	**Status/MAH**	**Active ingredients**	**Strength**	**ATC code**
Benalgin	OTC/Actavis	*metamizole sodium, caffeine, thiamine*	500 mg/50 mg/38.75 mg tabl. (adults and children over 12)	N02BB52
Paracofdal	OTC/Unipharm	*metamizole sodium, caffeine, codeine, paracetamol*	30 mg/20 mg/300 mg/200 mg tabl. (adults and children over 14)	N02BB52
Spasmalgon	OTC/Actavis	*metamizole sodium, pitofenone, fenpiverine*	500 mg/5 mg/0.1 mg tabl. (adults and children over 9)	A03DA02
Spasmalgon	*Rx*/Actavis	*metamizole sodium, pitofenone, fenpiverine*	500 mg/2 mg/0.02 mg/mL amp. (adults and children over 15)	A03DA02
Tempalgin	OTC/Sopharma	*metamizole sodium, triacetonamine-4-toluensulfonate*	500 mg/20 mg film-coated tabl. (adults and children over 15)	N02BB72
Sedalgin-Neo	*Rx*/Balkanpharma Dupnitza	*metamizole sodium, paracetamol, phenobarbital, caffeine, codeine*	300 mg/15 mg/150 mg/50 mg/10 mg tabl. (contraindicated for children, age not mentioned)	N02BE71

than decontamination was reported in only 5 of the cases.

Fatal cases. The absolute risk of mortality associated with metamizole appears to be similar to that for acetaminophen and substantially lower than the risk associated with other NSAIDs, like aspirin and diclofenac. The estimated excess mortality due to agranulocytosis, aplastic anemia, anaphylaxis, and serious upper gastrointestinal complications was 185 per 100 million for aspirin, 592 per 100 million for diclofenac, 20 per 100 million for acetaminophen, and 25 per 100 million for metamizole. The estimates were largely influenced by the excess mortality associated with upper gastrointestinal complications, an adverse effect more commonly associated with the use of aspirin and diclofenac than with the use of metamizole or acetaminophen. While the absolute values of the excess mortality varied according to patient age and history of peptic ulcer disease, the disparity in estimates between the agents remained (5, 54).

Contraindications, precautions and warnings

Metamizole is contraindicated in:

- Blood dyscrasias;
- Bone marrow suppression;
- Hypersensitivity to metamizole;
- Hypersensitivity (immunologic-based) to aspirin or other nonsteroidal anti-inflammatory drugs (e.g., symptomatic response of rhinitis, urticaria, asthma);
- Acute intermittent hepatic porphyria;
- Myeloic function disorders or hemopoietic system diseases;
- Children below 7 years of age.

Precautions:

- Cardiac conditions, including hypertension, aggravated by fluid retention and oedema;
- Glucose-6-phosphate dehydrogenase deficiency;
- History of gastrointestinal ulceration, bleeding, or perforation;
- Infection, pre-existing;
- Liver dysfunction;
- Porphyria;
- Renal dysfunction;
- Pregnancy and lactation.

Long-term safety:

Regarding the clinical experience with respect to the long-term safety of metamizole treatment, it has to be considered that the clinical studies on the efficacy and safety of metamizole exhibit substance-specific safety problems of long-term treatment. Blood dyscrasias (agranulocytosis, thrombocytopenia, aplastic anemia) have been reported. As mentioned already, metamizole has been used for almost 90 years (since 1922) in the treatment of fever and pain, and is, hence, a product with long-term marketing experience. Different opinions exist on the adverse event profile of metamizole. There is no doubt that the life-threatening adverse event of agranulocytosis can be related to metamizole. However, the appearance of this event depends on the dose and time of treatment. The clinical data support the view that during short-term treatment the incidence is low and even smaller than with other NSAID (32).

Overview of efficacy

Since its introduction in 1922, metamizole has been widely used as an effective analgesic and antipyretic drug. The antipyretic action of metamizole was one of the earliest observations that were made with this compound. The claimed efficacy in pain derives from the long-term therapeutic experience.

Therapeutic indications

1. Pain of different origin: headache, toothache, neuralgia, neuritis, myalgia, injuries, burns, postoperative pain, "phantom" pain, cancer pain
    a. Dysmenorrhea
    b. Abdominal colics
    c. Renal colics
    d. Biliary colics
2. Fever – as an antipyretic in the combined treatment of acute upper respiratory tract infections, tracheitis, tracheobronchitis, infectious diseases (flu, measles, varicella, etc.).

Pain

Pain is a common complaint of patients and its appropriate management is medical precept. Metamizole is indicated in the treatment of pain of various origin and intensity: toothache, headache, arthralgia, neuralgia, myositis, mild to moderate visceral pain, pain after surgery and trauma, pain associated with neoplastic diseases, colic pain etc. Single-dose metamizole appears to be of similar efficacy to ibuprofen 400 mg and other analgesics, as frequently used in the treatment of moderate to severe postoperative pain. In a meta-analysis, 15 studies were included; 8 used placebo and 7 used an active control (oral dexketoprofen 12.5 mg or 25 mg, oral ketorolac 10 mg, intramuscular pethidine 100 mg or ketorolac 30 mg, intravenous tramadol 100 mg or rectal suprofen 300 mg). In 5 trials (288 patients) the mean response rate (proportion of patients with at least 50 % pain relief) for single dose oral metamizole 500 mg was 73 % (range of 54 % to 87 %) and with placebo it was 32 % (19 % to 41 %) in moderate to severe postoperative pain over 4–6 hours. In 2 studies (113 patients) the response rate with oral metamizole 1 g was 69 % (61 % and 77 %) and with placebo it was 20 % (11 % and 25 %). In one study (70 patients) the response rate with intramuscular metamizole 2 g was 74 % compared to 46 % in the placebo group. The response rates in the active-controlled trials were similar to those reported in the placebo-controlled trials. The commonest adverse effects were somnolence, gastric discomfort, and nausea (31, 33).

In a randomised, double-blind multi-center study, 253 patients who had undergone extraction of the lower third molar, metamizole 2 g was superior to ibuprofen 600 mg. Metamizole 1 g and ibuprofen 600 mg showed similar therapeutic effect.

No serious adverse effects developed and none of the patients had to leave the study for this reason (74).

The objective of the study of Tulunay et al. (92) was to evaluate the analgesic effectiveness of metamizole, when given before removal of nasal packing in patients undergoing septoplasty (n = 38) in a placebo-controlled, randomised design. Metamizole 1 g IM was found to be effective in lowering initial pain intensity and in reducing it during the first 10 min after removal.

In a survey of postoperative pain treatment in 348 children 3–14 years of age, Baños et al. (11) determined that metamizole was the most prescribed drug, followed by propyphenazone, paracetamol, and codeine. The total daily dose of metamizole ranged between 1.6 g and 3.4 g.

In a prospective, randomized, double-blinded study, Rawal et al. (76) compared the analgesic efficacy of three drugs: tramadol 100 mg every 6 h, metamizole 1 g every 6 h, and paracetamol 1 g every 6 h in 120 patients scheduled to undergo ambulatory hand surgery with regional anesthesia. At discharge, oral analgesic tablets were prescribed. Tramadol was the most effective analgesic. However, the incidence of side effects was also increased with tramadol. Metamizole and acetaminophen provided good analgesia in about 70 % and 60 % of patients, respectively, with a decreased incidence of side effects.

Steffen et al. (89) investigated the analgesic combination of metamizole and diclofenac after trauma surgery with respect to the postoperative opioid consumption (via patient-controlled analgesia [PCA]) in the first 24 h after surgery, and the reduction of pain in the immediate postoperative period. In a double-blind randomized placebo controlled study, 48 patients received either metamizole (three doses of 1 g intravenously) and diclofenac (two doses of 100 mg suppository) or placebo, beginning immediately preoperatively and repeated postoperatively. All patients were allowed to order levomethadone from a PCA-pump for 24 h after surgery. The patients receiving verum had significantly less pain at all points in time except for 2 h and ordered a significantly lower cumulated dose of levomethadone during the first 24 h postoperatively than placebo-treated subjects (opioid-sparing effect after 24 h: −74 %). There were no significant differences in the incidence of side effects between the two groups. Perioperative application of metamizole and diclofenac results in better pain relief and significantly lowers opioid requirements in patients after minor trauma surgery.

Repeated doses of metamizole to 4 g per 24 h were identical in efficacy to 4 g of IV paracetamol after breast surgery with regard to analgesia achieved, opioid-rescue consumption, and patient satisfaction. Furthermore, it has been shown that combining an NSAID such a ketoprofen with metamizole increases the analgesic efficacy. Although the utilisation of metamizole as a peri-operative analgesic is not as well studied, there is a considerable clinical experience with its use as a component of multi-modal analgesia in countries where it is registered and its use widespread (83).

Perioperative metamizole, combined with opioids, provides effective analgesia of improved quality in postoperative pain treatment. In a double-blind, randomised, placebo-controlled trial the analgesic effect of perioperative high-dose metamizole infusion was examined in 155 patients undergoing orthopaedic or trauma surgery. Metamizole 5 g was given intravenously within 1 h, starting 30 min before the end of surgery. Quality of analgesia was improved with a significant reduction in the visual analogue scores (VAS) ($P < 0.006$) and the doses of opioids required ($P < 0.0001$), with no additional side effects. This trial showed a highly significant reduction of the first pain score after arrival in the recovery room in the metamizole group, with a significant reduction of subsequent requirements for rescue analgesia by opioid injection (21). The fact that typical toxic effects of NSAIDs such as compromised renal, hepatic and gastrointestinal function do not occur with metamizole use and as the risk of agranulocytosis linked to its use is extremely low, the substance offers advantages over NSAIDs.

Cesarean pain. Cesarean section is one of the most common operations. An open prospective study was conducted on women who had a cesarean section with epidural analgesia, during two consecutive periods of 3 months each. In the first group of 109 women, an oral solution of 1 g metamizole was allowed every 4 h, upon patient request. Patients requesting additional analgesia were administered a tablet of 30 mg immediate-release morphine sulfate. In the second group of 90 women, the same protocol was used; however, oral morphine was the drug of choice and metamizole was used for rescue analgesia. The results showed duration of analgesic effect of metamizole – 6.5 h, and the satisfaction score – 90. The duration of analgesic effect of oral morphine was 5.05 h and the satisfaction score was 83.7. Overall, patients in both groups requested only 25 % of the permissible dosage of analgesia. Oral analgesia following cesarean section provides satisfactory pain relief, is easily administered, and is a substantially less costly alternative to the new pain treatment technologies currently in use (48).

Headache and migraine. In 417 patients with moderate episodic tension-type headache the efficacy and safety of oral single doses of 0.5 g and 1 g metamizole versus 1 g acetylsalicylic acid (ASA) was assessed in a randomized, double-blind, placebo- and active-controlled, parallel, multicentre trial (62). Treatment arms were metamizole 0.5 g (n = 102), metamizole 1 g (n = 108), ASA 1 g (n = 102), and placebo (n = 105). The analgesic efficacy of 0.5 g and 1 g metamizole vs. placebo was highly statistically significant (a = 0.025; one-sided) for sum of pain intensity differences, maximum pain intensity difference, number of patients with at least 50% pain reduction, time to 50% pain reduction, maximum pain relief and total pain relief. A trend towards an earlier onset of a more profound pain relief of 0.5 g and 1 g metamizole over 1 g ASA was noticed.

All medications including placebo were almost equally safe and well tolerated. Twenty-two out of 28 patients assessed drug-related, mild to moderate adverse events. There were 4 in the 0.5 g metamizole group, 5 in the 1 g metamizol group, 6 in the 1 g ASA group, and 7 in the placebo group. Dyspepsia was the most frequent drug-related adverse event (16 patients). The authors concluded that metamizole showed slight advantages over ASA with regard to efficacy and safety.

In 2002, Bigal et al. (17, 18) presented two randomized, placebo-controlled and double-blind studies evaluating the efficacy of metamizole in patients that sought emergency room assistance with the complaint of acute migraine or acute episodic tension-type headache. In the first study, a small double-blinded, randomized, placebo-controled trial, metamizole successfully aborted pain in episodic tension-type headache. Sixty patients were randomized to receive placebo) or 1 g metamizole. The patients receiving metamizole (n = 30) showed a statistically significant improvement ($P < 0.05$) of pain compared to placebo up to 30 min after drug administration. There were statistically significant reductions in the recurrence (metamizole = 25 %, placebo = 50 %) and use of rescue medication (metamizole = 20 %, placebo = 47.6 %) for the metamizole group (17).

In the second study, Bigal et al. (18) studied 86 patients during an acute migrainous attack, with aura at the moment of the evaluation. Patients were randomized to receive one of the following substances, in a parenteral route: placebo, metamizole, chlorpromazine, and magnesium sulphate. Metamizole and chlorpromazine reduced the duration of the aura, when compared to placebo, 60 min following their administration.

In another recent study, Fernandes Filho et al. (34) conducted a pilot randomized study comparing intravenous metamizole to intravenous metoclopramide in 27 patients presenting acute crisis of migraine. In men, metoclopramide reduced pain in 80.0 % compared with 55.0 % from metamizole ($P = 0.052$). In women, there was a reduction of 65.0 % with metoclopramide and 71.2 % with metamizole ($P = 0.748$). The small number of patients in the study might have influenced these results. Significant collateral effects were not found. There was no difference either in the intensity of pain reduction, or in the development of collateral effects, comparing metamizole to metoclopramide.

A single-blind study for the effect of metamizole in the treatment of severe migraine attacks was published in 2008 by Krymchantowski et al. (53). The authors evaluated the efficacy and tolerability of the intravenous formulations of lysine clonixinate (LC) and metamizole. Thirty patients were randomized into 2 groups when presenting to an emergency department with severe migraine attack. Headache intensity, nausea, photophobia, and side effects were evaluated at 0 min, 30 min, 60 min, and 90 min after the drug administration. Rectal indomethacin as rescue medication (RM) was available after 2 h and its use compared between groups. At 30 min, 0 % of the metamizole group and 13 % of the LC group were pain-free. At 60 min and 90 min, 2 (13 %) and 5 (33 %) patients from the metamizole group and 11 (73 %) and 13 (86.7 %) patients from the LC group were pain-free ($P < 0.001$). At 60 min, significantly more patients from the LC group were nausea-free ($P < 0.001$). Regarding photophobia, there were no differences between the groups at 60 min. Pain and burning at the site of the injection was reported by more patients of the LC group compared to the metamizole group ($P < 0.0001$).

Cancer pain. Poor information is available about the isolated effectiveness of metamizole in the treatment of cancer pain; in fact, it is not a usual practice to treat cancer pain with a non-opioid drug alone, but rather to use these drugs in add-on therapy in order to achieve a sufficient analgesia where opioids alone cannot provide satisfactory pain relief. Indeed metamizole is a widely used add-on therapeutic in cancer patients (99). In a double-blind, randomised, parallel clinical trial, Rodriguez et al. (78) concluded that the analgesic effect of metamizole 2 g every 8 h for the treatment of cancer pain is similar to morphine 10 mg every 4 h. According to clinical experience, metamizole acts complementary to other analgesics such as opioids, like morphine. In a double-blind placebo-controlled randomized crossover study Duarte Souza et al. (29) evaluated whenever morphine was started, if associating metamizole with it would improve pain control and if this effect was time dependent. Thirty-four ambulatory cancer patients experiencing cancer-related pain for which oral morphine was to be started at the dose of 10 mg orally (PO) every 4 h, were randomized to take either metamizole 500 mg PO every 6 h or placebo. After 48 h, patients would be switched from metamizole to placebo and vice versa. At first, 16 patients were randomized to start with placebo (group 1) and 18 with metamizole (group 2). Pain scores for groups 1 and 2 were at baseline: 7.31 ± 0.29 vs 6.88 ± 0.28 ($P = 0.3$), at 48 h: 7.06 ± 0.32 vs 5.5 ± 0.31 ($P = 0.001$), and at 96 h: 3.18 ± 0.39 vs 1.94 ± 0.37 ($P = 0.03$). Both groups had significant improvements in pain scores after introducing metamizole ($P < 0.001$, for both). Main toxicities were nausea, vomiting, epigastric pain, and myalgias. Twenty-eight patients chose metamizole, four placebo, and two were indifferent. The authors conclude that metamizole adds significantly to the analgesic effect of morphine and, when given at the time of starting morphine, results in better pain scores even after metamizole is discontinued.

To collect data on pain management in paediatric oncology with respect to the WHO ladder approach, eight German tertiary care paediatric oncology centres prospectively documented all their inpatient pain treatment courses from June 1999 to December 2000. Two hundred and twenty-four patients (median age, 9 years; range 0.2–32.1) were enrolled. Three hundred and thirty-three pain episodes comprising a total of 2265 treatment days were documented. The most frequently administered non-opioid analgesics were metamizole and paracetamol. On WHO step 2, tramadol was almost the only opioid used. During tramadol monotherapy average daily pain scores were lower than with a combination of tramadol and non-opioid analgesics. On WHO step 3, morphine was at

least part of the analgesic regimen on most treatment days. Strong opioids were combined with a non-opioid analgesic on 41 % of the treatment days. The mean intravenous morphine equivalence dose was 0.034 mg/kg/h. During opioid and non-opioid combination therapy, adverse effects were more frequent, and average pain scored higher than on opioid monotherapy. In this patient group, there is no evidence that a combination of an opioid with a non-opioid is more effective than opioid therapy alone in inpatient paediatric oncology pain treatment (99).

Renal colics. Renal colic is a common disorder, with the main complaint of unbearable pain. NSAIDs and opioids have been widely used in the treatment of renal colic and their efficacy has been confirmed in many studies.

A randomized, double-blind, multicentre clinical trial was designed to compare the analgesic efficacy of i.m. metamizole 1 g and 2 g, IM diclofenac sodium and IM pethidine in acute renal colic. The study was carried out in 451 patients in 13 Spanish hospitals. The main parameter of drug efficacy was the need for rescue treatment –pethidine 100 mg i.m. 30 min after the experimental treatment. Rescue treatment was required in 93 patients: they represented 24.1 % of the group given metamizole 1 g; 22.3 % of those on metamizole 2 g; 16.4 % of those given diclofenac sodium; and 19.5 % of those on pethidine. The differences between the groups were not significant. In the remaining 358 patients, no difference between treatments was observed. The results suggest that in acute renal colic the use of metamizole 2 g is unjustified as metamizole 1 g is equally effective. Diclofenac sodium is a valid alternative, which shows similar analgesic efficacy (8).

Miralles et al. (64) in a randomized, double-blind clinical trial including 50 patients, compared the efficacy and tolerance of single doses of intramuscular diclofenac 75 mg and metamizole 2 g in acute renal colic. Both drugs were equally effective, but diclofenac was better in terms of complete relief of pain.

In a double-blind, double-dummy randomized controlled clinical trial, the onset and duration of the analgesic effect of metamizole, 1 g or 2 g, and diclofenac sodium, 75 mg, by either the IM or the IV route were compared in 293 patients with acute renal colic. The analgesic response was more marked and prolonged among patients receiving metamizole 2 g IM or metamizole 2 g IV. There were no significant differences between metamizole 1 g and diclofenac sodium 75 mg, by either the IM or the IV route. All treatment regimens were well tolerated (67).

To investigate the combined analgesic and spasmolytic effect of metamizole, 104 patients suffering from "severe" or "excruciating" colic pain due to a confirmed calculus in the upper urinary tract were randomized to receive IV either 2.5 g metamizole, 100 mg tramadol, or 20 mg butylscopolamine in a multicentre, observer-blind, parallel-group study conducted in 8 German centres. Metamizole was significantly more effective than tramadol in reducing pain for the primary endpoint, pain intensity differences (PID) at 20 min, 30 min, and 50 min after drug administration, and was significantly more effective than butylscopolamine at 30 min and 50 min for the secondary efficacy endpoint, pain intensity differences on a categorical scale. Only 5 patients receiving metamizole needed "rescue" medication as compared with 13 patients given tramadol and 11 patients receiving butylscopolamine. Adverse events were observed in 4 patients receiving butylscopolamine and in 1 patient each given metamizole and tramadol. One patient in the metamizole group experienced moderate "light-headedness" lasting for 0.25 h at roughly 15 min after the first injection. The same patient complained of nausea 35 min after receiving the drug and vomited at the end of the evaluation period. The relationship to the study drug was evaluated as "probable" (88).

Fever

Fever is a common childhood illness symptom, accounting for 19 % to 30 % of paediatric emergency visits. Antipyretic drugs are the main form of treatment. Metamizole should be given only when other measures to control severe or life-threatening fever have been unsuccessful, or if the patient is intolerant to other antipyretic agents. Metamizole should be administered for the shortest period possible. In a recent study, Alves et al. (4) performed a randomized clinical trial to evaluate the effectiveness of tepid sponging in addition to metamizole to promote fever control in children from six months to five years of age with axillary temperature greater than 38 °C in the emergency ward between January and July 2006. One hundred and twenty children were randomly assigned to receive oral metamizole (20 mg/kg) or oral metamizole and tepid sponging for 15 min. The primary outcome was mean temperature reduction after 15 min, 30 min, 60 min, 90 min, and 120 min. Secondary outcomes were crying and irritability. One hundred and six children finished the study. After the first 15 min, the fall in axillary temperature was significantly greater in the sponged group than in the control group ($P < 0.001$). From 30 min to 120 min, better fever control was observed in the control group. Crying and irritability were observed respectively in 52 % and 36 % of the sponged children and in none and only two of the controls. The authors concluded that tepid sponging plus metamizole cooled faster during the first 15 min, but metamizole alone presented better fever control over the two-hour period (4).

Only a few controlled clinical trials have compared metamizole with other analgesics in children. Much of the information has been derived from open uncontrolled trials and, although antipyresis was obtained, the data have not been validated. Several single-blind and double-blind studies have also evaluated metamizole using different galenic preparations in febrile children (2). In a randomized, single-blind clinical trial, Prado et al. (75) compared the antipyretic efficacy and tolerability of a single dose of oral ibuprofen (10 mg/kg), oral metamizole (15 mg/kg) or IM metamizole (15 mg/kg) in febrile children from six months to six years of age. Antipyretic efficacy and tolerability were similar for oral

ibuprofen, oral metamizole and intramuscular metamizole. There was a significant decrease in fever-associated symptoms for all groups. Six patients (four receiving oral metamizole and two receiving ibuprofen) were withdrawn because of vomiting within 20 min after the first dose of the study medication.

Fever is a common symptom in cancer patients. In a non-randomized, open-label pilot study, three intravenous antipyretics were tested in five groups of patients: diclofenac (75 mg, brief IV infusion) vs. metamizole (2500 mg or 1000 mg, brief IV infusion) vs. propacetamol (2000 mg or 1000 mg, slow IV injection or brief IV infusion). All tested antipyretics significantly improved the comfort in febrile patients. Overall, 87 % of patients declared improvement in their comfort after administration of antipyretics (69). Diclofenac and metamizole (both 2500 mg and 1000 mg) were tolerated at best.

Gozzoli et al. (40) investigated the metabolic, hemodynamic, and inflammatory responses of pharmacological and physical therapies aimed at reducing body temperature in febrile critically ill patients in an open-label, randomized trial in a surgical intensive care unit. Thirty patients were randomized to receive either IV metamizole, IV propacetamol, or external cooling. Body temperature decreased significantly in all treatment groups. Metamizole induced a significant decrease in arterial pressure and urine output compared to baseline and to the other two groups.

Comparative efficacy/Evaluation with other therapies

Acetaminophen. Metamizole 1.0 g, paracetamol 1.0 g and placebo were compared in a double-blind parallel-group study in 264 patients with episiotomy pain. Both drugs were more effective than placebo, and metamizole was significantly more effective than paracetamol, particularly where initial pain was severe. The efficacy of metamizole 1.0 g was also compared with paracetamol 1.0 g in relieving pain after tooth extraction in 90 patients. Metamizole was consistently and significantly more effective than paracetamol (38).

In a double-blind study in patients with typhoid fever, 25 patients received 500 mg metamizole and 28 received 500 mg paracetamol. The onset of antipyretic effect in patients given metamizole (30 min) was significantly different from that in patients given paracetamol (1 h). The area under the time-temperature curves was signicantly greater for patients given metamizole. Both treatments were well tolerated (3).

Ibuprofen. In a double-blind, randomized, international study that evaluated the effects of metamizole in 628 febrile children (mean age 6 months to 6 years), metamizole, ibuprofen, and acetaminophen decreased fever in 555 children (metamizole in 82 %, ibuprofen in 78 %, while the antipyretic effect of acetaminophen was statistically lower – 68 %). The onset of antipyretic effect of metamizole was statistically more rapid and the duration longer in comparison to ibuprofen and acetaminophen (98). All three drugs showed comparable tolerability profiles.

Prado et al. (75) performed a randomized, single-blind clinical trial, including 75 children who were randomly assigned to receive a single dose of oral ibuprofen (10 mg/kg), oral metamizole (15 mg/kg) or IM metamizole (15 mg/kg). There was a significant decrease in fever-associated symptoms for all groups. Six patients (four receiving oral metamizole and two receiving ibuprofen) were withdrawn because of vomiting within 20 min after the first dose of the study medication. Antipyretic efficacy and tolerability were similar for oral ibuprofen, oral metamizole, and IM metamizole.

In 22 healthy volunteers, the analgesic effect of 1 g metamizole, 1 g paracetamol, and 800 mg ibuprofen was compared in a double-blind crossover study (36). Ibuprofen, but not paracetamol, led to a decrease in pain perception similar to metamizole.

Acetylsalicylic acid. Metamizole 500 mg orally was considered superior to acetylsalicylic acid 500 mg in the treatment of postoperative pain in one study (7). In 17 gynaecological patients with postoperative pain the analgesic efficacy of IV lysine salicylate 1.8 g (corresponding to acetylsalicylic acid [ASA] 1.0 g) and metamizole 1.0 g were compared in a double-blind randomized study. In the ASA group, the mean pain relief and pain intensity difference scores reached a maximum 30 min after drug administration and remained at this level for the next 90 min. In the metamizole group, these scores reached their peak 60 min after drug administration and seemed to fall off during the next hour. The mean pain relief and intensity difference scores were greater following ASA than metamizole (19).

Ketoprofen. Dexketoprofen 50 mg administered as a single IV bolus was effective for the relief of moderate to severe pain in patients with renal colic, with a good safety profile and efficacy similar to i.v. metamizole 2 g. Dexketoprofen produced analgesia that was faster in onset. In this multicenter, randomized, double-blind, double-dummy, parallel, and active-controlled study 308 patients were randomized to dexketoprofen 25 mg (n = 101), dexketoprofen 50 mg (n = 104), and metamizole 2 g (n = 103). The study medications were tolerated well (82).

Comparison to opioids

Pethidine. In a double-blind parallel-group study metamizole 2.5 g IM was compared with pethidine 100 mg intramuscularly in patients with moderate or severe postoperative pain following abdominal surgery. Onset of pain relief was rapid within 30 min – and was maintained for 6 h. At the doses used, analgesia with metamizole was similar in terms of onset, degree and duration to that of pethidine. No side-effects were attributed to either drug in this study (72).

A randomized, double-blind, multicentre clinical trial was designed to compare the analgesic efficacy of IM metamizole 1 g and 2 g, IM diclofenac sodium and IM pethidine in acute renal colic. The study was carried out in 451 patients in 13 Spanish hospitals. The main parameter of drug efficacy was

the need for rescue treatment –pethidine 100 mg IM 30 min after the experimental treatment. Rescue treatment was required in 93 patients: they represented 24.1 % of the group given metamizole 1 g; 22.3 % of those on metamizole 2 g; 16.4 % of those given diclofenac sodium; and 19.5 % of those on pethidine. The differences between the groups were not significant. In the remaining 358 patients, no difference between treatments was observed. The results suggest that in acute renal colic the use of metamizole 2 g is unjustified as metamizole 1 g is equally effective (37).

Tramadol. Cander et al. (24) examined the relative efficacy of analgesics such as tramadol hydrochloride, metamizole sodium, and diclofenac sodium in 100 patients (12 to 66 years of age) who presented to the emergency service with traumatic injuries and fractures of the extremities. Pain became less severe after 15 min in 92 % of patients who received tramadol IV; pain became less severe after 30 min in 72 % of those who received metamizole IV. In contrast, pain became less severe after 45 min in 65 % of patients who received diclofenac IM. Tramadol was the most effective analgesic and was also more effective earlier than the other analgesics tested.

Opioid sparing effect. Pain is a very frequent problem in patients with cancer, with a prevalence of 90 % in advanced disease. Additive effects between opioids and NSAIDs, including metamizole have been reported in animals (65).

Metamizole has opiate-sparing effect in postoperative pain therapy with morphine and has been used for many years as a substitute for other opioid analgesics. A prospective double-blind study with intravenous patient-controlled analgesia using metamizole, buprenorphine, and morphine, concluded that metamizole was the drug of choice (91).

The aim of the prospective clinical study of Lempa and Kohler (56) was to test the feasibility of a metamizole/tramadol combination for pain therapy after laparoscopic and open obesity surgery. Following laparotomy, the combination infusion provided effective analgesia. On the first and fourth postoperative days, the pain scores at rest were 1.5 and 2.3, respectively. The pain scores did not increase significantly with movement (2.7 and 2.2, respectively). Following laparoscopic gastric banding the pain scores were less than 2.0 at rest and with movement on the first postoperative day. On the fourth postoperative day the pain scores at rest and with movement were 0.2. This feasibility study suggests that a combination of the strong non-opioid metamizole and the atypical opioid tramadol provides good analgesia following laparotomy and laparoscopic surgery for morbid obesity not only at rest, but also during mobilization.

In another prospective, randomised and double-blind clinical study, the analgesic efficacy of a continuous infusion of tramadol combined with metamizole was compared with tramadol alone or with placebo during the first 24 h postoperatively. Ninety patients were allocated into three study groups. In group 1, the patients received 600 mg tramadol with 2.5 mg droperidol; in group 2, 600 mg tramadol together with 4.0 g metamizole and 2.5 mg DHB; and in group 3, only 2.5 mg droperidol. Additionally, a patient-controlled analgesia (PCA) device with morphine was provided to each patient as a rescue in the case of insufficient pain relief. After the 24 h study period, a significant pain relief was observed in all three groups. The consumption of morphine via PCA, however, was significantly lower in group 2 (tramadol/metamizole) than in the tramadol or the placebo group, and also the patients in group 1 (tramadol) had received significantly less morphine than those in the placebo group. These data suggest a significantly superior analgesic efficacy of a continuous infusion of tramadol combined with metamizole compared to an infusion of tramadol alone or placebo (86).

Administration of metamizole 2 g following extended abdominal or urological surgery, reduced postoperative morphine requirements from 50 mg to 32 mg in the first 24 h postoperatively (58). Following musculoskeletal procedures, however, the opioid-sparing effect of metamizole was distinctly lower. This is explained by the minor anti-inflammatory effect of metamizole; it inhibits peripheral prostaglandin synthesis only a little and does not accumulate in inflamed tissues, gastrointestinal mucosa or the kidney.

To determine whether metamizole has an opioid-sparing effect in post-operative pain therapy, Tempel et al. (90) performed a randomized, observer-blind, parallel-group, placebo-controlled study. The effect of metamizole was compared to that of placebo during patient-controlled morphine therapy (PCA). One hundred and six adult patients who were to undergo abdominal or urological surgery under 90 min standardized inhalational anaesthesia were entered and 103 were included in the efficacy analysis (53 on metamizole, 50 on placebo). The drugs used were preprogrammed PCA (0.03 mg morphine/kg per bolus) with either metamizole (initially 2.0 g IV and 1.0 g/2 mL IV at 4 h, 8 h and 16 h) or placebo (saline). The total consumption of opiates in the metamizole group (median 31.6 mg) was significantly less than in the placebo group. Global assessment of efficacy was good to excellent in more than 90 % of cases in both groups. Adverse events were mainly nausea and/or vomiting (metamizole, n = 4; placebo, n = l); 1 patient in the placebo group had bradycardia. Authors made a conclusion, that concomitant administration of metamizole with on-demand morphine (PCA) reduces opiate consumption while maintaining post-operative pain relief with a low incidence of side-effects.

The aim of the Ozcakir et al. (71) study was to compare the postoperative analgesic effects of tramadol and tramadol-metamizole and tramadol-lornoxicam combinations administered by intravenous PCA in lower abdominal surgery. Sixty adult patients undergoing lower abdominal surgery were included in the study. Patients were randomly allocated into one of three groups. The solutions were prepared containing 500 mg tramadol in 50 mL saline (10 mg/mL tramadol) for Group I (n = 20), 250 mg tramadol + 3000 mg metamizole in 50 mL saline (5 mg/mL tramadol + 60 mg/mL metamizole) for Group II (n = 20), and 250 mg tramadol + 20 mg lornoxicam

in 50 mL saline (5 mg/mL tramadol + 0.4 mg/mL lornoxicam) for Group III (n = 20). In all groups the loading dose (10 mL) was administered 40 min before the end of operation. PCA was started at the first complaint of pain. There were no significant differences between the groups in terms of first analgesic requirement time, peripheral oxygen saturation, and heart rates. Total tramadol and anti-emetic consumption, postoperative nausea and vomiting were significantly higher in Group I as compared with other groups ($P < 0.05$). Tramadol–metamizole and tramadol–lornoxicam combinations administered by intravenous PCA provide efficient analge sia with less side effects.

Use in special groups of patients

Pregnancy and lactation. Metamizole permeates the placenta. Three cases of acute renal failure with oligohydramnios have been described with high dose, overdose and/or prolonged ingestion of metamizole during pregnancy (73, 80**, 97**). Metamizole-induced renal failure during pregnancy may be explained by induction of reversible renal ischemia secondary to inhibition of prostaglandin synthesis, and acute tubulointerstitial nephritis. A weak association with Wilms' tumor in children of women who took metamizole during pregnancy has been also proposed (20, 85). Two population-based case-control studies (1, 26), performed in Hungary and Brazil reported no association of metamizole with the outcomes of congenital abnormalities, intrauterine death, preterm birth, or low birth weight.

After ingestion by the mother, metamizole and its metabolites appear in breast milk in rather large amounts (102). It is found in the blood and urine of breastfed infants and can cause pharmacological effects in the breastfed infant. Despite the fact that metamizole is not recommended during breastfeeding, Chaves et al. (25) reported metamizole as the most common self-medication drug used by nursing mothers in Brazil (31.5 % used metamizole vs. 17.9 % – paracetamol).

Paediatric patients. Metamizole should be given only when other measures to control severe or life-threatening fever have been unsuccessful, or if the patient is intolerant to other antipyretic agents.

Geriatric patients. Clinical studies of metamizole did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients (103).

Comorbidity. Brunk et al. (23) studied the metabolism of metamizole in patients with thyroid abnormalities. In 8 normal subjects, no change in metamizole metabolism was detected when liothyronine was given. The effect of hypothyroidism on metamizole metabolism was studied in six patients; and the effect of hyperthyroidism, in two patients. In the hypothyroid subjects, plasma metamizole levels were elevated and urinary excretion of 4-aminoantipyrine (AA, active metabolite of metamizole) was decreased; treatment with liothyronine partially corrected this. In the hyperthyroid subjects, plasma metamizole levels were normal and the urinary excretion of AA was decreased; treatment increased the excretion of AA toward normal. These findings suggest that in humans an absence of thyroid hormone decreases the N-demethylation of metamizole and that excessive endogenous thyroid hormone may have a similar effect.

Effects on ability to drive and use machines. At recommended doses, no impairment of the vigilance is known. Undesirable effects on the ability to drive and use machines have not yet been reported after use of metamizole. However, at higher doses or in case of concomitant alcohol intake, it should be considered that the ability of driving, operating machines, or performing dangerous activities may be reduced.

Marketing experience

Analgesic agents make up well over half of the OTC drug market. The estimated consumption of analgesics is (20–60) g/capita/year in industrialized countries. Metamizole was first synthesized in 1920 by the German company Hoechst AG(now part of Sanofi–Aventis), and its mass production started in 1922. It stayed freely available worldwide until the 1970s, when the drug was discovered to pose a risk of agranulocytosis. As already mentioned, in Sweden, all metamizole-containing products were first withdrawn in March 1974; the ban was lifted in 1995 only to be re-introduced in 1999. Metamizole was banned in the USA in 1977, and since then, in more than 30 other countries (including Japan, Australia, Iran, and several EU member states). In Germany, Hungary, Italy, Portugal and Spain it is a prescription drug. In other parts of the world (including Bulgaria, Mexico, India, Egypt, Brazil, Poland, Russia, Turkey, the Republic of Macedonia, Romania, Israel, and some developing countries) metamizole is still freely available OTC, and remains one of the most popular analgesics, commonly used in self-medication. Possibly no other analgesic is subject to as much controversy, especially the exact level of risk of haematological toxicity associated with its use. Differences in the methods used in the various pharmacovigilance studies and concurrent drug use probably account for the widely differing estimates of the risk of blood dyscrasias associated with metamizole. The polarisation of opinions on metamizole seems never ending (58, 63, 66).

Market place of metamizole in Bulgaria

Metamizole continues to be traditionally the most used painkiller in Bulgaria and one of the strongest Bulgarian brands. However, in many countries, among them Bulgaria, the drug is widely used as an OTC product in different pharmaceutical forms, as monotherapy or included in combination with other drugs, and considered safe (**Table 2**).

Systemic analgesics remain the most popular type of OTC analgesics on the Bulgarian market, and the most popular product among them is Analgin® (metamizole sodium), which has been a favourite of Bulgarians since its launch in 1954.

TABLE 3

Market share in units for general pain relief drugs for adults for 2008–2011

	Units YEAR 2008 (Absolute)	**Units YEAR 2009 (Absolute)**	**Units YEAR 2010 (Absolute)**	**Units YEAR 2011 Absolute)**
02A1 GENERAL PAIN RELIEF ADULTS	25 056 876	24 379 744	23 436 951	26 244 921
ANALGIN	**8 272 174**	**7 949 625**	**6 979 943**	**7 070 527**
ACETYSAL	4 608 093	5 069 811	3 878 763	4 057 325
PARACETAMOL	3 713 909	3 725 478	2 697 693	2 444 829
UPSARIN C	1 674 545	1 469 955	1 258 537	1 407 384
BENALGIN	862 122	761 603	1 578 502	1 741 095
NUROFEN	800 160	568 014	608 625	568 465
ASPIRIN C	651 777	790 295	653 295	615 563
PARACETAMAX	0	0	854 002	1 782 073

TABLE 4

Market share in value (EURO) for general pain relief drugs for adults for 2008–2011

	EURO Sales MNF YEAR 2008 (Absolute)	**EURO Sales MNF YEAR 2009 (Absolute)**	**EURO Sales MNF YEAR 2010 (Absolute)**	**EURO Sales MNF YEAR 2011 (Absolute)**
02A1 GENER PAIN RELIEF ADULTS	15 444 018	16 252 422	17 077 994	20 048 941
ANALGIN	**4 115 330**	**4 156 153**	**4 046 267**	**3 986 822**
PARACETAMOL	1 859 966	1 975 598	1 428 815	1 286 785
UPSARIN C	1 542 056	1 553 127	1 544 862	1 961 896
NUROFEN	1 272 633	1 043 898	1 145 242	1 092 135
ACETYSAL	1 269 939	1 670 748	1 572 630	1 933 757
ASPIRIN C	927 478	1 322 223	1 506 473	1 549 819
BENALGIN	778 832	831 783	1 138 365	1 230 073
PARACETAMAX	0	0	395 525	824 111

Furthermore, for years it was the only systemic analgesic product on the market, and therefore remained popular even when competitive products became available. Out of about 160 OTC analgesics available on the market, metamizole is the number one most used OTC analgesic for the last ten years (2001–2010) (55).

The analgesics category was valued at BGN 88.8 m ($66.4 m) in 2009, representing a Compound Annual Growth Rate (CAGR) of 11.6 % since 2004. By the end of 2014, the analgesics category will be worth BGN 125.3 m ($93.7 m), with an expected CAGR of 7.1 % between 2009 and 2014. Analgin® has been the top-selling item on the Bulgarian market for years. In the period January 2000–August 2010, approximately 140 million packs of Analgin® were sold.

In 2011 the tendency for the analgesics market – more drugs for more money – was restored. According to the analysis of IMS Health (47), the general pain relief drugs share was worth 20 048 941 Euro for 2011, with an expected CAGR of 15 % between 2010 and 2011.

According to the IMS Health official data (47) about the market share of the analgesics on the Bulgarian market, Analgin® is the leader in:

- market share in units for 2008, 2009, 2010, 2011 (33 %, 32.6 %, 29.8 %, and 26.9 % from the sales in units for all the general pain relief agents on the Bulgarian market, respectively) (**Table 3**);
- market share in value for 2008, 2009, 2010, 2011 (26.6%, 25.6%, 23.7%, and 19.9% from the sales in value for all the general pain killers on the Bulgarian market, respectively) (**Table 4**).

The Bulgarian pharmaceutical market grew in terms of value in 2011, but shrank in terms of volume. Bulgaria's pharmaceutical market continues to be under pressure owing to the current economic crisis. The decrease in the Analgin®

shares in value and in units (2008–2011) is due to a weakening economic outlook and tightening of publicly funded healthcare services.

In conclusion, these data show that metamizole is widely used in Bulgaria and the drug may be considered relatively safe.

Integrated overview and conclusions

This review is intended to examine the current state of scientific knowledge available on the clinical properties of metamizole and the risk–benefit ratio in the intended indications. Metamizole was introduced into the clinical practice in 1922 and is still in use in many European and non-European countries. Agranulocytosis, metamizole's most serious and potentially fatal adverse effect, has led to its withdrawal in several countries. However, in many countries, incl. Bulgaria, metamizole is still widely used even as an OTC product. There is no doubt that metamizole causes agranulocytosis, although its estimation varies widely.

Similar to other NSAIDs, metamizole exhibits analgesic and antipyretic activity, but no anti-inflammatory activity when administered in therapeutic doses. Its spasmolytic effect on the smooth muscle of the sphincter of Oddi, urinary tract, and the gall bladder is comparable to the effects of buthylscopolamine. In therapy, metamizole can be used as an analgesic in post-surgical pain, patient-controlled analgesia, in cancer pain and in pains of different origin (post-traumatic pain, pain at myocardial infarction, and invasive diagnostic interventions), as well as in pain of neuromuscular origin, headache and migraine. Metamizole is a useful antipyretic both in adults and children. Further, its spasmolytic effect in connection with strong analgesic activity is useful in various colic attacks. Its adverse effects are not pronounced and drug interactions are minimal.

Metamizole is a well-known drug with respect to the overall pharmaco-toxicological and clinical properties as well as its clinical use. Due to the well-established clinical use of metamizole in the treatment of fever and pain of various origins, there is sufficient evidence that there is no concern about any currently unknown hazardous potentials of the substance. However, due to risk of agranulocytosis, the duration of therapy should be kept as short as possible. In summary, metamizole has a well-established medicinal use, in principle, with recognised efficacy and an acceptable level of safety.

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BMC Research Notes

RESEARCH NOTE

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Mortality risk of bloodstream infection caused by either *Escherichia coli* or *Klebsiella pneumoniae* producing extended-spectrum β-lactamase: a prospective cohort study

Osman Sianipar[1*], Widya Asmara[2], Iwan Dwiprahasto[3] and Budi Mulyono[1]

Abstract

Objective: Several studies reported that infection of extended-spectrum β lactamase (ESBL)-producing *Escherichia coli* (*E. coli*) or *Klebsiella pneumoniae* (*K. pneumoniae*) contributed to higher mortality rates but others found it was not associated with mortality. A prospective cohort study which involved 72 patients was conducted to assess the risk of mortality of bloodstream infection due to ESBL-producing *K. pneumoniae* or *E. coli* as compared to those infected by either *K. pneumoniae* or *E. coli* which not produce ESBL.

Result: Mortality in the group of patients infected with ESBL-producing bacteria was 30.6%, whereas in another group which was infected with non ESBL-producing bacteria was 22.2% ($p = 0.59$). Kaplan–Meier's analysis showed that the survival rate during 14-days follow-up among these two group was not significantly different ($p = 0.45$) with hazard ratio 1.41 (95% CI 0.568–3.51). Stratification analysis found that adult and elderly patients, patients with sign of leukocytosis, and patients treated with carbapenem were modifier effect variables.

Keywords: Bloodstream infection, *K. pneumoniae*, *E. coli*, Extended-spectrum β-lactamase, Mortality

Introduction

Bloodstream infection is known as the presence of positive blood culture with clinical signs and symptoms of infection for which contamination can be excluded. Gram negative rod bacteria are frequently found as the cause of infection [1, 2]. Among this group, *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) are the most common bacteria reported as the etiology of bloodstream infection [1–4].

Antimicrobia resistance rates increased worldwide as reported in a recent World Health Organization (WHO) global report on antimicrobial resistance surveillance. *K. pneumoniae* and *E. coli* were 2 out of 7 species of bacteria in which antimicrobial resistance was surveyed [5]. These 2 clinical isolates could produce extended-spectrum β lactamase (ESBL) which could give rise to multi resistant. Recent study reported that the prevalence of ESBL-producing *K. pneumoniae* and ESBL-producing *E. coli* in Pekanbaru Indonesia were 66.2% and 62.2% respectively [6]. Another study conducted in Banda Aceh, Indonesia reported that prevalence of ESBL-producing *K. pneumoniae* and ESBL-producing *E. coli* were 80% and 85% respectively [7].

Risk of mortality was reported higher among patients who were infected with resistant strains of microbes [5, 8, 9]. Mortality rates of patients infected by ESBL-producing *E. coli* or *K. pneumoniae* were higher compared to those infected by non ESBL-producing *E. coli* or *K. pneumoniae* [10, 11]. But some studies reported that risk of mortality of patients infected by ESBL-producing *E. coli*/or *K. pneumoniae* was not statistically different compared with those infected by non ESBL-producing *E. coli* or *K. pneumoniae* [12–15]. The aim of this study was to

*Correspondence: osmansianipar@ugm.ac.id
[1] Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Radioputro Building 5th Floor, Jalan Farmako, Sekip Utara, Yogyakarta, Indonesia
Full list of author information is available at the end of the article

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assess the risk of mortality of bloodstream infection due to ESBL-producing *K. pneumoniae* or *E. coli* as compared to those infected by either *K. pneumoniae* or *E. coli* which not produce ESBL.

Main text

Methods

This was a prospective cohort study that involved 72 patients who suffered from bloodstream infection caused by either *E. coli* or *K. pneumoniae* with Pitt bacteremia score less than 4. This score was measured according to previous study [10]. The subject of the study were recruited consecutively up to number of sample in each group were sufficient. One group consisted of 36 subjects infected by ESBL-producing *E. coli* or *K. pneumoniae* (exposed group), whereas another group consisted of 36 subjects infected by non ESBL- producing *E. coli* or *K. pneumoniae* (un-exposed group). These 2 groups were observed prospectively for 14 days starting right after diagnosis was determined based on positive blood culture to assess patient survived or died during this period. Mortality was defined as the suspension or cessation of vital processes of the body, as heart beat and respiration. Exposure was bloodstream infection caused by ESBL-producing *E. coli* or *K. pneumoniae*. It was determined whenever one set blood culture (2 bottles) gave consistent result of bacterial growth of either *E. coli* or *K. pneumoniae*. Identification of these isolates and also ESBL-producing bacteria was done by microdilution broth method using Vitek 2 system.

Blood samples were inoculated into 2 bottles aerobic blood culture media (ratio sample: media approximately 1:10), and then incubated in an automatic incubator. After the growth of bacteria was detected, samples were further processed for gram staining and microscopic examination as well as sub-cultured onto McConkey and blood agar media. Identification and antimicrobial susceptibility tests were conducted from the colony that grew on these 2 media. Identification of isolates were performed using the Vitek 2 system.

Source of laboratory data were from both Clinical laboratory of Dr. Sardjito and Panti Rapih Hospitals. Whereas source of clinical data was from both Medical Record Unit of Dr. Sardjito and Panti Rapih Hospitals. A clinical research form was used to collect data from each subject of study.

Sample size was calculated based on mortality of patients suffer from bloodstream infection caused by ESBL-non producing *E. coli* or *K. pneumoniae* 15%. Risk of death among those suffer from bloodstream infection caused by ESBL producing *E. coli* or *K. pneumoniae* 3 times. We considered power of the study 80%, confidence interval of 95%, and 10% drop out. Finally we defined number of subject in each group (expose and unexposed) was 36 subject.

Data collected were analyzed by descriptive statistics. Difference in mean and proportion among exposed and un-exposed group were tested using independent *t* test and Chi square test respectively. Survival analysis was conducted using Kaplan–Meier analysis in order to analyze probability of surviving in 14 days of both exposed and un-exposed group. Stratification analysis was conducted using Mantel Haenzel test to identify modifier effect variable.

Results

Characteristics of study subjects

Subjects of this study consisted of 44 males and 28 females. The clinical diagnosis/condition of the study subjects as the reason for blood culture was mostly suspected sepsis. Among those infected by the ESBL producing bacteria 63.9% were diagnosed as sepsis, 13.9% each were diagnosed as SIRS and other infections, and 8.3% suffered from fever. Meanwhile among those infected by ESBL non-producing bacteria, 36.1% were diagnosed as sepsis and other infections, 19.4% diagnosed as systemic inflammatory response syndrom (SIRS), and 8.3% were diagnosed as fever.

The underlying diseases or comorbidities among study subjects were mostly due to malignant disease, and chronic illness, or malignant disease and chronic diseases. Among those infected with the ESBL producing bacteria, 27.8% suffered from malignant disease, 16.7% each suffered from chronic illness, and congenital disease, 8.3% each suffered from cholestasis, and malignant disease mixed with chronic diseases. Meanwhile the underlying disease/comorbidity among those infected by the ESBL non-producing bacteria were as follows: 33.3% suffered from malignant disease, 22.2% suffered from chronic disease, 13.9% suffered from malignant disease and chronic diseases, 8.3% suffered from chronic and endocrine diseases, and 5.6% suffered from cholestasis. The underlying disease/comorbidity which was categorized as other diseases accounted for 19.4% among those infected by the ESBL producing bacteria, and 11.1% among those infected by ESBL non-producing bacteria (Table 1).

During 14 days follow-up, after bloodstream infection caused by either *E. coli*/*K. pneumoniae* was determined, 53 subjects remained alive, while 19 subjects died (26.4%). The mortality among those infected by the ESBL producing bacteria was 11 subjects (30.6%), while mortality among those infected by ESBL non-producing bacteria was 8 patients (22.2%). The proportion of death among these 2 group was not significantly different ($p = 0.59$).

Table 1 Comparison between ESBL and non-ESBL producing of *E. coli* or *K. pneumoniae* based on clinical variables

No	Variable	Bloodstream infection due to either *E. coli* or *K. pneumoniae*		*p*
		ESBL-producing	Non ESBL-producing	
1	Type of ward, n (%)			0.32
	General	9 (25.0)	12 (33.3)	
	Malignancy	7 (19.4)	12 (33.3)	
	Intensive	12 (33.3)	5 (13.9)	
	Surgery	3 (8.3)	3 (8.3)	
	Infection	2 (5.6)	3 (8.3)	
	Other	3 (8.3)	1 (2.8)	
2	Length of stay (day)			0.85
	Mean	10.52	11.21	
	SD	15.77	15.58	
3	Diagnosis, n (%)			0.08
	Sepsis	23 (63.9)	13 (36.1)	
	SIRS	5 (13.9)	7 (19.4)	
	Fever	3 (8.3)	3 (8.3)	
	Other infection	5 (13.9)	13 (36.1)	
4	Underlying disease/comorbid, n (%)			0.09
	Malignant disease	10 (27.8)	12 (33.3)	
	Chronic disease	6 (16.7)	8 (22.2)	
	Malignant and chronic diseases	3 (8.3)	5 (13.9)	
	Chronic and endocrine disease	0 (0)	3 (8.3)	
	Cholestasis	3 (8.3)	2 (5.6)	
	Congenital disease	6 (16.7)	0 (0)	
	Other	7 (19.4)	4 (11.1)	
5	Survival in 14 days, n (%)			0.59
	Alive	25 (69.4)	28 (77.8)	
	Died	11 (30.6)	8 (22.2)	
6	Source of infection, n (%)			0.60
	Unknown	14 (38.9)	20 (55.6)	
	Lung	8 (22.2)	4 (11.1)	
	Gastrointestinal tract	3 (8.3)	4 (11.1)	
	Urinary tract	4 (11.1)	3 (8.3)	
	Skin	3 (8.3)	1 (2.8)	
	Other	4 (11.1)	4 (11.1)	

ESBL extended-spectrum β lactamase, *SD* standard deviation, *SIRS* systemic inflammatory response syndrome

The underlying diseases/comorbidities of 11 cases of death in patients with bloodstream infections due to *K. pneumoniae* was mostly malignant disease (5 subjects), followed by chronic illness (3 subjects), postoperative complication (1 subject), congenital disease (1 subject), and Human Immunodeficiency Virus (HIV) disease stage 3—malnutrition (1 subject). Similarly, the underlying diseases/co-morbidities of 8 cases of death in bloodstream infections due to *E. coli* were mostly malignant disease (5 subjects), followed by chronic diseases (3 subjects).

Survival analysis

Among those who suffered from bloodstream infection caused by the ESBL producing bacteria, mortality was 30.6% subjects (11/36). Whereas mortality among those infected by non ESBL-producing bacteria was 22.2% (8/36).

Kaplan–Meier's survival analysis results (Fig. 1) showed that the survival of these two groups did not differ significantly ($p = 0.450$) with a hazard ratio of 1.41 (95% confidence interval = 0.57–3.51). The results of stratified analysis in those infected by *K.*

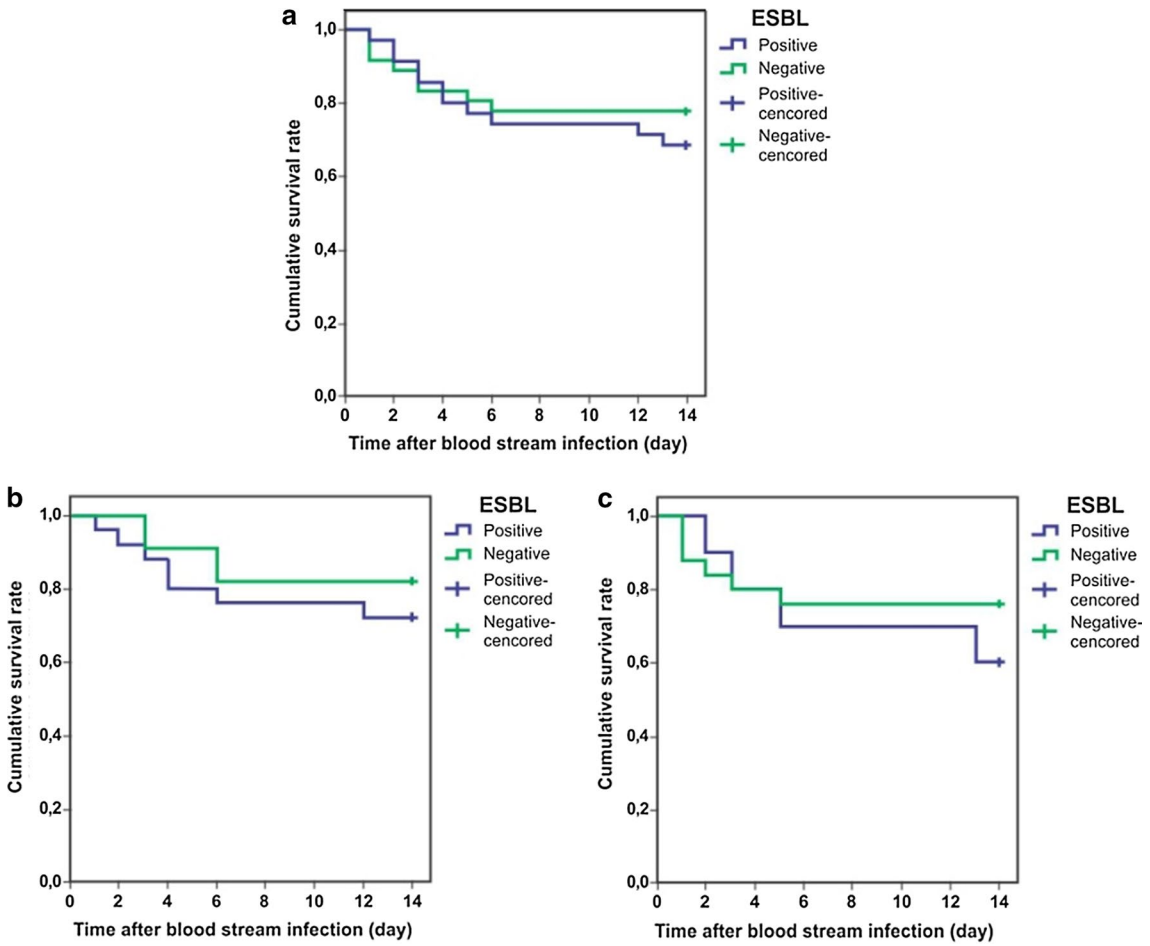


Fig. 1 Survival analysis. **a** Survival of those infected by either *E. coli or K. pneumoniae;* **b** Survival of those infected by *K. pneumoniae;* **c** Survival of those infected by *E. coli*

pneumoniae showed that the survival rate was not significantly different among the patients infected by ESBL producing bacteria, and by ESBL non-producing bacteria ($p = 0.53$). In addition, stratification analysis among those infected by *E. coli* showed a similar result ($p = 0.45$).

Stratification analysis

This analysis was done in order to identify modifier variables. Eventhough, overall risk of mortality is not different significantly between exposed and un-exposed group but 3 modifier variables could be identified namely those patient with age group adult to elderly, those patient with sign of leukocytosis, and those patient treated with carbapenem. These 3 modifier effect variables were identified if the different between adjusted relative risk (RR_{MH}) and relative risk crude (RR_{crude}) was at least 10% [16] (Table 2).

Discussion

The underlying diseases/comorbidities of the study subjects were mostly malignant disease, and chronic illness, or malignant disease and chronic diseases. Almost all of the study subjects have an underlying disease/comorbidity. This finding is similar to previous studies [8, 17–19].

In this study, overall mortality among exposed group was 26.4% (19/72). Another similar study reported that 28 day-mortality rate for patients with blood-stream infection was 24.6% (47/191) [19]. Flokas et al. in 2017 reported that mortality among neonates who suffer from bloodstream infection due to the ESBL producing *Enterobacteriaceae* was 36% [20]. In patients suffering from bacteremic pneumonia caused by ESBL-producing *E. coli* or *K. pneumoniae,* 30 day-mortality was reported as 40.5% (45/111) [21].

Mortality of those who suffered from bloodstream infection due to *E. coli* was 30.8% (8/26). Another similar study reported that 7 days-mortality was 8.5% (128/1499)

Table 2 Stratification analysis to evaluate mortality risk among those infected by either *E. coli* or *K. pneumoniae* producing ESBL

Strata	RR_{Strat}	95% CI	*p*	RR_{Crude}	RR_{MH}
Males	1.89	0.59–6.01	0.43	1.38	1.40
Females	0.84	0.2–3.55	1		
Neonates up to 17 years old	0.78	0.2–2.98	1	1.38	1.64
Adult and elderly	2.57	1.04–6.36	0.04		
Primary bloodstream infection	1.17	0.33–4.10	0.57	1.38	1.43
Secondary bloodstream infection	1.65	0.61–4.47	0.53		
Length of stay > 2 days (before bloodstream infection established)	2.13	0.71–6.38	0.29	1.38	1.25
Length of stay ≤ than 2 days (before bloodstream infection established)	0.62	0.21–1.79	0.68		
Infected by *E. coli*	0.96	0.29–3.17	0.95	1.38	1.47
Infected by *K. pneumoniae*	2.05	0.62–6.76	0.37		
Leukocytosis	3.60	1.44–9.02	0.01	1.38	1.68
Non-leukocytosis	0.52	0.13–2.04	0.91		
Neutropenia	0.75	0.11–5.18	1.00	1.38	1.45
Non-neutropenia	1.69	0.66–4.34	0.41		
Underlying disease, malignancies	1.31	0.48–3.58	0.90	1.38	1.46
Underlying disease, non malignancies	1.65	0.48–5.74	0.48		
Inappropriate antimicrobial prescription in definitive therapy	9.53	0.60–152.02	0.70	1.38	1.42
Appropriate antimicrobial prescription in definitive therapy	0.74	0.28–1.93	0.77		
Definitive therapy using carbapenem	3.10	0.21–46.34	0.29	1.38	1.63
Definitive therapy using non-carbapenem	1.25	0.49–3.21	0.45		
Empiric therapy using cephalosporin	1.10	0.39–3.10	1.00	1.40	1.39
Empiric therapy using non-cephalosporin	2.08	0.51–8.52	0.27		

RR_{strat} relative risk from stratification analysis, RR_{crude} relative risk from total sample, RR_{MH} relative risk from Mantel Haenzel analysis

among those who were infected by *E. coli* [15]. Thirty days-mortality of this *E. coli* infection was reported as high as 28.5% (101/354) [11]. Number of subject infected by ESBL-producing *E. coli* was 10 patients, and 3 of them (30.0%) died during 14 days observation, whereas the mortality among those infected by ESBL non-producing *E. coli* was 31.25% (5/16). Thirty days-mortality among those infected by ESBL producing *E. coli* as reported in other study were as follows 26.4% (14/53) [18] and 21.6% [22]. Another study reported 3 months-mortality as high as 18% (34/232) for older adults and 5.7% (7/145) for younger adults [23].

Mortality of those who suffered from bloodstream infection caused by *K. pneumoniae* was 23.9% (11/46). This mortality was lower compared with another study with 46.2% (48/104) [12]. Twenty-eight days-mortality of bloodstream infection caused by *K. pneumoniae* was reported in 2 studies as high as 47.9% (91/190) [24], and 22.8%, respectively [25]. Seven days-mortality of this infection was 9.4% (33/352) [15]. In this study, mortality among those infected by ESBL producing *K. pneumoniae* and ESBL non-producing *K. pneumoniae* were 30.8% (8/26) and 15.0% (3/20), respectively. Another study reported mortality rates among those infected by ESBL-producing *K. pneumoniae* and non ESBL-producing *K. pneumoniae* in an intensive care unit were 9.6% (7/73) and 13.6% (3/22), respectively [26].

In this study risk of mortality among those who suffered from bloodstream infection caused by ESBL producing *E. coli* or *K. pneumoniae* was not significantly different. This result was similar to the finding in another study in which they reported the hazard ratio was 1.65 (95% CI 0.75–3.64) [14]. In addition, this result was also similar to the findings in 2 other studies [13, 15].

Overall risk of mortality among exposed group was not statistically different with those un-exposed group. However, in stratification analysis showed that the exposed group had higher mortality risk as compared to un-exposed group especially in adult and elderly patients, patients with sign of leukocytosis, and patients treated with carbapenem. Most probably these 3 modifier effect variables were closely related with more severe clinical condition of the patients. In addition, the relationship between ESBL enzyme and virulence factor needs to be considered. The relationship between these two factors is not yet known with certainty. There are four factors that are suspected to have an effect on the increasing antimicrobial resistance relationship with virulence, namely

(1) bacterial species; (2) specific virulence and resistance mechanisms; (3) environmental or ecological niche; and (4) the patient (immune system) [27]. Other studies suggest there is no convincing evidence that infections caused by ESBL producing bacteria are associated with poor outcomes (deaths) compared to those caused by non ESBL-producing bacteria, except in cases where antimicrobials were not provided optimally [9, 28].

Limitation

Mortality of patients suffer from bloodstream infection caused by *E. coli* or *K. pneumoniae* might be due to infection of ESBL producing bacteria and also severity of the disease. In this study, severity of bloodstream infection was controlled by Pitt bacteremia score less than 4 for inclusion criteria for inception cohort. Mortality might also be due to progression or severity of underlying disease and/or co-morbid. Unfortunately, we were not able to control severity of these underlying diseases and co-morbid.

Abbreviations

E. coli: *Escherichia coli*; *K. pneumoniae*: *Klebsiella pneuomiae*; ESBL: extended-spectrum β-lactamase; WHO: World Health Organization; HIV: human immunodeficiency virus; CI: convidence interval; LOS: length of stay; SIRS: systemic inflammatory response syndrome; SD: standard deviation; RR_{strat}: relative risk from stratification analysis; RR_{crude}: relative risk from total sample; RR_{MH}: relative risk from Mantel-Haenzel analysis; HR: hazard ratio.

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Authors' contributions

OS contributed in preparing and implementing the study protocol, preparing the report and manuscript. WA contributed in quality assurance of culture, data analysis, and reviewing the manuscript. ID contributed in research method, data analysis, and reviewing manuscript. BM contributed design and implement study, data analysis, and reviewing manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and additional tables.

Ethics approval and consent to participate

Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine Gadjah Mada University—Dr. Sardjito Hospital Yogyakarta, Indonesia has approved the protocol as a quality assurance study as stated in Ref: KE/FK/1140/EC/2016. Written consent had been obtained from all study subjects after sufficient information regarding this study provided.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1] Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Radioputro Building 5th Floor, Jalan Farmako, Sekip Utara, Yogyakarta, Indonesia. [2] Department of Microbiology, Faculty of Veterinary Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia. [3] Department of Pharmacology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Radioputro Building 2nd Floor, Jalan Farmako, Sekip Utara, Yogyakarta, Indonesia.

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Chronic Kidney Disease and Risk of Death from Infection

Henry E. Wang[a] Christopher Gamboa[b] David G. Warnock[c] Paul Muntner[b, c]

Departments of [a]Emergency Medicine and [b]Epidemiology, and [c]Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Ala., USA

Key Words
Chronic kidney disease · Infection · Sepsis · Mortality

Abstract
Background: Infection, bacteremia and sepsis are major sources of morbidity and mortality in patients with end-stage renal disease. This study sought to determine the association between predialysis chronic kidney disease (CKD) and infection-related mortality. ***Methods:*** We analyzed participants in the Third National Health and Nutrition Examination Survey (NHANES III). The study included adults ≥45-years-old without end-stage renal disease. Estimated glomerular filtration rate (eGFR) was categorized as ≥60, 45–59.9 and <45 ml/min per 1.73 m^2, and urinary albumin-to-creatinine ratio (ACR) as <30, 30–299.9 and ≥300 mg/g. The study identified infection-related mortality, including septicemia, respiratory, abdominal and gastrointestinal, cardiac, kidney and genitourinary, neurologic, and other infections over a median of 13 years using the National Death Index. ***Results:*** Of 7,400 participants included in the study, 206 died from infections. Compared to individuals with eGFR ≥60 ml/min per 1.73 m^2, infection-related mortality was higher for those with lower eGFR [adjusted HR = 1.36 (95% CI: 0.81, 2.30) and 2.36 (1.04, 5.38) for eGFR of 45–59.9 and <45 ml/min per 1.73 m^2, respectively; p trend = 0.06]. Compared to individuals with ACR <30 mg/g, infection-related mortality was higher for ACR levels of 30–299 and ≥300 mg/g [adjusted HR = 1.68 (95% CI: 0.97, 2.92) and 2.84 (0.92, 8.74), p trend = 0.02]. ***Conclusions:*** Reduced eGFR and albuminuria are associated with increased risk for infection-related mortality. Efforts are needed to reduce its incidence and mitigate the effects of infections among individuals with CKD.
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Introduction

Chronic kidney disease (CKD) is a major public health problem affecting approximately 11.5% of US adults [1]. CKD is associated with poor outcomes including an increased risk of kidney failure, cardiovascular disease and mortality [1–4]. These associations may result from the presence of traditional risk factors as well as biochemical abnormalities such as increased inflammatory factors, endothelial dysfunction and enhanced coagulation [3].

Microbial infection may result in bacteremia, triggering exaggerated inflammation and sepsis [5]. Infection, bacteremia and sepsis are major sources of morbidity and mortality in patients with end-stage renal disease receiving chronic hemodialysis therapy [6, 7]. For example, using the US Renal Data System, Powe et al. [7] found that during 7 years of follow-up, 11.7% of all hemodialysis patients and 9.4% of peritoneal dialysis patients had at least one episode of septicemia, and Sarnak and Jaber [6] found that the sepsis mortality was 100- to 300-times higher for chronic dialysis patients than the general public. Hypoth-

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Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

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Henry E. Wang, MD, MS
Department of Emergency Medicine, University of Alabama at Birmingham
619 19th Street South, OHB 251
Birmingham, AL 35249 (USA)
Tel. +1 205 996 6526, E-Mail hwang@uabmc.edu

esized reasons for this association include increased susceptibility to infection, the presence of comorbidities such as diabetes, and repetitive exposure to pathogens during hemodialysis.

In contrast to the approximately 500,000 dialysis patients, over 20 million US adults have CKD [1, 8]. An important unanswered question is whether the increased risk of infection and infection-associated mortality extends from dialysis patients to the much larger population of patients with predialysis CKD. An association between earlier stages of CKD and infection or infection-associated mortality has important implications for clinical care, pointing to infection prevention and mitigation as important strategies for reducing mortality in this population.

The objective of this study was to determine the association between moderate-to-severe CKD and death attributed to infection. To address this objective, we evaluated the association of reduced estimated glomerular filtration rate (eGFR) and increased albuminuria with infection-related mortality in the general US population ≥45 years of age using data from the Third National Health and Nutrition Examination Survey (NHANES III) Mortality Follow-Up Study.

Materials and Methods

Study Design and Setting

The protocol for NHANES III was approved by the Institutional Review Board of the National Center for Health Statistics of the Centers for Disease Control and Prevention. All participants gave written informed consent. The Institutional Review Board of the University of Alabama at Birmingham determined the analysis of NHANES III data to be exempt research.

NHANES III was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention [9]. Few infection-related deaths occurred among adults <45 years of age. Therefore, we limited the current analysis to participants ≥45 years of age. Between 1988 and 1994, 9,787 adults 45 years of age and older participated in NHANES III.

Baseline Data Collection

NHANES III baseline data were collected during an in-home interview and a subsequent visit to a mobile examination center (National Center for Health Statistics 1994). Information on demographics, education, cigarette smoking and physical activity were collected using a standardized questionnaire. Blood pressure and waist circumference to the nearest 0.1 cm were measured during the in-home interview and/or participant visit to the mobile examination center.

We used serum and urine laboratory assay values as obtained and reported by NHANES [9, 10]. Serum C-reactive protein (CRP) was quantified using latex-enhanced nephelometry, a low sensitivity assay. Since a large proportion of participants had CRP values below the limit of detection, we categorized participants as having CRP <3.0 (i.e. below the limit of detection), between 3.0 and 9.9, or ≥10.0 mg/l. We defined diabetes mellitus as a fasting plasma glucose ≥126 mg/dl, a nonfasting plasma glucose ≥200 mg/dl and/or a self-reported history of diabetes with concurrent use of antidiabetes medication. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation and categorized as ≥60, 45–59.9 and <45 ml/min per 1.73 m^2 [11]. Urinary albumin-to-creatinine ratio (ACR) was categorized as <30, 30 to 299.9 and ≥300 mg/g.

Outcomes and Covariates

The primary outcome was death due to infection. Adult NHANES III participants were followed for mortality through December 31, 2006. Probabilistic matching was used to link NHANES III participants with the National Death Index to ascertain vital status and cause of death [9]. The National Death Index is a central index of death record information from all US states, including information on the underlying cause of death as reported by the certifying physician. Probabilistic matching was based on 12 identifiers for each participant (e.g. Social Security number, sex, date of birth) [12].

The International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) revision 9 was used for classifying deaths occurring between 1988 and 1998, and ICD revision 10 (ICD-10) for deaths occurring between 1999 and 2006. Prior studies of hospital discharge and mortality data have used ICD-9 and ICD-10-based taxonomies to identify infection-related diagnoses and deaths [13, 14]. Using this strategy, we identified cause of death categories related to infections, including septicemia, respiratory (e.g. pneumonia), abdominal and gastrointestinal (e.g. appendicitis, diverticulitis), cardiac (e.g. endocarditis), kidney and genitourinary (e.g. pyelonephritis, pelvic inflammatory disease), neurologic (meningitis), and other infections (online suppl. Appendix 1, www.karger.com/doi/10.1159/000330673). Based on the available data, we could not distinguish hospital or institutional-acquired infections.

Follow-up for each study participant consisted of the time between their NHANES III examination and the date of death. Follow-up was censored at December 31, 2006 for those who did not die.

Data Analysis

We defined baseline eGFR by the categories ≥60, 45–59.9 and <45 ml/min/1.73 m^2 and albuminuria by the categories <30, 30–299.9 and ≥300 mg/g. Using Cox proportional hazards regression models, we calculated hazard ratios for infection-related mortality associated with eGFR and ACR. Initial models included adjustment for age (using a linear spline with a knot at 60 years of age), race/ethnicity and sex. Subsequent models included additional adjustment for tobacco use, waist circumference, total cholesterol, hypertension, diabetes mellitus, history of stroke or myocardial infarction CRP, serum phosphorus, serum albumin, and serum 25(OH)D. We also fit a multivariable model with additional adjustment for log-transformed ACR and eGFR. To test for linear trends across levels of eGFR and ACR, we included the median eGFR and ACR value within each eGFR and ACR level as a continuous variable in the Cox regression models.

Finally, we fit a multivariable-adjusted Cox regression model with cross-categorized eGFR and ACR. For this final analysis, we a priori grouped those with eGFR levels of 45–59.9 and <45 ml/

Table 1. Baseline characteristics of adult participants in the Third NHANES by level of eGFR and albuminuria

Characteristic	eGFR, ml/min/1.73 m^2			ACR, mg/g		
	≥60 (n = 6,404)	45–59 (n = 687)	<45 (n = 309)	<30 (n = 6,097)	30–299 (n = 1,059)	≥300 (n = 244)
Age, years	59.3 (0.3)	72.8 (0.6)	74.3 (0.8)	59.9 (0.3)	65.7 (0.7)	67.1 (1.3)
Race/ethnicity						
White	81.9	85.7	86.0	83.3	77.3	65.4
Black	8.3	7.4	9.5	7.6	11.8	19.1
Mexican-American	3.4	1.1	1.4	3.1	3.6	5.8
Other	6.4	5.8	3.1	6.1	7.3	9.7
Female	52.7	59.6	58.3	53.2	55.8	44.2
Education, less than HS graduate	30.2	49.2	46.6	30.4	40.4	57.0
Physically inactive	24.4	30.3	37.9	23.9	33.0	41.9
Current smoker	22.8	12.8	10.3	21.5	24.0	23.1
Waist circumference, cm	96.3 (0.3)	98.5 (0.8)	96.8 (0.9)	95.9 (0.3)	99.7 (0.7)	103.0 (2.2)
Systolic blood pressure, mm Hg	131.1 (0.4)	143.1 (1.2)	145.0 (1.6)	130.4 (0.4)	144.4 (1.2)	153.2 (2.6)
Antihypertensive medication use	21.7	49.1	63.9	21.9	43.2	52.7
Total cholesterol, mg/dl	220.3 (1.0)	230.8 (2.70)	234.6 (4.7)	220.6 (1.0)	226.7 (2.1)	229.0 (5.2)
Diabetes mellitus	9.5	16.4	19.9	7.6	27.6	37.7
CRP, mg/l						
3–9.9	25.7	31.5	31.7	25.7	31.4	25.8
≥10	9.4	14.3	24.2	8.7	19.6	23.3
Serum phosphorus, mg/dl	3.41 (0.01)	3.47 (0.03)	3.53 (0.04)	3.42 (0.01)	3.40 (0.02)	3.40 (0.06)
Serum albumin, g/dl	4.10 (0.02)	4.04 (0.02)	3.98 (0.05)	4.10 (0.02)	4.09 (0.02)	3.81 (0.04)
Serum 25(OH)D, ng/ml	28.2 (0.3)	28.4 (0.5)	26.1 (0.7)	28.6 (0.3)	25.9 (0.4)	23.7 (1.3)
History of stroke	3.0	8.5	12.9	3.3	6.3	6.4
History of myocardial infarction	6.3	14.9	23.1	6.7	12.1	11.9

Values are either means (standard error) or percentages. HS = High school.

min/1.73 m^2 as well as those with ACR levels of 30–299.9 mg/g and ≥300 mg/g due to the relatively low number of cases in these groups. We calculated hazard ratios for infection-related mortality for participants with (1) eGFR <60 ml/min/1.73 m^2 and ACR <30 mg/g, (2) eGFR ≥60 ml/min/1.73 m^2 and ACR ≥30 mg/g, and (3) eGFR <60 ml/min/1.73 m^2 and ACR ≥30 mg/g, each compared to the reference group of (4) eGFR ≥60 ml/min/1.73 m^2 and ACR <30 mg/g.

All data were analyzed using SUDAAN (version 9.0; Research Triangle Institute, Research Triangle Park, N.C., USA) to account for the complex NHANES sampling design, including unequal probabilities of selection, oversampling, and nonresponse.

Results

For the current analysis, we excluded 1,784 participants who were missing data for serum creatinine, 25 participants with an eGFR <15 ml/min/1.73 m^2, 570 participants who were missing data for urinary albumin or urinary creatinine, and 8 participants who did not have follow-up information. We included the remaining 7,400 NHANES III participants ≥45 years of age in the analysis. Participants who were excluded due to missing data were older and more likely to be non-Hispanic Black. However, the gender distribution was similar between included and excluded individuals.

Participant Characteristics

The prevalence of eGFR levels of ≥60, 45–59.9 and <45 ml/min/1.73 m^2 were 90.2, 7.0 and 2.8%, respectively. The prevalence of ACR levels of <30, 30–299.9 and ≥300 mg/g were 87.2, 11.0 and 1.8%, respectively. Participants with lower eGFR and higher ACR were older, had less education and were more likely to be physically inactive, taking antihypertensive medication, have diabetes, and a have history of stroke and myocardial infarction (table 1). Additionally, on average, participants with lower eGFR and higher ACR levels had a larger waist circumference, higher levels of systolic blood pressure, total cholesterol and CRP, and lower levels of serum albumin and serum

Table 2. Hazard ratios for infection-related mortality by eGFR and ACR among adult participants of the Third NHANES

	eGFR, ml/min/1.73 m^2				ACR, mg/g			
	≥60	45–59	<45	p trend	<30	30–299	≥300	p trend
Outcomes								
Infection-related deaths, n	146	37	23		155	42	9	
Infection-related mortality (per 1,000 person-years)	1.2	4.6	10.3		1.3	3.1	7.0	
Regression model		HR (95% CI)	HR (95% CI)			HR (95% CI)	HR (95% CI)	
Model 1[a]	1 (ref.)	1.47 (0.88, 2.47)	3.17 (1.59, 6.30)	0.008	1 (ref.)	1.80 (1.11, 2.93)	3.79 (1.35, 10.64)	0.001
Model 2[b]	1 (ref.)	1.45 (0.86, 2.44)	3.18 (1.55, 6.51)	0.01	1 (ref.)	1.71 (0.99, 2.98)	3.28 (1.02, 10.52)	0.01
Model 3[c]	1 (ref.)	1.36 (0.81, 2.29)	2.36 (1.04, 5.38)	0.06	1 (ref.)	1.68 (0.97, 2.92)	2.84 (0.92, 8.74)	0.02

[a] Adjusted for age (modeled using a linear spline), race/ethnicity and sex.
[b] Adjusted for Model 1 covariates, smoking status, waist circumference, total cholesterol, hypertension, diabetes mellitus, history of stroke or myocardial infarction, serum 25(OH)D, serum phosphorus, and serum albumin.
[c] Adjusted for Model 2 covariates and log-transformed ACR or eGFR.

25(OH)D. Participants with a lower eGFR level had higher serum phosphorus levels, but little difference was observed by ACR level.

Over a median follow-up of 13 years (maximum follow-up: 18), there were 206 deaths attributed to infection: 13 abdominal, 129 respiratory, 51 septicemia, 1 kidney/genitourinary and 12 cardiac, neurological or other infections (online suppl. Appendix 1).

eGFR and Infection-Related Mortality

The infection-related mortality rates were higher in individuals with lower baseline eGFR levels (table 2 and online suppl. Appendix 2). Lower eGFR levels were associated with higher hazard ratios for infection-related death after adjustment for age, race/ethnicity, sex and other confounders. Although attenuated, increased hazard ratios for infection-related mortality at lower eGFR levels remained present after multivariable adjustment (p trend = 0.01) and additional adjustment for log-transformed ACR (p trend = 0.06).

ACR and Infection-Related Mortality

Infection-related mortality rates were higher among participants with higher baseline ACR levels (table 2 and online suppl. Appendix 2). Higher ACR was associated with increased hazard ratios for infection-related mortality after adjustment for age, race/ethnicity and sex. Although the hazard ratios for infection-related mortality remained increased after further adjustment for eGFR, the 95% CI were wide and included the null. However, the trend for increased infection-related mortality at higher ACR levels was statistically significant (p trend = 0.02).

Table 3. Hazard ratios (95% CI) for infection-related mortality by level of eGFR and albuminuria among adult participants 45 years and older of the Third NHANES

ACR, mg/g	eGFR, ml/min/1.73 m^2	
	<60	≥60
≥30	2.59 (1.07, 6.24)	2.11 (1.21, 3.66)
<30	1.94 (1.14, 3.30)	1 (ref.)

Adjusted for age (modeled using a linear spline), race/ethnicity, sex, smoking status, waist circumference, total cholesterol, hypertension, diabetes mellitus, history of stroke or myocardial infarction, serum 25(OH)D, serum phosphorus and serum albumin.

Cross-Categorization of eGFR/ACR with Infection-Related Mortality

In a multivariable model incorporating both eGFR and ACR, the hazard ratios for infection-related mortality were higher for those with lower eGFR, higher ACR or both (table 3). Multiplicative interaction between eGFR <60 ml/min/1.73 m^2 and ACR ≥30 mg/g on infection-related mortality was not present (p = 0.36).

Discussion

In the current study, we report an association between CKD and an increased risk of death from infections. This association was graded across lower eGFR and higher ACR levels and robust to multivariable adjustment for

multiple potential confounders. Additionally, when considered jointly, individuals with both reduced eGFR and high ACR had an especially high risk for infection-related mortality. Prior studies have reported an increased risk of infection, bacteremia, sepsis and sepsis mortality among patients receiving chronic hemodialysis [6, 7, 15]. The present study extends these previous findings to the substantially larger population of patients with predialysis CKD.

Using provincial administrative data from Calgary, Canada, James et al. [16] identified a higher risk of bloodstream infection in older patients with CKD and subsequent 30-day death. Our study focused on infection-attributed mortality and encompassed all infections, which is clinically relevant since patients are susceptible to and die from a range of infection types – not just bacteremia. In contrast to the 3.2 years of follow-up in the James et al. study, our study followed participants for a median of 14 years, affirming the long-term persistence of infection-mortality risk.

While the high rate of infection among dialysis patients may be related to dialysis-related exposures, CKD patients do not have chronic exposure to hemo- or peritoneal dialysis. Also, the associations of our study persisted even after adjustment for comorbidities such as diabetes and hypertension. These results suggest that other mechanisms may increase the risk for infection among patients with CKD. We were unable to distinguish whether increased infection-related mortality is due to heightened susceptibility or impaired ability to respond to the acute infection.

Numerous studies have linked CKD with all-cause and cardiovascular mortality [3, 4, 17]. In an analysis of 1.1 million adults in the Kaiser Permanente Renal Registry, Go et al. [3] found increasing risks of all-cause mortality and cardiovascular death with worsening eGFR, and attributed these associations with prior cardiovascular disease, inflammatory factors, enhanced coagulopathy, anemia, left ventricular dysfunction, endothelial dysfunction, etc. While our study cannot elucidate the factors linking CKD with heightened infection mortality, infection, sepsis and cardiovascular disease share many of the same hypothesized risk factors and mechanisms. For example, sepsis is characterized by exaggerated inflammatory response to infection [5]. Coagulation and endothelial dysfunction have been implicated in sepsis pathophysiology [18]. Sepsis outcomes are worse in obese patients as well as those with diabetes [19–21]. Cardiovascular disease compromises the host response to sepsis and septic shock, pointing to connections between cardiovascular and infection risk in this population [22]. In this context, cardiovascular mortality may be a competing risk for (i.e. precluding the occurrence of) infection-related mortality. Additional study is warranted to identify the independent and overlapping factors that potentiate infection susceptibility and mortality in CKD patients.

This study has important implications for clinical care of patients with CKD. Strategies to reduce infection may involve the prevention or mitigation of downstream inflammatory responses to infection. For example, avoidance of unnecessary vascular access or invasive procedures may reduce exposure to pathogens. Vaccination may also play an important role in infection prevention. Optimal management of cardiovascular disease risk factors such as hypertension, diabetes, obesity and tobacco use may improve a patient's ability to respond to infection and sepsis. Prior studies suggest that statin use among end-stage renal disease patients may protect against sepsis [23]. Finally, due to very low rates of awareness, detection of CKD is essential [24]. In a study of 3,803 adult with coronary heart disease in the REGARDS cohort, McClellan et al. [25] found that less than 10% of individuals with CKD (defined by eGFR <60 ml/min/1.73 m^2) were aware of their condition.

Despite ample data describing the clinical and physiologic course of acute sepsis, there is relatively little knowledge regarding risk factors for sepsis or potential preventive measures [14]. Prospective population-based studies are necessary to elucidate these risk factors. A broader understanding of infection and sepsis risk factors may lead to key knowledge to reduce CKD mortality.

Limitations

A major limitation of the current study is the lack of data on nonfatal events. Infection-related mortality captures only the most severe events. Based on the available data, we could not distinguish hospital or institutionally acquired infections. Additionally, the current study relied on the National Death Index for determining cause of death. Although the reliability of mortality follow-up through the National Death Index is very high (98.5%), this method relies on death certificates which may contain inaccurate information [26].

Certain individuals may have had a secondary infection that played prominent roles in their death. Because the public-use NHANES data set does not have information on contributing causes of death, we relied on the assigned underlying cause alone. The cause of death cat-

egories may have excluded important infections such as peritonitis, pyothorax or abscesses. Furthermore, for analytic purposes we combined all infections together, but select patients may have responded differently to individual infections. However, we lacked an adequate number of outcomes to ascertain mortality from specific infection groups. While other competing conditions may have influenced the incidence of infection-related death, we did not perform a formal competing-risks analysis.

We inferred eGFR and ACR levels from a single baseline visit. Approximately 50% of individuals with ACR ≥30 mg/g on a single measurement do not have persistent albuminuria [27]. The public-use NHANES data set did not have HIV status available. Because participants in NHANES III were examined at baseline only without follow-up testing, we were unable to ascertain changes in subject characteristics over time. We were also unable to account for changing patterns of immunization or infection over time.

Conclusions

In conclusion, reduced eGFR and albuminuria were each associated with an increased risk for infection-related mortality in this general population sample of US adults. Efforts are needed to reduce the incidence and mitigate the effects of infections among individuals with CKD.

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Disclosure Statement

The authors declare no conflicts of interests.

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Critical Care

RESEARCH Open Access

Frequency and mortality of septic shock in Europe and North America: a systematic review and meta-analysis

Jean-Louis Vincent[1*], Gabriel Jones[2], Sholto David[2], Elena Olariu[2] and Kevin K. Cadwell[2]

Abstract

Background: Septic shock is the most severe form of sepsis, in which profound underlying abnormalities in circulatory and cellular/metabolic parameters lead to substantially increased mortality. A clear understanding and up-to-date assessment of the burden and epidemiology of septic shock are needed to help guide resource allocation and thus ultimately improve patient care. The aim of this systematic review and meta-analysis was therefore to provide a recent evaluation of the frequency of septic shock in intensive care units (ICUs) and associated ICU and hospital mortality.

Methods: We searched MEDLINE, Embase, and the Cochrane Library from 1 January 2005 to 20 February 2018 for observational studies that reported on the frequency and mortality of septic shock. Four reviewers independently selected studies and extracted data. Disagreements were resolved via consensus. Random effects meta-analyses were performed to estimate pooled frequency of septic shock diagnosed at admission and during the ICU stay and to estimate septic shock mortality in the ICU, hospital, and at 28 or 30 days.

Results: The literature search identified 6291 records of which 71 articles met the inclusion criteria. The frequency of septic shock was estimated at 10.4% (95% CI 5.9 to 16.1%) in studies reporting values for patients diagnosed at ICU admission and at 8.3% (95% CI 6.1 to 10.7%) in studies reporting values for patients diagnosed at any time during the ICU stay. ICU mortality was 37.3% (95% CI 31.5 to 43.5%), hospital mortality 39.0% (95% CI 34.4 to 43.9%), and 28-/30-day mortality 36.7% (95% CI 32.8 to 40.8%). Significant between-study heterogeneity was observed.

Conclusions: Our literature review reaffirms the continued common occurrence of septic shock and estimates a high mortality of around 38%. The high level of heterogeneity observed in this review may be driven by variability in defining and applying the diagnostic criteria, as well as differences in treatment and care across settings and countries.

Keywords: Sepsis, Intensive care, Heterogeneity, Outcome, Sepsis definition

Introduction

Sepsis, the association of organ dysfunction with an infection, is a complex multifactorial disease that has severe health and economic burden on both the patient and healthcare systems worldwide. Sepsis is one of the leading causes of death and critical illness in the world [1, 2], with in-hospital mortality rates in the USA as high as 25–30% [3]. Data drawn principally from large retrospective database studies point to high population-level incidence rates for sepsis among patients hospitalized in high-income countries; indeed, admissions of patients with sepsis exceed those of patients who have suffered myocardial infarction or stroke [4, 5]. The incidence of sepsis in developed countries has been reported to be increasing [6, 7], although this is controversial and may in large part be a phenomenon of reporting bias related to financial reimbursement, increased awareness of sepsis definitions among medical professionals, and changes in diagnostic codes [8–11]. A recent study in which sepsis was defined according to the latest guidelines suggested relative stability in the rate of sepsis from 2002 to 2012 [12].

Septic shock, characterized by arterial hypotension, altered tissue perfusion, and increased blood lactate levels [13, 14], is the most severe form of sepsis. In 2016,

* Correspondence: jlvincent@intensive.org
[1]Department of Intensive Care, Erasme Hospital, Université libre de Bruxelles, Route de Lennik 808, 1070 Brussels, Belgium
Full list of author information is available at the end of the article

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Shankar-Hari et al. [15] conducted a systematic review to evaluate clinical criteria currently used to identify septic shock. They reported worldwide estimates for hospital mortality but provided no information on intensive care unit (ICU) or 28-/30-day mortality rates or on the frequency of septic shock. Moreover, Shankar-Hari et al. included data from patients enrolled between 1989 and 2015 (publications from 1992 to 2015), yet our awareness of sepsis has increased considerably since then and patient management has also changed.

We therefore conducted an updated systematic review to identify observational studies conducted in Europe and North America that reported epidemiological data of patients with septic shock. This was followed by a quantitative meta-analysis to determine the frequency of septic shock and its associated mortality.

Materials and methods

A systematic review protocol was prepared based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [16] and in accordance with established guidelines from The Cochrane Handbook for Systematic Reviews of Interventions [17] and the Center for Reviews and Dissemination [18].

Search strategy

A comprehensive literature search strategy combining Medical Subject Headings (MeSH) and free text terms for the epidemiology of septic shock, health-related quality of life, costs, and treatment guidelines was used to retrieve articles of interest from MEDLINE, MEDLINE In-Process Citations & Daily Update, Embase, and the Cochrane Library databases. Searches were limited to papers published between 1 January 2005 and 20 February 2018. Full search strategies are provided in Additional file 1.

Study selection criteria

Observational studies of adult patients (aged ≥ 15 years) with sepsis were eligible for inclusion if they reported data on either frequency or mortality of septic shock. Studies were limited to those conducted in Europe, the USA, or Canada. For the frequency assessment, they must have included cohorts of ≥ 100 patients, and for the mortality assessment, cohorts of ≥ 15 patients. Non-observational studies or studies of patients within specific disease groups or other exclusive populations were excluded. Conference abstracts, reviews, systematic reviews, and studies indexed as case reports, editorials, and letters were also excluded. The full list of inclusion and exclusion criteria is available in Additional file 1.

Screening and study selection

Double screening was performed, with four authors (K.K.C., E.O., S.D., and G.J.) in pairs providing an independent assessment of the titles and abstracts of all records retrieved in the electronic searches. The full text of each study that met the criteria for inclusion was then reviewed, with discrepancies between the reviewers resolved through discussion.

Data extraction

The following data were extracted from papers identified at full-text screening: article identifiers (authors, year of publication, objective), study identifiers (sample size, design, country, length of follow-up, inclusion criteria, definition and criteria used for identifying septic shock, comorbidities, number of organ failures), setting and population (age, sex, reason for admission, severity scores, acquisition of infection, microorganisms identified), and outcome measures (frequency, incidence, mortality).

Assessment of methodological quality

Quality assessments of the studies that were eligible for meta-analysis were performed using "The Joanna Briggs Institute Critical Appraisal Checklist for studies reporting prevalence data" [19] for frequency studies, with a modified version of "The Joanna Briggs Institute Critical Appraisal Checklist for case series" [20] used for studies reporting mortality.

Statistical analysis and meta-analyses

Random effects meta-analyses were performed to estimate pooled frequencies of septic shock diagnosed at admission or during the ICU stay and to estimate septic shock mortality in the ICU, hospital, and at 28 or 30 days. Separate analyses were performed on studies in which The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [14] were used, as this introduced hyperlactatemia as a component for septic shock. Using frequency and mortality rates from patients diagnosed with Sepsis-3 definitions was considered a potential source of heterogeneity given the more narrowly defined, more severe patients these criteria would identify with the addition of this component. Unless otherwise stated, estimates given are derived from studies in which any criteria except Sepsis-3 are used to identify septic shock. Confidence intervals for individual studies were calculated using the Clopper-Pearson method and between-study variances were estimated using the DerSimonian-Laird technique. For frequency, data were pooled using the inverse-variance method and the Freeman-Tukey double arcsine transformation to calculate an overall proportion, before back transformation to the original scale and the logit transformation were used to pool hospital mortality data. A continuity correction of 0.5 was applied in studies with zero cell frequencies. Statistical heterogeneity was assessed

visually using forest plots and formally using the I^2 statistic; heterogeneity was considered to be high for I^2 values greater than 75% [21].

For frequency, two meta-analyses were performed according to the time of septic shock diagnosis reported in the study (at ICU admission or at any time during the ICU stay). For mortality, three meta-analyses were performed according to the type of reported mortality: ICU mortality, in-hospital mortality, and mortality at either 28 or 30 days. Subgroup meta-analyses for frequency and mortality were performed for European vs North American studies, and for single center vs multicenter studies. Publications that did not report data as proportions (n/N) but as percentages were excluded if the proportions could not be accurately back-calculated. Studies that reported 1-day point prevalence estimates were also excluded from the meta-analyses.

All analyses were performed using R software (www.R-project.org) and the package "meta" (general package for meta-analysis) (https://cran.r-project.org/web/packages/meta/meta.pdf).

Results

Study selection

The literature search identified 6291 records following de-duplication. Following title and abstract screening 460 articles met the criteria for full-text evaluation. A total of 71 met the eligibility criteria and were included in the qualitative systematic review; 50 publications reported data from Europe and 21 publications reported data from North America. Full details of study selection and exclusions are shown in the PRISMA flow diagram in Additional file 1: Figure S1.

Frequency data were reported in 36 of the 71 publications covering 27 individual studies/datasets [22–57] (Additional file 1: Table S1). Data from the Sepsis Occurrence in Acutely Ill Patients (SOAP) study were reported in four separate publications [26–28, 32]; data from a single 1-day frequency study from Germany were reported in two publications [29, 34]; the French EPIdemiology of Septic Shock study (EPISS) was detailed in two publications [46, 47]; a multicenter study from the Piedmont Intensive Care Unit Network in Italy was reported in two publications [48, 49]; the OUTCOMEREA database was used for three publications [22, 36, 51]; and the Portuguese Community-Acquired Sepsis (SACiUCI) study was reported in two publications [37, 39]. Mortality data were reported in 62 publications covering 57 individual studies [10, 23–28, 31, 32, 34, 35, 37–43, 45–48, 50–52, 54, 55, 57–91] (Additional file 1: Table S2).

Quality assessment

The proportion of studies that fulfilled each item on the quality assurance checklist is shown in Additional file 1: Tables S3 and S4 for the studies that report frequency data and mortality data, respectively. For frequency, the areas that raised concern were the validity of methods used for identification of septic shock, the reliability of septic shock diagnosis among patients, and rate of response and methods employed to manage low response rate. For mortality, the areas that raised concern were, again, the reliability of septic shock diagnosis among patients, in addition to completeness of inclusion, and clear reporting of demographics of the septic shock patients.

Frequency estimates

Frequency estimates ranged from 2.5% [25] to 23.4% [57] when septic shock was diagnosed at ICU admission (Additional file 1: Table S1). Three studies reported 1-day point prevalence estimates for frequency and were excluded from the meta-analyses [29, 34, 53]. The overall pooled frequency of septic shock was estimated at 10.4% (95% CI 5.9 to 16.1%) with a high level of heterogeneity ($I^2 = 100\%$; $p = 0$) (Fig. 1). This pooled frequency decreased to 6.5% (95% CI 5.6 to 7.5%) when using Sepsis-3 criteria. When septic shock was diagnosed at any time during the ICU stay, estimates ranged from 1.4% [41] to 27.6% [38] (Additional file 1: Table S1) and the overall pooled frequency of septic shock was estimated at 8.3% (95% CI 6.1 to 10.7%) with a high level of heterogeneity ($I^2 = 99\%$; $p = 0$) (Fig. 2). Estimates for septic shock frequency at admission and at any time during the ICU stay were higher in European populations than in North American populations (11.4% vs. 6.0% and 8.9% vs. 4.6% respectively; see Additional file 1: Figures S2 and S3). Estimates for septic shock frequency at admission were higher in multicenter than in single-center studies (10.6% vs. 9.0%), but the reverse was true for septic shock frequency during the ICU stay (7.6% vs. 9.9%); none of these differences were statistically significant (Additional file 1: Figures S4 and S5).

Mortality

Mortality rates in the included studies are reported in Additional file 1: Table S2. Three random-effects meta-analyses were performed to evaluate the mortality of septic shock in the ICU, in the hospital and at 28/30 days; these are shown in Figs. 3, 4, and 5. For seven of the publications reporting mortality, the number of patients could not be calculated and these were excluded from the meta-analyses [37, 39, 58, 67, 79, 88, 90]. One study reported a 1-day point prevalence estimate for hospital mortality and was excluded from the meta-analysis [34]. The mean mortality was 37.3% (95% CI 31.5% to 43.5%) in the ICU and 39.0% (95% CI 34.4% to 43.9%) in-hospital. Mortality at 28/30 days was estimated at 36.7% (95% CI 32.8% to 40.8%). Statistically significant heterogeneity was observed in all meta-analyses with

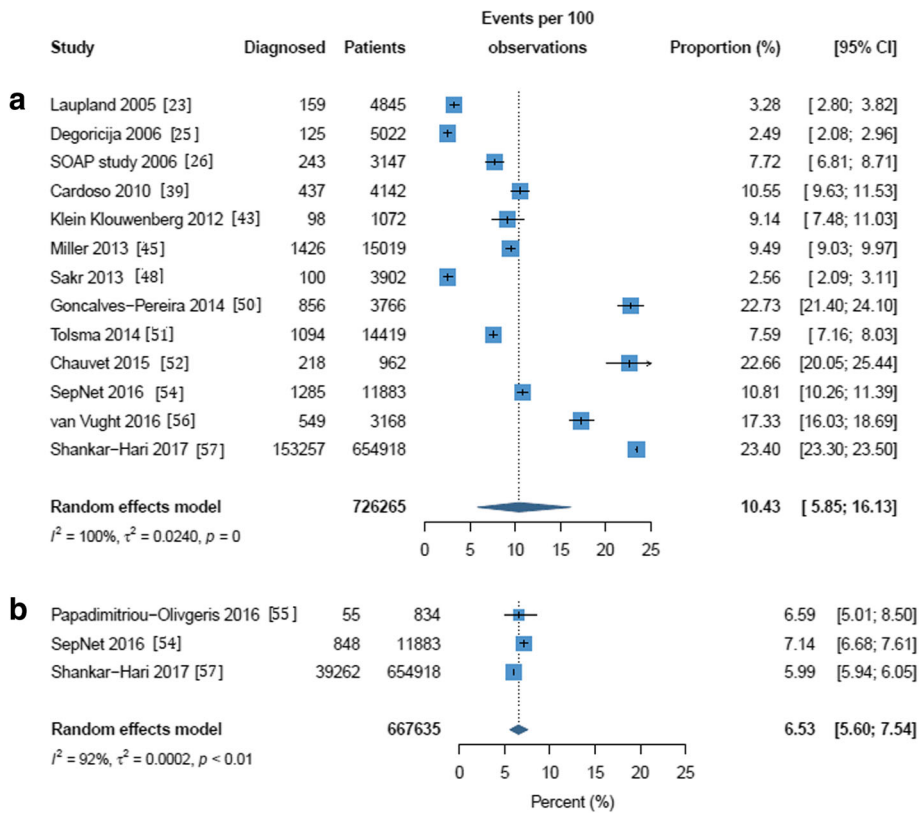


Fig. 1 Frequency of septic shock in a cohort of patients admitted to the intensive care unit and diagnosed on admission. (a) All definitions except Sepsis-3. (b) Sepsis-3 only. The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the Freeman–Tukey double arcsine transformation and the DerSimonian–Laird method estimates between-study variance

reported I^2 values of 98, 100, and 90 for in-ICU, in-hospital, and 28-/30-day mortality, respectively. ICU and hospital mortality estimates increased to 51.9% (95% CI 43.9 to 59.8%) and 52.1% (95% CI 51.6 to 52.6%) respectively when septic shock was diagnosed using Sepsis-3 criteria. As with frequency, estimates for mortality in the ICU and hospital and at 28/30 days were all higher in European populations than in North American populations (37.9% vs. 32.8%, 42.7% vs. 32.3%, and 38.5% vs. 33.2%) though not significantly so (see Additional file 1: Figures S6–S8). Estimates for ICU, hospital, and 28-/30-day mortality were higher in multicenter than in single-center studies (41.8% vs 37.1%, 43.1% vs. 34.0%, and 37.2% vs. 36.2%, respectively; Additional file 1: Figures S9-S11); none of these differences were statistically significant.

Discussion

Our systematic review shows that approximately 10% of ICU patients have septic shock at admission and 8% of patients admitted to the ICU have septic shock sometime during their ICU stay. Populations assessed using Sepsis-3 criteria had a lower estimate at admission (approximately 7%). This may be a result of the narrower definition used in comparison to previous consensus criteria [92]. Earlier versions of the sepsis consensus definitions did not take into account lactate levels and required that patients met 2 or more systemic inflammatory response syndrome (SIRS) criteria; therefore, they are likely to be more inclusive [38, 93, 94]. The high occurrence of septic shock among ICU patients supports current efforts to raise awareness of the condition among healthcare professionals and the general public, but caution should be exercised when interpreting our pooled estimates given the high heterogeneity observed between studies. This variability in estimates could be driven by patient populations and, as the European- and North American-specific estimates suggest, country of origin. The different methods of identifying cases, using discharge codes, administrative data, or electronic chart reviews, might also account for some of the differences. For example, some coding abstraction methods may underestimate the diagnosis [95] and significant numbers of patients may be misclassified by electronic health record-based definitions when the frequency of the condition is low [96]. Additionally, the higher number of septic shock cases reported in some countries

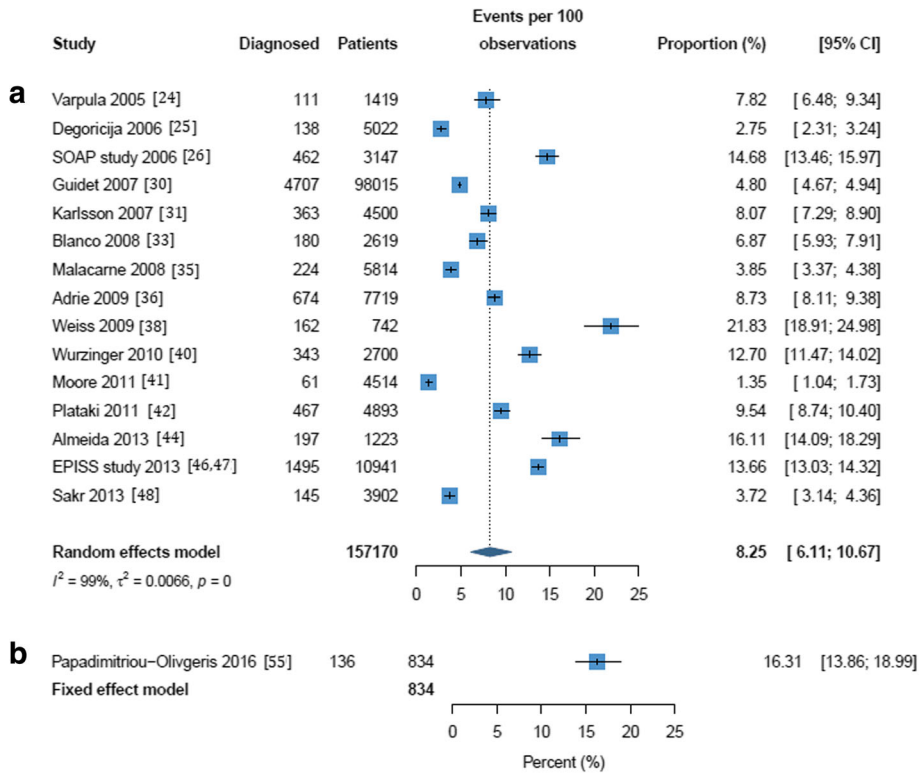


Fig. 2 Frequency of septic shock within a cohort of patients admitted to the intensive care unit and diagnosed at some time during stay. (a) All definitions except Sepsis-3. (b) Sepsis-3 only. The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the Freeman–Tukey double arcsine transformation and the DerSimonian–Laird method estimates between-study variance

may partly be explained by the lower number of ICU beds resulting in a concentration of more severely ill patients. For example, a study of Portuguese ICUs revealed an unusually high frequency of septic shock diagnosed at admission (approximately 23%) that the authors suggested was most probably related to the lack of ICU services in Portugal [50]. The differences observed might also be due to seasonal variations in the epidemiology of septic shock as the time period of the studies varied widely from a single day to several years. Additionally, the reporting of the data was not always satisfactory. Many studies collected data from a mix of patients diagnosed either at admission or screened prospectively during their ICU stay. These data were often not reported separately, so our estimates may be a mix of frequency and incidence rates.

Our results show that, regardless of the time-point of assessment, the septic shock mortality rate is approximately 38%. This is somewhat lower than the results of the systematic review conducted by Shankar-Hari et al. that estimated a septic shock-associated crude mortality of 46.5% [15]. This may be a result of the inclusion of some long-term follow-up data by Shankar-Hari et al. whereas the current review focused on short-term mortality. Moreover, the Shankar-Hari review included studies in which patient data were collected prior to 1995 when mortality rates may have been higher on average than in more recent studies. Indeed, 20–25 years ago, non-selected populations had a crude mortality rate for septic shock of more than 50% [97, 98]. In the years since, observational studies have reported higher survival rates [7, 46, 99–102], likely because of improvements in the general management of patients with septic shock. Our estimates for 28–30-day mortality are higher than those identified by a systematic review on long-term mortality [103], which reported post-acute phase mortality (difference in proportion between cumulative 1-year mortality and acute mortality) of 16.1% (95% CI 14.1 to 18.1%), levels that are likely to incur a high burden on overall costs and quality of life. Estimates for ICU and in-hospital mortality were higher using Sepsis-3 criteria than non-Sepsis-3 criteria (52% vs. 37% and 52% vs. 39%), which may be a result of the greater severity of disease associated with the addition of hyperlactatemia as a component for septic shock diagnosis. This is consistent with previous research that found that Sepsis-3 identified patients who were more advanced

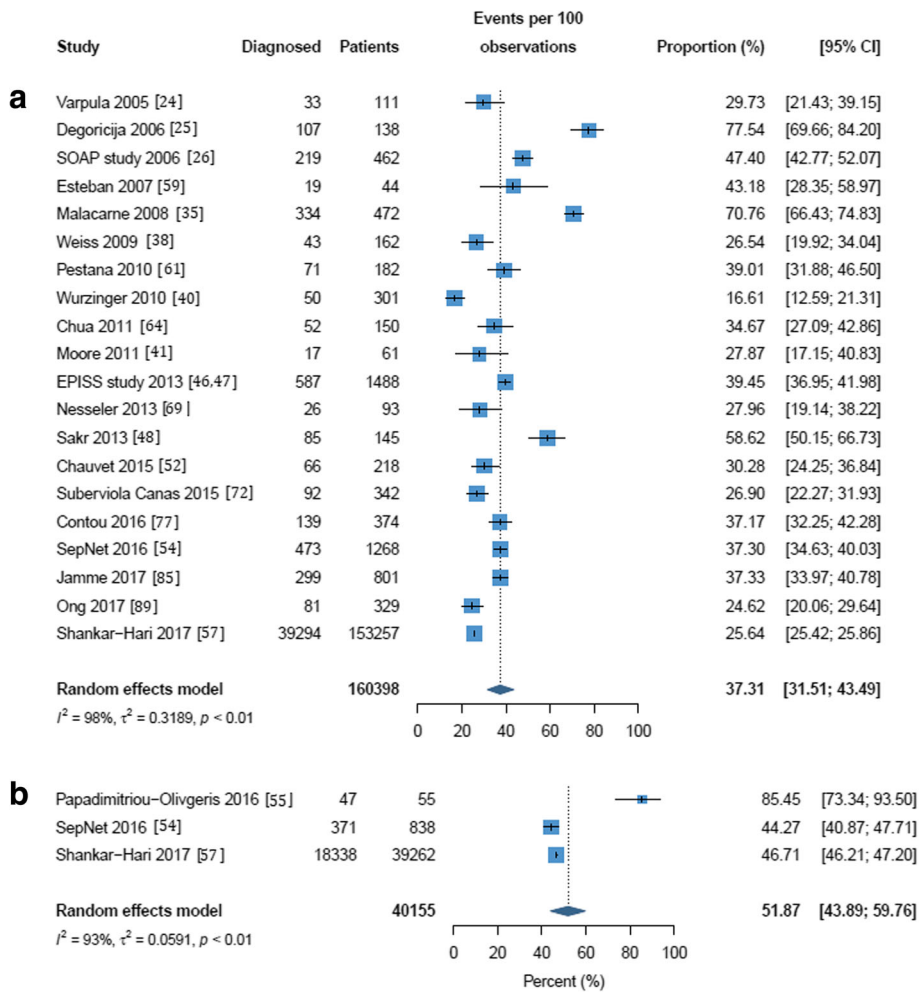


Fig. 3 Random effects meta-analysis of studies reporting intensive care unit mortality of septic shock patients. (a) All definitions except Sepsis-3. (b) Sepsis-3 only. The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the logit transformation and the DerSimonian–Laird method estimates between-study variance

in the course of their disease and in whom a poor outcome was more likely than in those identified using Sepsis-2 criteria [104]. Our results thus support previous studies postulating that the significant shift in the diagnostic criteria from SIRS criteria to a focus on organ dysfunction would have a major impact on mortality [38, 94].

An up-to-date understanding of the incidence of septic shock and associated mortality is important to help guide resource allocation and inform healthcare budgets. Indeed, the economic costs of sepsis are a significant burden on healthcare systems. In the USA, approximately US$20 billion is spent annually on hospital care for sepsis patients, with septic shock requiring longer ICU care and higher hospitalization costs [105]. In the UK, recent data suggest total annual hospital costs of just over £1 billion for patients with sepsis [106]. The effects of sepsis on patient health last beyond hospital discharge, with an increased mortality risk for years after hospitalization [107–109]. Nearly a quarter of sepsis survivors are readmitted to hospital within 30 days of discharge [110], and survivors often exhibit profound immune suppression, physical and psychological disorders, and impaired quality of life [107, 109, 111]. These long-term consequences greatly contribute to the high total economic cost of the disease, which is estimated to be around US$67 billion yearly in the USA alone [105]. In the UK, the total annual costs of sepsis taking into account these indirect costs are estimated at around £10 billion [106].

The results of our review should be interpreted with consideration of certain limitations. Firstly, we only included studies published in English, potentially leading to language bias as relevant studies published

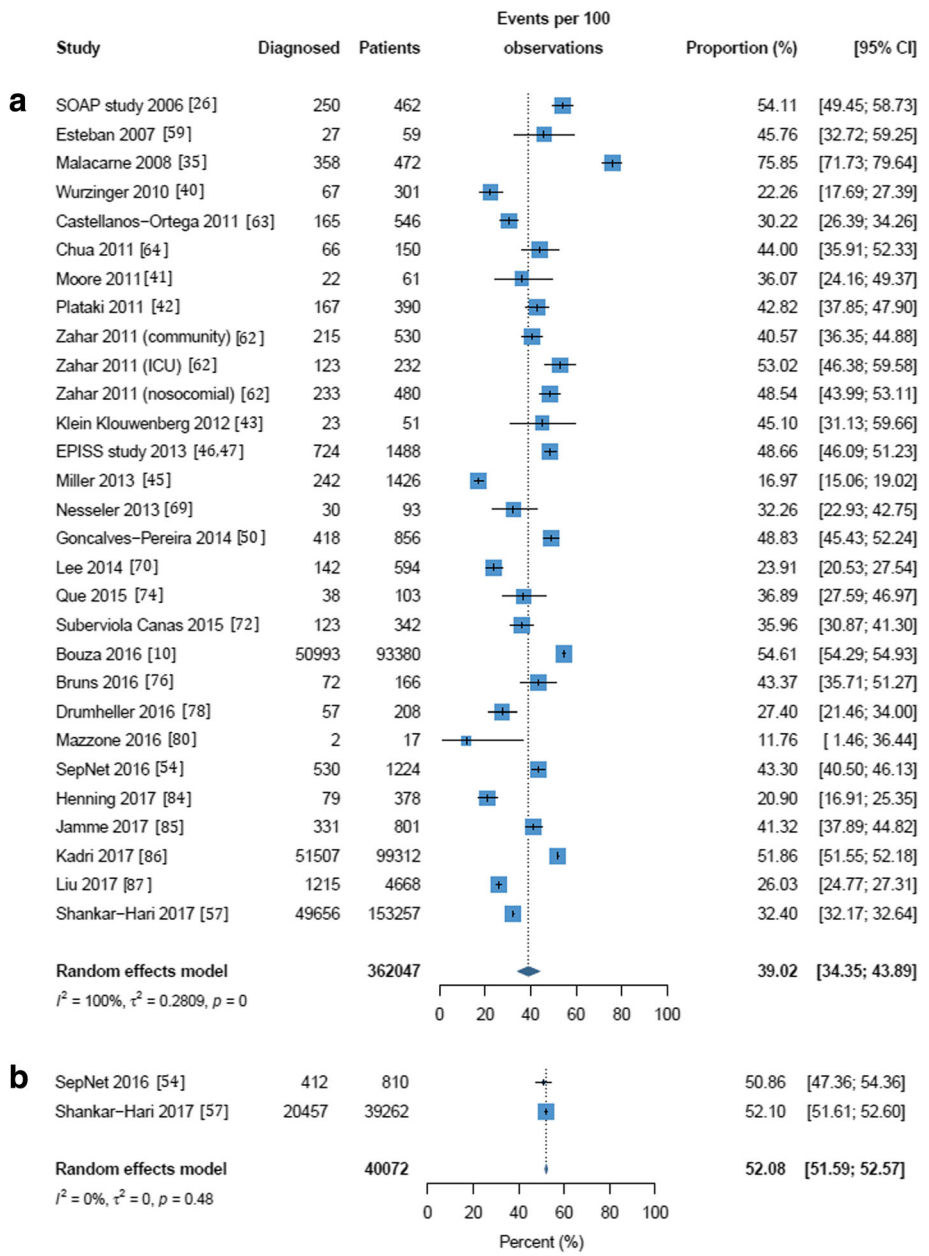


Fig. 4 Random effects meta-analysis of studies reporting hospital mortality of septic shock patients. (a) All definitions except Sepsis-3. (b) Sepsis-3 only. The forest plots contain exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summaries are obtained using the logit transformation and the DerSimonian–Laird method estimates between-study variance

in other languages were not included. Secondly, estimates using Sepsis-3 criteria were derived from very few studies.

Conclusion

Our findings suggest that septic shock occurs frequently in ICU patients and mortality remains high. Considerable differences in diagnostic criteria have been employed in the different studies over the last 15 years. Our review indicates that the adoption of Sepsis-3 criteria is still at an early stage (≤ 3 studies); however, as Sepsis-3 is increasingly adopted and more epidemiological studies are published in which these criteria are used, a more complete picture will emerge concerning what differences, if any, exist between countries and different care settings. This would allow a more accurate estimation of the burden of septic shock, thus enabling the development of better policies for public health planning and hospital management.

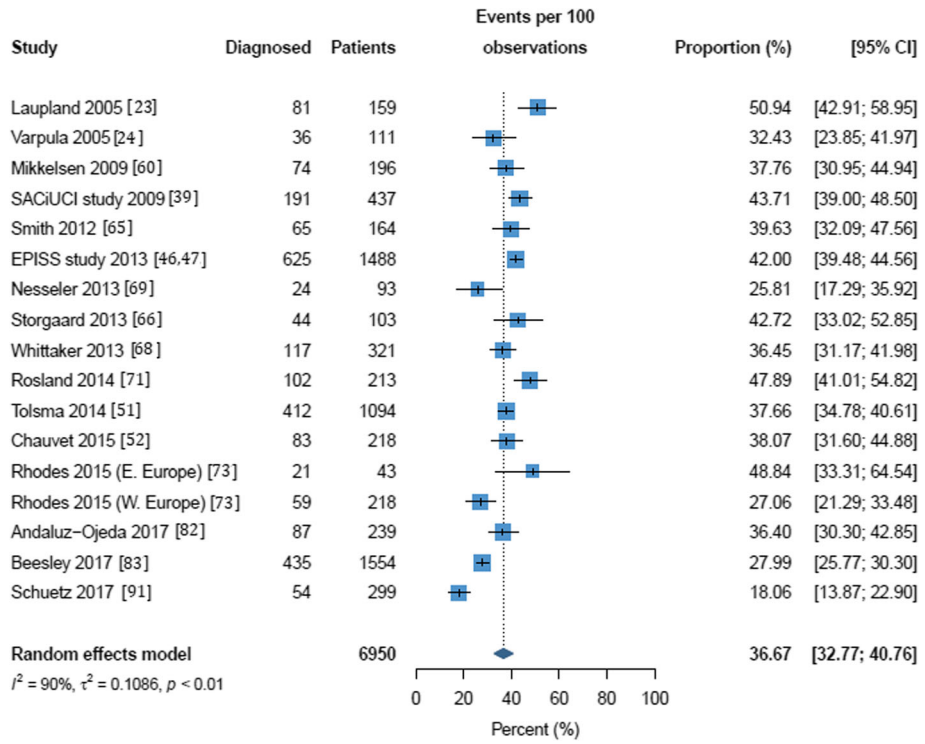


Fig. 5 Random effects meta-analysis of studies reporting 28-/30-day mortality in septic shock patients. The forest plot contains exact 95% confidence intervals, and specific studies are weighted using the inverse-variance method. The pooled summary is obtained using the logit transformation and the DerSimonian–Laird method estimates between-study variance

Additional file

Additional file 1: Search strategy and inclusion and exclusion criteria, **Tables S1–S4** and **Figures S1–S11.** (PDF 1970 kb)

Abbreviations

CI: Confidence interval; EPISS: EPIdemiology of Septic Shock study; ICD: International Classification of Diseases; ICU: Intensive care unit; MeSH: Medical Subject Headings; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; SACiUCI: Portuguese Community-Acquired Sepsis study; SIRS: Systemic inflammatory response syndrome; SOAP: Sepsis Occurrence in Acutely Ill Patients study

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Availability of data and materials

Not relevant.

Authors' contributions

EO and KKC produced the protocol. GJ, SD, EO, and KKC screened publications for inclusion in the review and carried out data extraction, validation and quality assessment of the included studies. EO and KKC wrote the manuscript with some support from GJ. SD and GJ conducted the meta-analysis and produced the forest plots. JLV provided disease area expertise and reviewed the manuscript for critical content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

JLV is the Editor-in-Chief of Critical Care. He has no other conflicts of interest to declare.
SD declares no competing interests.
GJ, EO, and KKC were employees of PHMR Ltd. when this work was performed. PHMR Ltd. was contracted by Ferring Pharmaceuticals to perform this systematic review and meta-analysis.

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Author details

[1]Department of Intensive Care, Erasme Hospital, Université libre de Bruxelles, Route de Lennik 808, 1070 Brussels, Belgium. [2]PHMR Ltd., Berkeley Works, Berkley Grove, London NW1 8XY, UK.

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PERITONITIS-RELATED MORTALITY IN PATIENTS UNDERGOING CHRONIC PERITONEAL DIALYSIS

Miguel Pérez Fontán,[1,3] Ana Rodríguez-Carmona,[1] Rafael García-Naveiro,[1] Miguel Rosales,[2,3] Pedro Villaverde,[1] and Francisco Valdés[1]

Divisions of Nephrology[1] and Public Health,[2] Hospital Juan Canalejo; Department of Medicine,[3] University of A Coruña, A Coruña, Spain

Peritonitis is a well-known cause of mortality in peritoneal dialysis (PD) patients. We carried out a retrospective study to disclose the clinical spectrum and risk profile of peritonitis-related mortality. We analyzed 693 episodes of infectious peritonitis suffered by 565 patients (follow-up 1149 patient-years). Death was the final outcome in 41 cases (5.9% of episodes), peritonitis being directly implicated in 15.2% of the global mortality and 68.5% of the infectious mortality observed. In 41.5% of patients with peritonitis-related mortality, the immediate cause of death was a cardiovascular event. Highest mortality rates corresponded to fungal (27.5%), enteric (19.3%), and *Staphylococcus aureus* (15.2%) peritonitis. Multivariate analysis disclosed that the baseline risk of peritonitis-related mortality was significantly higher in female [relative risk (RR) 2.13, 95% confidence interval (CI) 1.24 – 4.09, $p = 0.02$], older (RR 1.10/year, CI 1.06 – 1.14, $p < 0.0005$), and malnourished patients (RR 2.51, CI 1.21 – 5.23, $p = 0.01$) with high serum C-reactive protein (s-CRP) levels (RR 4.04, CI 1.45 – 11.32, $p = 0.008$) and a low glomerular filtration rate (RR 0.75 per mL/minute, CI 0.64 – 0.87, $p < 0.0005$). Analysis of risk after a single episode of peritonitis and/or subanalysis restricted to peritonitis caused by more aggressive micro-organisms disclosed that overall comorbidity [odds ratio (OR) 1.21, CI 1.05 – 1.71, $p = 0.005$], depression (OR 2.35, CI 1.14 – 4.84, $p = 0.02$), and time on PD at the time of the event (OR 1.02/month, CI 1.00 – 1.03, $p = 0.02$) were other predictors of mortality.

In summary, the etiologic agent is a definite marker of peritonitis-related mortality but gender, age, residual renal function, inflammation (s-CRP), malnutrition, and depression are other significant correlates of this outcome. Most of these risk factors are common to cardiovascular and peritonitis-related mortality, which may explain the high incidence of cardiovascular event as the immediate cause of death in patients with peritonitis-related mortality.

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Correspondence to: M. Pérez Fontán, Servicio de Nefrología, Hospital Juan Canalejo, Xubias 84, 15006 A Coruña, Spain.
mfontan@canalejo.org

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Despite significant advances in prevention and therapy during the past two decades, peritonitis is still a significant cause of morbidity and technique failure among patients undergoing peritoneal dialysis (PD) (1). Moreover, these infections carry a relatively low but definite risk of direct mortality, estimated in 1% – 6% of episodes in different studies (2). Peritonitis has been considered to play a significant role in as many as one sixth of the deaths occurring in the course of PD therapy (3). The etiologic agent is undoubtedly a strong marker of outcome after a single episode of peritonitis, with the highest mortality rates recorded after enteric (4–6), fungal (7,8), and, to a lesser extent, gram-negative (9,10) and *Staphylococcus aureus* (10,11) infections; coagulase-negative staphylococci represent the most benign agents of peritonitis in terms of mortality (9–11).

Many studies have explored the prognostic spectrum of PD-related peritonitis (4–15), in most cases emphasizing the relevance of factors such as the etiologic agent(s), the severity of the initial clinical presentation, or the efficacy of different therapeutic approaches. Hospitalization, peritoneal catheter loss, and technique failure, with dropout to hemodialysis (HD), are the most frequently quoted serious consequences of these infections, while direct peritonitis-related mortality has generally been considered as a most severe but secondary outcome, due to the relatively low incidence of this event. On the other hand, few studies have analyzed the specific clinical spectrum of peritonitis-related mortality (3,16) and the association of this outcome with baseline or single-episode-related risk factors other than the etiologic agent or the immediate clinical aggressiveness of the infection. It is conceivable that the many debilitating conditions that frequently concur in dialysis patients may contribute to defining the outcome of

PD-related peritonitis, but this possibility has been insufficiently studied.

We performed a retrospective study to assess the clinical spectrum and risk profile of peritonitis-related mortality in a wide population of patients undergoing PD in a single center for a period exceeding 18 years.

POPULATION AND METHOD

We analyzed retrospectively the information recorded in an extensive prospective database of patients undergoing PD in our unit between 1 January 1986 and 31 March 2004, with the aims of establishing the incidence, clinical spectrum, and risk profile for peritonitis-related mortality during the aforementioned period.

STUDY POPULATION

During the study period, 565 patients underwent PD therapy in our unit. Their main baseline characteristics are displayed in Table 1. Total follow-up was 1149 patient-years (range 1 – 125 months).

All patients used standard continuous ambulatory PD (CAPD) or automated PD systems. Y-set systems were progressively introduced starting in 1987, and only 36 patients (6.4%) used traditional spike systems for CAPD exchanges at any time during follow-up.

DEFINITION OF VARIABLES

We defined "peritonitis-related mortality" as the death of a patient due to any immediate cause but under one of three circumstances:

1. During the course of a clinically active peritonitis (persistent abdominal pain and/or turbid dialysate);
2. During the week following complete clinical, bacteriologic, and cytological remission of an episode of peritonitis;
3. In the case of a refractory peritonitis demanding catheter removal, before hospital discharge for reinitiation of regular dialysis therapy (PD or HD).

Peritoneal dialysis-related peritonitis was diagnosed according to standard criteria. The term "complicated peritonitis" was used generically to include any episode of infectious peritonitis deserving an approach beyond simple antibiotic therapy. We diagnosed "refractory peritonitis" in the presence of persistent clinical activity and/or bacteriologic positivity after 5 days of appropriate antibiotic therapy. The definition of "enteric peritonitis" was based on bacteriologic criteria: growth in dialysate of one or more anaerobic intestinal bacteria and/or at least two micro-organisms characteristic of intestinal flora (including *Enterobacteriaceae*, *Enterococcus spp*, and yeasts, among others).

TABLE 1
Baseline Characteristics of the Study Population.
Values expressed as [*n* (%)] unless otherwise.

Patients (*n*)	565
Age (years)	57.9±11.1 (range 7–87)
Gender (male/female)	310/255 (55/45)
Underlying disease	
Glomerular	60 (10.6)
Interstitial	68 (12.0)
Vascular	55 (9.7)
Polycystic kidney diseases	42 (7.4)
Systemic	23 (4.1)
Diabetic nephropathy	171 (30.3)
Other/unknown	146 (25.8)
Diabetes	190 (33.6)
Major comorbidities	1.0±1.6
None	280 (49.6)
1	145 (25.7)
>1	140 (24.8)
GFR (mL/min)	4.4±3.2 (range 0–16.0)
Malnutrition by Subjective Global Assessment	
No	494 (87.5)
Moderate	52 (9.2)
Severe	19 (3.4)
Obesity (BMI>30 kg/m^2) (*n*=529)	69 (13.0)
Depression	48 (8.5)
Chronic hemodialysis before PD	38 (6.7)
Previous renal transplant	21 (3.7)
Immunosuppression	38 (6.7)
Mode of PD (CAPD/A PD)	344/221 (61/39)
Need for a dialysis partner	265 (46.9)
D/P creatinine[a]	0.64±0.13 (range 0.30–0.97)
Hemoglobin (g/dL)	10.1±1.7 (range 5.6–15.7)
Plasma albumin (g/L)	37.2±5.7
>30 g/L	509 (90.1)
≤30 g/L	56 (9.9)
Serum CRP (mg/L) (*n*=330)	6.7 (range 1–198)
<7 mg/L	169 (51.2)
≥7 mg/L	161 (48.8)

GFR = glomerular filtration rate; BMI = body mass index; PD = peritoneal dialysis; CAPD = continuous ambulatory PD; APD = automated PD; D/P = dialysate-to-plasma ratio; CRP = C-reactive protein.

[a] After 240 minutes baseline peritoneal equilibration test.

Values express mean (standard deviation), number of cases (%), or median (range) (C-reactive protein).

The determinant role of the etiologic agent on peritonitis-related mortality may compound any strategy of analysis of risk factors for this complication of PD. Trying to overcome this methodological limitation, we performed a specific subanalysis restricted to episodes of peritonitis caused by more aggressive micro-organisms, which were grouped under the term "severe peritonitis." We included in this subset fungal (primary or secondary) and enteric peritonitis, as well as infections caused by mycobacteria, *Staphylococcus aureus,* and *Pseudomonas aeruginosa* and related bacteria.

TREATMENT OF PERITONITIS

Our protocol of empiric antibiotic therapy for PD-related peritonitis has been based on intraperitoneal ciprofloxacin during the past 16 years, and has been described in detail elsewhere (17). During follow-up, antibiotic therapy may be modified according to bacterial antibiotic sensitivity and clinical course. Management of complicated peritonitis includes catheter removal in case of fungal (immediate) or refractory peritonitis. Indication for exploratory laparotomy during enteric peritonitis is individualized, based on clinical presentation and/or diagnostic workup (including routine abdominal computed tomographic scan). These criteria remained stable during the study follow-up.

STRATEGY OF ANALYSIS

The analysis was carried out over two secondary data files based on patients and individual episodes of peritonitis respectively. The first was used to establish the baseline risk profiles for presenting at least one episode of infectious peritonitis (any type) or severe peritonitis, and for peritonitis-related mortality. The second file allowed mathematic modeling of the risk of death associated with a single episode of peritonitis (any) or severe peritonitis.

The baseline variables considered for analysis included age, gender, underlying renal disease, diabetes mellitus, mode of PD (assignment according to intention-to-treat criteria in case of change), partial or complete incapacity for self-dialysis (requiring a dialysis partner), peritoneal transport characteristics at the start of PD [as estimated from dialysate-to-plasma ratio (D/P) of creatinine after 240 minutes in a standard peritoneal equilibration test (PET)], glomerular filtration rate (GFR; estimated from mean renal clearance), major comorbidities, malnutrition [standard Subjective Global Assessment (SGA)], obesity (body mass index > 30 kg/m^2), depression (ongoing antidepressant therapy at the start of PD therapy), procedure other than conservative therapy (HD, previous renal transplant), previous or current immunosuppressive drug therapy, and hemoglobin, plasma albumin (by automatic analyzer), and serum C-reactive protein (s-CRP) levels (by immunoturbidimetry; Roche Diagnostics, Mannheim, Germany). The comorbidity score was applied as the sum of all the major comorbidities (both cardiovascular and non-cardiovascular) present at the time of initiation of PD therapy, without correction for severity. Depression and malnutrition received specific attention and were not computed in the general comorbidity score. Given the low prevalence of severe malnutrition, moderate and severe malnutrition were grouped as one binary variable (present/absent).

For the analysis of risk after a single episode of peritonitis, some baseline variables, including age, accumulated comorbidity, mode of PD, malnutrition, obesity, antidepressant and immunosuppressive therapy, and hemoglobin and albumin values, were updated to the last control available before the event. Other variables considered for this part of the analysis included time on PD at the time of the event, etiologic agent, baseline peritoneal cell count, and some basic clinical markers of aggressiveness (hospital admission, peritoneal catheter removed, laparotomy performed, relapse, superinfection, and simultaneous exit-site infection).

All variables were available for study in at least 95% of the cases, with the exceptions of D/P creatinine (n = 323), GFR (n = 508), body mass index (n = 529), and s-CRP (n = 330).

STATISTICS

Univariate statistical analysis was based on Student's t-test (unpaired data), chi-square distribution, analysis of variance, and Mann–Whitney's test. The multivariate approach included Cox's proportional hazard model (patient-based risk profiles) and logistic regression analysis (peritonitis-based risk profiles). In the former case, patients were censored in case of renal transplant, loss to follow-up, or death due to causes other than peritonitis (peritonitis-related mortality). The strategy of multivariate analysis included creating a best-fit model for the explored event and then introducing other variables, alone or in combination, to obtain adjusted estimations of the independent relative risk (RR; Cox's model) or odds ratio (OR; logistic regression) associated with these secondary variables. Statistical analysis was produced with the help of the SPSS 12.0 software (SPSS Inc., Chicago, Illinois, USA).

RESULTS

GENERAL OVERVIEW

We recorded 733 episodes of peritonitis during follow-up, but 40 cases were excluded from analysis due to noninfectious etiology (eosinophilic, chemical, icodextrin). The incidence of peritonitis declined progressively during the study follow-up (Figure 1), but the absolute number of infections increased during the same period due to the growing number of patients undergoing PD in our unit (20 patients treated in 1986, compared with 123 in 2003). The etiologic spectrum of infectious peritonitis and the corresponding accumulated mortality rates are presented in Table 2. The distribution of peritonitis by etiologic agent was relatively homogeneous in time, with the exceptions of *Staphylococcus aureus* infections (21 of 46 episodes before the end of 1990, when mupirocin was introduced for treatment of carriers) and enteric peritonitis, which, for unclear reasons, had a peak incidence during the period 1998–2000. Figure 2 depicts the time courses of global and peritonitis-related mortalities. Our criteria for the diagnosis of severe peritonitis was met in 159 episodes of peritonitis (including 18 superinfections by yeasts) suffered by 127 patients.

TABLE 2
Etiologic Agents of Peritonitis. Values expressed as [*n* (%)].

Micro-organism	Episodes	Mortality
Staphylococcus aureus[a]	46 (6.6)	7[c] (15.2)
Coagulase-negative staphylococcus	206 (29.7)	1 (0.5)
Enterococcus spp[a]	22 (3.2)	1 (4.5)
Streptococcus spp	113 (16.3)	5[d] (4.4)
Other gram-positive bacteria	23 (3.3)	0 (0)
Enterobacteriaceae	85 (12.3)	4 (4.7)
Pseudomonas aeruginosa and related gram-negative bacteria	9 (1.3)	1 (11.1)
Other gram-negative bacteria	11 (1.6)	0 (0)
Polymicrobial non-enteric	26 (3.8)	1[c] (3.8)
Enteric	62 (8.9)	12 (19.4)
Fungal (primary)[b]	22 (3.2)	6 (27.3)
Tuberculosis	3 (0.4)	2 (66.7)
Negative culture	65 (9.4)	1 (1.5)
Total	693 (100)	41 (5.9)

[a] Vancomycin sensitive in all cases.
[b] Other 18 peritonitis by yeasts were the consequence of superinfections of primary bacterial peritonitis. In all, 11/40 patients (27.5%) died after fungal peritonitis, either primary or secondary.
[c] One superinfection by yeast.
[d] Three superinfections by yeasts.

RISK OF PRESENTING PERITONITIS

Only 267 patients (47.3%) remained free of peritonitis by the end of their follow-up. Univariate analysis of the baseline risk profile for presenting at least one episode of peritonitis disclosed that this event was more likely in older patients (mean age 60.1 years if peritonitis, compared with 55.3 if no peritonitis, $p < 0.001$) undergoing CAPD (56.4% presented peritonitis, compared with 46.4% of patients undergoing automated PD, $p = 0.012$), needing a dialysis partner (58.0% with peritonitis, compared with 47.5% of patients able to perform self-dialysis, $p = 0.012$), previously treated with HD (71.1% had peritonitis, compared with 51.1% of patients with PD as first renal replacement therapy, $p = 0.014$), with a poorer GFR (mean 3.9 vs 4.9 mL/minute, $p = 0.001$), lower hemoglobin levels (mean 9.9 vs 10.2 g/dL, $p = 0.03$), higher s-CRP levels (median 10.3 vs 5.2 mg/L, $p = 0.001$ Mann–Whitney), and a longer follow-up on PD therapy (mean 32.2 vs 16.0 months, $p < 0.001$); other variables were not significant (NS).

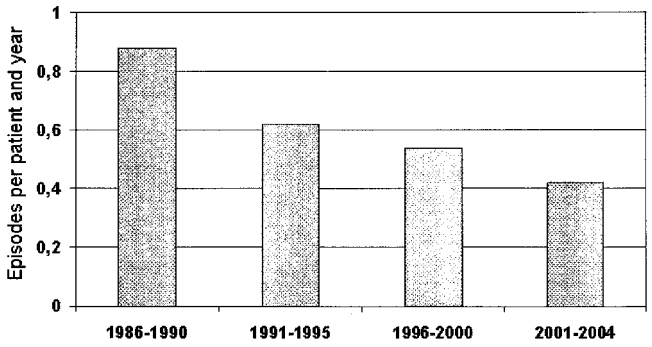


Figure 1 — Time course of the incidence of peritonitis during the study period.

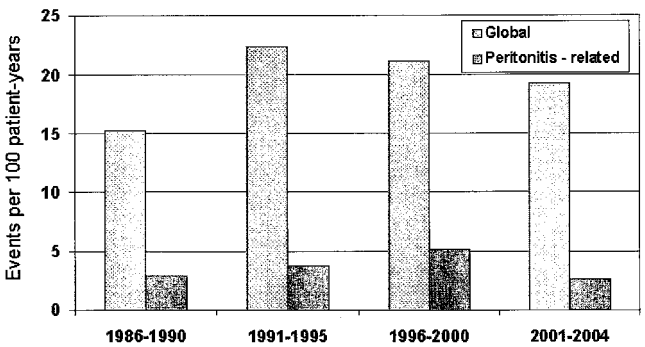


Figure 2 — Accumulated global and peritonitis-related mortality rates in different phases of follow-up.

The baseline risk of suffering at least one instance of severe peritonitis appeared to be higher in women (26.0% suffered severe peritonitis, compared with 14.6% of males, $p = 0.001$), older patients (mean age 60.3 vs 57.2 years, $p = 0.07$), needing a dialysis partner (25.2% had severe peritonitis, compared with 14.9% of patients able to perform self-dialysis, $p = 0.003$), previously treated with HD (42.1% compared with 18.5% of patients coming from conservative therapy, $p = 0.001$), with more comorbidities (mean 1.2 vs 0.9 per patient, $p = 0.013$), poorer GFR (mean 3.2 vs 4.7 mL/min, $p = 0.001$), a depressive background (31.3% compared with 18.6% of non-depressed patients, $p = 0.016$), lower hemoglobin levels (mean 9.6 vs 10.2 g/dL, $p = 0.02$), higher baseline s-CRP levels (median 12.2 vs 6.5 mg/L, $p = 0.06$ Mann–Whitney), and a longer follow-up on PD therapy (mean 32.9 vs 22.0 months, $p < 0.001$); other variables were NS.

The results of multivariate analysis of the risk profiles for presenting at least one episode of peritonitis or severe peritonitis are presented in Table 3. A baseline s-CRP level ≥7 mg/L carried a relative risk of 1.62 (95% confidence interval 1.10 – 2.38, $p = 0.015$) of presenting at least one episode of peritonitis during follow-up.

SPECTRUM OF PERITONITIS-RELATED MORTALITY

In all, 41 patients died as a consequence of peritonitis. In 24 cases (58.5%), peritonitis was considered the main cause of death; in 13 other cases (31.7%), the infection had a clearly significant role as a cause of death but other previous conditions, including dementia/failure to thrive ($n = 9$), cardiovascular disorders ($n = 4$), and neoplastic/ischemic abdominal disease ($n = 4$), contributed significantly to the final outcome. Finally, in 4 other cases (9.8%), the role of peritonitis was uncertain but probably not determinant as a cause of death. Table 4 displays the immediate circumstances of death in the 41 patients who suffered peritonitis-related mortality. Remarkably, the immediate cause of demise was a cardiovascular event in 41.5% of the cases. Six patients died suddenly during the course of a HD session during the days following removal of the peritoneal catheter.

BASELINE RISK PROFILE OF PERITONITIS-RELATED MORTALITY

Table 5 depicts the main baseline characteristics of patients with peritonitis-related mortality, compared with survivors and patients dying for reasons other than peritonitis. The results of multivariate analysis of the baseline risk profile for peritonitis-related mortality are presented in Table 6. A baseline s-CRP level ≥7 mg/L portended a RR of 4.04 (95% confidence interval 1.45 – 11.32, $p = 0.008$) of peritonitis-related mortality.

TABLE 4
Immediate Cause of Death in Patients with Peritonitis-Related Mortality ($n = 41$)

Cause	*N* (%)
Peritonitis-related sepsis	12 (29.3)
General deterioration/withdrawal from dialysis	12 (29.3)
Sudden death/lethal arrhythmia	8 (19.5)
Acute pulmonary edema	4 (9.8)
Myocardial infarction	2 (4.9)
Lower limb gangrene	2 (4.9)
Secondary mesenteric ischemia	1 (2.4)

TABLE 3
Baseline Risk Profile for Presenting at Least One Episode of Infectious Peritonitis (All) or Severe Peritonitis. Multivariate Analysis.

	All			Severe		
	RR	95% CI	*p* Value	RR	95% CI	*p* Value
Age (per year)	1.01[a]	1.00–1.02	0.04	1.01[a]	1.00–1.03	0.09
Female sex	1.04	0.82–1.26	0.88	2.03[a]	1.29–3.16	0.002
Automated PD (vs CAPD)	0.85[a]	0.59–0.95	0.02	1.03	0.67–1.63	0.90
Glomerular filtration rate (per mL/min)	0.96[a]	0.92–0.99	0.034	0.88[a]	0.81–0.95	0.003
Serum C-reactive protein ($\log_{10}$)	1.56[a]	1.12–2.19	0.009	1.39	0.93–2.51	0.13
Depression	1.13	0.85–1.50	0.37	1.44[a]	0.99–2.13	0.052
Incidence of peritonitis (per episode/patient-year)	—	—	—	1.62	1.34–2.04	0.0005

RR = relative risk; 95% CI = 95% confidence interval; PD = peritoneal dialysis; CAPD = continuous ambulatory PD.
[a] Included in best model.
Cox's model. The table includes only the variables that were significant in at least one model.

TABLE 5
Baseline Risk of Peritonitis-Related Mortality: Comparison with Patients Dying from Other Causes and Survivors. Univariate Analysis.

	Peritonitis-related mortality (*n*=41)	Death from other causes (*n*=200)	Survivors (*n*=324)
Age (years)	71.1±9.2	64.7±10.5[a]	51.8±17.3[a,d]
Gender (male/female)	15/26 (36.6/63.4)	120/80 (60/40)[b]	175/149 (54.0/46.0)[e]
Diabetes	11 (26.8)	94 (47)[c]	87 (26.8)
Comorbidities (*n*)	1.1±1.2	1.4±1.2	0.6±1.0[f]
Glomerular filtration rate (mL/min)	2.5±2.2	3.9±3.2[b]	4.9±3.2[f]
Malnutrition	11 (26.8)	38 (18.9)	22 (6.8)[c]
Obesity	4 (9.8)	22 (12)	43 (13.3)
Depression	7 (17.1)	24 (12.0)	17 (5.2)
Previous hemodialysis	5 (12.2)	17 (8.5)	16 (4.9)
Previous renal transplant	0	8 (4.0)	13 (4.0)
Immunosuppression	3 (7.3)	14 (7.0)	21 (6.5)
Mode of PD (CAPD/APD)	23/18 (56.1/43.9)	130/70 (65.0/35.0)	191/133 (59.0/41.0)
Need for a dialysis partner	33 (80.5)	126 (63.0)[b]	106 (32.7)[c]
D/P creatinine: baseline PET	0.68±0.09	0.68±0.11	0.63±0.13[d]
Hemoglobin (g/dL)	9.5±1.8	9.8±1.6	10.3±1.8[f]
Baseline plasma albumin (g/L)	37.1±5.5	36.2±5.5	38.0±5.7
Serum C-reactive protein (mg/L)	19.4 (3.3–98)	10.3 (1.0–198)	5.2 (1.0–48)[c]
Follow-up on PD (months)	25.1±20.7	26.6±21.8	23.2±20.9
Time to first peritonitis (months)	11.0±9.7	15.7±15.0[b]	14.3±15.0
Number of peritonitis (per patient)	2.4±2.5	1.2±1.7[b]	1.2±1.8[b]

PD = peritoneal dialysis; CAPD = continuous ambulatory PD; APD = automated PD; D/P = dialysate-to-plasma ratio; PET = peritoneal equilibration test.
[a] $p < 0.001$ versus peritonitis-related mortality.
[b] $p < 0.01$ versus peritonitis-related mortality.
[c] $p < 0.01$ versus any other group.
[d] $p < 0.02$ versus mortality for other causes.
[e] $p < 0.05$ versus peritonitis-related mortality.
[f] $p < 0.05$ versus any other group.
Figures denote number of cases (%), mean±standard deviation, or median (serum C-reactive protein). Comparisons by chi-square, Student's t-test, and Mann–Whitney test.

RISK PROFILE OF MORTALITY AFTER A SINGLE EPISODE OF PERITONITIS

Univariate analysis of the risk profile for mortality after a single episode of infectious peritonitis indicated that this outcome was associated with older age (mean 73.3 years for lethal vs 61.7 for nonlethal infection, $p < 0.001$), female sex (63.4% of lethal infections vs 45.8% of nonlethal infections, $p = 0.02$), and overall comorbidity (mean 1.6 points if lethal infection, compared with 0.9 if nonlethal infection, $p = 0.02$) and malnutrition at the time of the episode (31.7% of lethal infections vs 12.2% of nonlethal infections, $p = 0.001$). As expected, lethal peritonitis was accompanied by features of clinical aggressiveness (hospital admission, peritoneal catheter removal, laparotomy performed; all $p < 0.01$ vs nonlethal peritonitis). Finally, there was a minor trend to higher peritoneal leukocyte counts in lethal peritonitis (median 1865 cells/mm^3, compared with 1280 in nonlethal peritonitis; $p = 0.10$, Mann–Whitney). Table 7 presents the results of multivariate analysis of risk factors of mortality after a single episode of peritonitis (all) or severe peritonitis.

DISCUSSION

Our results show that peritonitis represents a significant cause of mortality in patients undergoing PD therapy. The accumulated peritonitis-related mortality rates observed in our center (15.2% of deaths and 68.5% of infectious deaths) match well with values reported previously (3). On the other hand, peritonitis-related

TABLE 6
Baseline Risk Profile for Peritonitis-Related and All-Cause Mortalities. Multivariate Analysis. Cox's Model.

	Peritonitis-related mortality			All-cause mortality		
	RR	95% CI	*p* Value	RR	95% CI	*p* Value
Age (per year)	1.10[a]	1.06–1.14	0.0005	1.03[a]	1.02–1.04	0.0005
Female sex	2.13[a]	1.24–4.09	0.02	1.07	0.81–1.41	0.65
Glomerular filtration rate (per mL/min)	0.75[a]	0.64–0.87	0.0005	0.89[a]	0.84–0.93	0.0005
Malnutrition	2.51[a]	1.21–5.23	0.011	1.65[a]	1.17–2.32	0.004
Serum C-reactive protein (log_{10})	3.51[a]	1.46–8.45	0.005	1.25[a]	1.05–2.55	0.03
Incidence of peritonitis (per episode/patient/year)	1.88	1.49–2.36	0.0005	1.13	0.98–1.31	0.08
Diabetes	0.95	0.47–1.94	0.89	1.41[a]	1.07–1.86	0.014
Comorbidity (per point)	1.11	0.88–1.40	0.37	1.23[a]	1.10–1.36	0.0005
Depression	1.65	0.90–3.01	0.11	1.64[a]	1.25–2.15	0.0005
Immunosuppression	1.43	0.42–4.83	0.57	1.76[a]	1.03–2.99	0.038
Plasma albumin (per g/L)	1.01	0.94–1.09	0.73	0.97[a]	0.94–0.99	0.014
D/P creatinine after 240 minutes; baseline PET (per point)	1.03	0.96–1.10	0.41	1.03[a]	1.00–1.05	0.018
Automated PD (vs CAPD)	1.33	0.71–2.50	0.38	0.93	0.70–1.24	0.63
Need for dialysis partner	1.61	0.65–4.00	0.30	1.25	0.92–1.70	0.15
Previous hemodialysis	1.85	0.62–5.59	0.27	1.04	0.58–1.87	0.88
Obesity	1.50	0.49–5.50	0.42	0.55	0.29–1.11	0.10
Hemoglobin (per g/dL)	0.83	0.67–1.10	0.15	0.95	0.87–1.04	0.24

RR = relative risk; 95% CI = 95% confidence interval; PD = peritoneal dialysis; D/P = dialysate-to-plasma ratio; PET = peritoneal equilibration test; CAPD = continuous ambulatory PD.
[a] Variable included in best model.

TABLE 7
Mortality After a Single Episode of Peritonitis (All) or Severe Peritonitis. Multivariate Analysis. Logistic Regression Analysis.

	All peritonitis (*n*=693)			Severe peritonitis (*n*=159)		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Age (per year)	1.11[a]	1.06–1.15	0.0005	1.15[a]	1.07–1.23	0.0005
Female sex	2.41[a]	1.18–4.83	0.015	2.08	0.77–5.59	0.14
Comorbidities (per point)	1.22	0.89–1.44	0.15	1.21[a]	1.05–1.71	0.005
Malnutrition	2.89[a]	1.71–5.17	0.0005	1.30	0.57–2.95	0.54
Depression	2.35[a]	1.14–4.84	0.02	2.02	0.72–5.69	0.19
Time on PD until peritonitis (per month)	1.02[a]	1.00–1.03	0.02	1.02[a]	1.00–1.05	0.04
Automated PD (vs CAPD)	1.48	0.75–2.94	0.26	1.25	0.46–3.38	0.67
Need for a dialysis partner	1.16	0.54–2.48	0.71	0.74	0.27–2.05	0.56
Diabetes	0.68	0.32–1.46	0.33	0.60	0.21–1.70	0.34
Obesity	1.44	0.68–3.6	0.40	1.40	0.59–4.29	0.70
Immunosuppression	0.75	0.22–2.63	0.61	0.62	0.11–3.51	0.59
Plasma albumin (per g/L)	1.07	0.98–1.17	0.20	1.09	0.99–1.20	0.07
First episode of peritonitis	0.97	0.58–1.62	0.91	0.86	0.38–1.93	0.71
Hospital admission	44.85	16.11–124.88	0.0005	10.38	2.83–38.05	0.0005
Catheter removed	12.89	6.10–27.23	0.0005	2.87	1.09–7.55	0.03
Laparotomy performed	17.78	6.04–52.30	0.0005	6.95	1.86–26.03	0.004
Relapse	1.08	0.53–2.21	0.84	0.64	0.20–2.06	0.46
Superinfection	2.10	1.15–3.82	0.016	0.90	0.43–1.68	0.64
Simultaneous exit-site infection	2.78	0.75–10.29	0.13	1.04	0.21–5.06	0.97
Dialysate cell count at the start of peritonitis (log_{10})	1.74	0.77–3.17	0.19	2.26	0.71–6.15	0.16

OR = odds ratio; 95% CI = 95% confidence interval; PD = peritoneal dialysis; CAPD = continuous ambulatory PD.
[a] Variable included in best model.

mortality rates did not change markedly during a long study follow-up (Figure 2) and did not improve significantly on results reported in older studies (3,16). There are two possible explanations for this seemingly unexpected finding. First, technical advances in PD therapy have been relatively successful at preventing some of the less aggressive forms of peritonitis (including coagulase-negative staphylococci infections) but, with the possible exception of *S. aureus* (1), their impact on the incidence of the most severe forms of peritonitis (namely fungal and enteric infections) has been small, if any (2). Second, the clinical condition (age, diabetes, comorbidity) of patients starting PD therapy has declined markedly in past years (18). The combination of relatively higher incidences of more aggressive forms of peritonitis affecting progressively more debilitated patients may underlie the lack of improvement in peritonitis-related mortality rates, as observed in our study.

Our study confirms also the definite role of the etiologic agent in the outcome of PD-related peritonitis. Infections by *S. aureus* (10,11), *Pseudomonas aeruginosa* (3,9,14), fungi (3,7,8), mycobacteria (19), and enteric micro-organisms (5,6,20,21), which together formed the severe peritonitis group, are well known for their significant morbidity and mortality rates. On the contrary, single gram-negative bacteria and vancomycin-sensitive *Enterococcus spp* may be less consistently associated with a complicated course and mortality after peritonitis, as shown by our own results (Table 2); consequently, we excluded these two groups from the subset of severe peritonitis.

It is noteworthy that, in 41.5% of patients with peritonitis-related mortality, the immediate cause of death was a cardiovascular event, representing indirect evidence of the impact of preexisting cardiovascular disease on the outcome of PD-related peritonitis. This association has been suggested by some previous studies (3,16,20) and our results provide further evidence of the high incidence of cardiovascular mortality during the period surrounding an episode of severe peritonitis. Our analysis of the risk profile for peritonitis-related mortality provides new clues to understanding this correlation.

In past years, several studies have clearly demonstrated that residual renal function is a strong correlate of overall survival of PD patients (22–25). Our study is the first to demonstrate that baseline GFR has a specific and consistent inverse correlation with the later incidence of peritonitis (Table 3) and peritonitis-related mortality (Table 6). It is evident that a lower number of bag exchanges in patients with a significant GFR may reduce the chances for contamination and subsequent infection, but this explanation seems clearly insufficient to justify such a strong correlation. On the other hand, low or absent GFR at the start of dialysis is a hallmark of delayed referral (a variable not explored in this study) (26) and secondary selection of PD (after chronic HD), and is associated with inadequacy of dialysis, malnutrition (22), inflammation (27), and volume overload (28), among other complications. It is true that the correlation between GFR and peritonitis outcomes persisted after controlling for the effects of malnutrition (SGA) and s-CRP levels (Tables 3 and 6), but residual renal function may still have predicted the risk of peritonitis by performing as a marker of poor medical and nonmedical conditions of PD patients.

Baseline s-CRP levels were strongly predictive of the later risk of presenting both peritonitis and severe peritonitis (Table 3), as well as of peritonitis-related mortality (Table 6). Previous attempts to establish this correlation have been unsuccessful (29), but peritonitis is generally recognized as a potential source of inflammation in patients undergoing PD therapy (30). Several studies (29,31–34) have explored the correlation between s-CRP and general mortality in PD patients, confirming the well-known association between this marker of inflammation and cardiovascular risk in chronic renal failure (35). Our study provides the first evidence of an association between a baseline inflammatory state and the later incidence of peritonitis and peritonitis-related mortality.

The background of the correlation between a baseline inflammatory state and the following risk of peritonitis and peritonitis-related mortality in PD patients is not clear. We cannot even discard a chance association, as some subsets of patients could present, for independent reasons, increased s-CRP levels and high incidences of peritonitis. Alternatively, inflammatory states are strongly associated with cardiovascular disease, malnutrition, and, in general, clinical deterioration of affected patients (30). Thus, similar to the case of GFR, inflammation may define a subgroup of debilitated patients prone to more frequent infections and complicated clinical courses. A third, more speculative hypothesis may be based on the potential links between inflammatory states and intestinal permeability. First, it is conceivable that a functionally (*e.g.*, due to wall edema in volume overloaded patients) or anatomically (*e.g.*, colonic diverticulosis) disrupted intestinal wall, with recurrent microbial transmigration, may be a source of inflammation in some patients. On the other side, we know, mainly from studies in critical patients (36), that proinflammatory cytokines may induce dysfunction of the gut mucosal barrier. In either of those cases, high s-CRP levels could be, in some patients, a marker for a disabled

antimicrobial intestinal barrier, with a potentially increased risk of peritonitis by intestinal micro-organisms during PD therapy. Our results are consistent but do not provide evidence favoring this hypothesis.

Advancing age was strongly associated with the risk of presenting PD-related peritonitis (Table 3). Previous information on the relative incidence of these infections in elderly patients is controversial [reviewed in Ref. (37)] but our results demonstrate that older PD patients experience a definite risk of severe peritonitis (Table 3) and peritonitis-related mortality (Tables 5, 6, 7). On the other hand, our study showed that female patients were more likely to present severe peritonitis but not all-cause peritonitis (Table 3) than were males. As an expected consequence, the risk of peritonitis-related mortality was also higher in women (Tables 6 and 7). The explanation for this previously unreported finding is not clear but the female genitourinary tract may act as a potential reservoir for yeasts and other micro-organisms causing aggressive peritonitis during PD therapy.

Depressive disorders are relatively frequent in patients on dialysis and have been demonstrated to be associated with malnutrition (38), hospitalization (39), general mortality (39,40), and, in the case of PD patients, a high incidence of peritonitis (41). Our study confirmed a consistent association between depressive disorders and general mortality in PD patients and showed clear, previously unreported trends to correlation between baseline depression and a following incidence of severe peritonitis (Table 3) and peritonitis-related mortality (Table 6). Moreover, the risk of death after a single episode of peritonitis was significantly higher in patients with a depressive background (Table 7).

Incidence of peritonitis was a strong independent predictor of peritonitis-related mortality and showed a clear trend to predicting overall mortality (Table 6), which is in agreement with previous studies (3). On the other side, to our knowledge, the direct correlation between time on PD at the time of the event and peritonitis-related mortality (Table 7) has not been reported previously. The incidence of severe peritonitis was particularly high in patients with a background of frequent infections and a longer follow-up on PD (Table 3), an observation that may provide an explanation for that finding.

Some relevant variables did not behave as predictors of peritonitis or peritonitis-related mortality and deserve some comment. Our results do not indicate an increased risk of presenting peritonitis in hypoalbuminemic patients (42), neither do they support a predictive role of plasma albumin levels for peritonitis-related mortality, as suggested by previous studies based on univariate strategies of analysis (4,12,16). The relatively low prevalence of severe hypoalbuminemia among our patients (Table 1) and better performance by other markers of malnutrition and inflammation (SGA, s-CRP) in the regression models may explain this discrepancy. On the other hand, the debate over the relative risk of PD-related peritonitis in patients with diabetes mellitus is still open after many years (43), but our results do not show even a minor trend to such an association. Finally, immunosuppressive drug therapy was independently associated with all-cause mortality (Table 6) but not with the risk of peritonitis or peritonitis-related mortality, and our results do not support recent reports (44) suggesting a high risk of peritonitis-related mortality in patients starting PD with a failing renal allograft, although, in this case, the validity of our conclusions may be limited by an evident lack of statistical potency.

In summary, peritonitis represents a significant cause of mortality in patients undergoing PD therapy. The etiologic agent is an essential predictor of peritonitis-related mortality but advancing age, female gender, poor residual renal function, a baseline inflammatory state (as estimated from s-CRP levels), malnutrition, a depressive background, and a high incidence of peritonitis are other significant predictors of this complication. Time on dialysis at the time of the event is associated with increased mortality after a single episode of peritonitis. Most of these risk factors are common to cardiovascular and peritonitis-related mortality, which may help to explain the high incidence of cardiovascular events as an immediate cause of death in patients with severe peritonitis.

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ORIGINAL ARTICLE

Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization

Alan S. Go, M.D., Glenn M. Chertow, M.D., M.P.H., Dongjie Fan, M.S.P.H., Charles E. McCulloch, Ph.D., and Chi-yuan Hsu, M.D.

ABSTRACT

BACKGROUND

End-stage renal disease substantially increases the risks of death, cardiovascular disease, and use of specialized health care, but the effects of less severe kidney dysfunction on these outcomes are less well defined.

METHODS

We estimated the longitudinal glomerular filtration rate (GFR) among 1,120,295 adults within a large, integrated system of health care delivery in whom serum creatinine had been measured between 1996 and 2000 and who had not undergone dialysis or kidney transplantation. We examined the multivariable association between the estimated GFR and the risks of death, cardiovascular events, and hospitalization.

RESULTS

The median follow-up was 2.84 years, the mean age was 52 years, and 55 percent of the group were women. After adjustment, the risk of death increased as the GFR decreased below 60 ml per minute per 1.73 m² of body-surface area: the adjusted hazard ratio for death was 1.2 with an estimated GFR of 45 to 59 ml per minute per 1.73 m² (95 percent confidence interval, 1.1 to 1.2), 1.8 with an estimated GFR of 30 to 44 ml per minute per 1.73 m² (95 percent confidence interval, 1.7 to 1.9), 3.2 with an estimated GFR of 15 to 29 ml per minute per 1.73 m² (95 percent confidence interval, 3.1 to 3.4), and 5.9 with an estimated GFR of less than 15 ml per minute per 1.73 m² (95 percent confidence interval, 5.4 to 6.5). The adjusted hazard ratio for cardiovascular events also increased inversely with the estimated GFR: 1.4 (95 percent confidence interval, 1.4 to 1.5), 2.0 (95 percent confidence interval, 1.9 to 2.1), 2.8 (95 percent confidence interval, 2.6 to 2.9), and 3.4 (95 percent confidence interval, 3.1 to 3.8), respectively. The adjusted risk of hospitalization with a reduced estimated GFR followed a similar pattern.

CONCLUSIONS

An independent, graded association was observed between a reduced estimated GFR and the risk of death, cardiovascular events, and hospitalization in a large, community-based population. These findings highlight the clinical and public health importance of chronic renal insufficiency.

From the Division of Research, Kaiser Permanente of Northern California, Oakland (A.S.G., D.F.); and the Departments of Epidemiology and Biostatistics (A.S.G., G.M.C., C.E.M.) and Medicine (A.S.G., G.M.C., C.-y.H.), University of California, San Francisco, San Francisco. Address reprint requests to Dr. Go at the Division of Research, Kaiser Permanente of Northern California, 2000 Broadway, 3rd Fl., Oakland, CA 94612-2304, or at alan.s.go@kp.org.

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More than 400,000 Americans have end-stage renal disease, and over 300,000 of these patients require maintenance dialysis.[1] Mortality rates remain above 20 percent per year with the use of dialysis, with more than half of the deaths related to cardiovascular disease. The annual direct medical costs for end-stage renal disease are nearly $23 billion.[1] Although an estimated 8 million adults in the United States have chronic kidney disease of at least stage 3 (as defined by an estimated glomerular filtration rate [GFR] of less than 60 ml per minute per 1.73 m² of body-surface area),[2] less is known about the rates of death, cardiovascular disease, and resource use among persons with a reduced estimated GFR who are not yet receiving maintenance dialysis.

Several, but not all, previous studies suggested that mild-to-moderate elevations in serum creatinine levels are associated with increased rates of death from any cause[3-9] and from cardiovascular causes,[5,7,10-13] but whether chronic kidney disease independently increases the risk of any type of cardiovascular disease has not been established.[4-7,14] Furthermore, previous studies have been limited by the inclusion of relatively small numbers of persons with kidney disease,[3-8,11-17] the use of dichotomous groups of estimated kidney function,[3-8,15] the use of the serum creatinine level alone as a proxy for GFR and nonuniform cutoff values to define kidney disease,[3-11,15] lack of information on longitudinal changes in GFR and coexisting conditions,[3-11,14-17] selected populations,[6,8,11,14,16] and populations with limited racial or ethnic diversity. In addition, few studies have investigated the association between chronic kidney disease and the risk of hospitalization,[18] which has important economic implications.

Using longitudinal measures of estimated GFR, a more accurate method of assessing kidney function than the measurement of serum creatinine alone, we examined the effect of the severity of kidney dysfunction on the risks of death, cardiovascular events, and hospitalization among a large, diverse group of adults. We hypothesized that there would be a graded, independent association between the estimated GFR and the risks of these outcomes.

METHODS

STUDY SAMPLE AND MEASURES OF KIDNEY FUNCTION

The Kaiser Permanente Renal Registry included all adult members (20 years of age or older) of Kaiser Permanente of Northern California, a large integrated health care system insuring more than 35 percent of the adult population of the San Francisco Bay Area, whose kidney function was known. To be eligible for the registry, the subjects had to have had one or more outpatient determinations of serum creatinine levels recorded in a health-plan laboratory database between January 1, 1996, and December 31, 2000. We excluded subjects who had already received a kidney transplant or who were receiving maintenance dialysis at entry. Given the nature of the study, the institutional review board of the Kaiser Foundation Research Institute determined that informed consent was not required.

We used the abbreviated Modification of Diet in Renal Disease (MDRD) equation to estimate the GFR.[19,20] We calibrated the measurement of serum creatinine by the Kaiser regional laboratory against that of the MDRD core laboratory.[21] The date of the first measurement of GFR during the study period was considered the subject's index date (baseline). Changes in GFR during follow-up were estimated from serum creatinine determinations not associated with hospitalizations to reflect more accurately stable estimates of kidney function. We used a modified National Kidney Foundation classification of chronic kidney disease,[22] which classifies estimated GFR in the following ranges: at least 60 ml per minute per 1.73 m², 45 to 59 ml per minute per 1.73 m² (stage 3a), 30 to 44 ml per minute per 1.73 m² (stage 3b), 15 to 29 ml per minute per 1.73 m² (stage 4), and less than 15 ml per minute per 1.73 m² (stage 5).

CHARACTERISTICS OF THE SUBJECTS

Data on age, sex, and racial or ethnic group were obtained from health-plan databases. All names and identifiers were removed before any data were analyzed, according to procedures approved by the institutional review board at Kaiser.

We identified coexisting illnesses using validated methods[23-26] based on health-plan databases for hospitalization-discharge diagnoses, ambulatory diagnoses, laboratory results, and medication prescriptions, as well as regional cancer-registry data[24] (diagnostic criteria are listed in the Appendix). These diagnoses included coronary disease, stroke or transient ischemic attack, heart failure, peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, lung or liver disease, cancer, and dementia. We also evaluated laboratory-database entries for serum albumin to identify subjects with a value of 3.5 g per deciliter or less. The pres-

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ence of proteinuria was based on laboratory-database entries of urine dipstick results of 1+ or greater (approximately 30 mg per deciliter or greater) in the absence of a possible urinary tract infection (i.e., concomitant positive test for urinary nitrite or esterase).

Socioeconomic status was assigned with the use of 2000 U.S. Census-block data, which generally correspond to city blocks or neighborhoods.[28] Subjects with a low income were defined as those living in a Census-block group with a median annual household income under $35,000, and those with a low level of education were categorized as those living in a Census-block group in which more than 25 percent of residents older than 25 years had less than a 12th-grade education.

OUTCOMES

Data on subjects were censored if they underwent kidney transplantation or disenrolled from the health plan, which was defined as a continuous gap in membership of more than 90 days without the interim use of services. Incident end-stage renal disease, defined by the receipt of maintenance dialysis or a kidney transplant, was identified from a comprehensive health-plan registry.[29] The primary outcomes of interest included death from any cause, cardiovascular events, and hospitalizations through December 31, 2000. Death was identified from a search of health-plan databases and the California death registry.[30] A cardiovascular event was defined as hospitalization for coronary disease, heart failure, stroke, or peripheral arterial disease (see the Appendix).

STATISTICAL ANALYSIS

Event rates were directly adjusted for age with the use of the age distribution of the adult source population and are presented as the number of events per 100 person-years, with 95 percent confidence intervals. To evaluate the independent effect of the estimated GFR on outcomes, we used Cox proportional-hazards models with time-dependent covariates for changing GFR and coexisting illnesses. All variables known to be associated with either the estimated GFR or the outcomes were included in the final models, along with any variables associated with a reduced estimated GFR (i.e., less than 60 ml per minute per 1.73 m^2) in univariate analyses with a P value of less than 0.01. Age was entered as a categorical variable (20 to 49, 50 to 59, 60 to 69, 70 to 79, and 80 years or older), with other covariates included as dichotomous variables. For recurrent outcomes of cardiovascular events and hospitalizations, we used a "sandwich" estimate of the variance–covariance matrix to obtain standard errors accommodating the clustering of observations on subjects.[31] In the model for death, we did not include cardiovascular events or hospitalizations that occurred after the index date, since they were hypothesized to be part of the pathway by which reduced GFR may increase the risk of death.

Each subject and time was assigned an estimated GFR with the use of the last-value-carried-forward method. Given the varying numbers and spacing of measurements of GFR for each subject, this approach may preferentially attribute outcome events to higher levels of GFR. To address this possibility we analyzed a subgroup of subjects who had had regular serum creatinine determinations spaced between 1 and 14 months apart throughout follow-up. Also, although age and sex are important predictors of adverse events and are incorporated into the MDRD equation, we found no interactions among age, sex, and GFR and thus present only the main-model results.

All analyses were conducted with the use of SAS software (version 8.2). The institutional review board of each collaborating institution approved the study.

RESULTS

BASELINE CHARACTERISTICS

We identified 1,120,295 adults who had had one or more outpatient measurements of serum creatinine, had not previously received dialysis or a kidney transplant, and were alive on the index date. The median number of outpatient measurements of serum creatinine per subject during follow-up was three (interquartile range, one to four).

Subjects with a low estimated GFR at baseline were older than those with an estimated GFR of at least 60 ml per minute per 1.73 m^2, and there was greater minority-group representation among subjects with a low estimated GFR (Table 1). As compared with the group with an estimated GFR of at least 60 ml per minute per 1.73 m^2, the groups with a reduced estimated GFR also had a higher prevalence of prior cardiovascular disease, proteinuria, diabetes, hypertension, a serum albumin level of 3.5 g per deciliter or less, prior hospitalizations, and other coexisting illnesses (Table 1). Among the 60.7 percent of subjects who had one or more urine

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Table 1. Baseline Characteristics of 1,120,295 Ambulatory Adults, According to the Estimated GFR at Baseline.*

Characteristic	Total Cohort (N=1,120,295)	Estimated GFR at Baseline				
		≥60 ml/min/1.73 m² (N=924,136)	45–59 ml/min/1.73 m² (N=153,426)	30–44 ml/min/1.73 m² (N=34,275)	15–29 ml/min/1.73 m² (N=7085)	<15 ml/min/1.73 m² without dialysis (N=1373)
Age (yr)	52.2±16.3	49.1±15.1	65.4±13.5	71.2±12.9	70.1±14.5	63.0±16.1
Female sex (%)	54.6	53.4	60.7	61.6	57.7	50.6
Race or ethnic group (%)†						
White	50.9	47.2	68.4	71.4	66.3	54.9
Black	7.4	7.2	4.7	6.7	10.6	16.8
Hispanic	5.9	6.3	3.9	3.9	5.4	6.8
Asian	8.1	8.5	6.4	6.3	7.6	11.9
Pacific Islander	0.04	0.03	0.03	0.1	0.2	0.4
Native American	0.5	0.5	0.5	0.6	0.7	0.7
Mixed or nonblack	2.4	2.4	2.2	2.9	4.0	4.5
Other or unknown	24.8	27.4	13.9	8.0	5.3	4.2
Medical history (%)						
Coronary heart disease	6.3	4.5	13.2	20.6	24.5	17.9
Stroke or transient ischemic attack	2.6	1.7	5.7	10.2	12.8	10.2
Peripheral arterial disease	1.8	1.1	3.9	8.2	12.0	8.9
Chronic heart failure	2.1	1.0	5.2	12.6	20.8	18.5
Known proteinuria	6.3	5.1	8.9	17.7	33.7	50.2
Diabetes mellitus	9.6	8.6	12.3	19.6	28.2	31.1
Diagnosed hypertension	19.1	15.4	33.7	45.8	49.6	50.3
Dyslipidemia	27.9	26.8	33.4	30.9	29.3	28.0
Chronic lung disease	19.1	18.6	21.2	22.4	20.7	19.1
Chronic liver disease	0.2	0.2	0.3	0.6	0.9	1.4
Cancer	2.9	2.5	4.6	5.5	5.7	5.8
Serum albumin ≤3.5 g/dl	1.7	1.2	2.8	5.9	13.7	24.0
Diagnosed dementia	0.8	0.5	1.9	3.2	4.0	3.1
Prior hospitalizations	22.4	20.3	29.4	41.2	50.4	51.1

* Plus–minus values are means ±SD. Because of rounding, percentages may not total 100.
† Information on race and ethnic group was reported by the subjects; information was not available for 5.3 percent of the subjects.

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dipstick determinations at any time during follow-up, 17.6 percent were found to have proteinuria. Among the 21.2 percent of subjects who had one or more serum albumin determinations at any time during follow-up, 27.8 percent were found to have reduced levels.

OUTCOMES ACCORDING TO THE ESTIMATED GFR

The median follow-up among the 1,120,295 subjects was 2.84 years (interquartile range, 1.65 to 4.01), which amounts to 3,132,192 person-years. Overall, 21.8 percent of subjects disenrolled during follow-up, but those who disenrolled were substantially younger, were relatively unlikely to have a reduced estimated GFR, and had fewer coexisting illnesses than those who remained enrolled (data not shown). The vital status was complete for all subjects.

During follow-up, 3171 (0.28 percent) subjects began maintenance dialysis and 329 (0.03 percent) underwent kidney transplantation. There were 51,424 deaths, 138,291 cardiovascular events, and 554,651 hospitalizations. Age-standardized rates of death, cardiovascular events, and hospitalization increased substantially with progressively lower estimated GFRs (Fig. 1).

The group of subjects with an estimated GFR of at least 60 ml per minute per 1.73 m² was used as the reference group in the analysis of the association between the level of the estimated GFR and each outcome. After adjustment for differences in sociodemographic characteristics and the presence or absence of prior cardiovascular disease, prior hospitalizations, diabetes, hypertension, dyslipidemia, lung or liver disease, cancer, a serum albumin level of 3.5 g per deciliter or less, dementia, proteinuria, and the initiation of dialysis during follow-up, the risk of death from any cause increased sharply as the estimated GFR declined, ranging from a 17 percent increase in risk with an estimated GFR of 45 to 59 ml per minute per 1.73 m² to a nearly 600 percent increase with an estimated GFR of less than 15 ml per minute per 1.73 m² (Table 2). The adjusted risk of any cardiovascular event also increased as the estimated GFR decreased, ranging from a 43 percent increase in risk with an estimat-

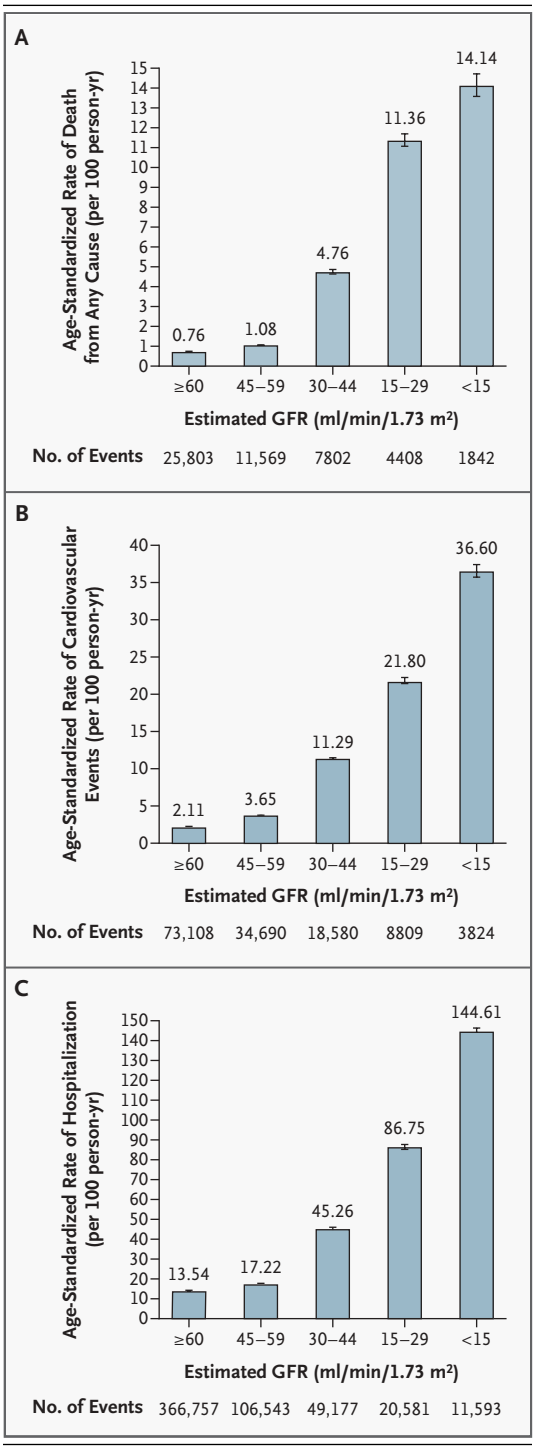


Figure 1. Age-Standardized Rates of Death from Any Cause (Panel A), Cardiovascular Events (Panel B), and Hospitalization (Panel C), According to the Estimated GFR among 1,120,295 Ambulatory Adults.

A cardiovascular event was defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease. Error bars represent 95 percent confidence intervals. The rate of events is listed above each bar.

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ed GFR of 45 to 59 ml per minute per 1.73 m² to a 343 percent increase with an estimated GFR of less than 15 ml per minute per 1.73 m² (Table 2). Finally, the adjusted risk of hospitalization increased as the estimated GFR decreased, ranging from an increase of 14 percent with an estimated GFR of 45 to 59 ml per minute per 1.73 m² to an increase of 315 percent with an estimated GFR of less than 15 ml per minute per 1.73 m² (Table 2). The presence of documented proteinuria was also an independent predictor of death (adjusted hazard ratio, 1.3; 95 percent confidence interval, 1.3 to 1.4), cardiovascular events (adjusted hazard ratio, 1.3; 95 percent confidence interval, 1.2 to 1.3), and hospitalization (adjusted hazard ratio, 1.4; 95 percent confidence interval, 1.4 to 1.4).

In a subgroup of 172,144 subjects who had regular measurements of serum creatinine during follow-up (mean [±SD] number of measurements, 3.3±2.1; mean interval between measurements, 7.5±3.4 months), the adjusted risks of adverse outcomes differed materially from those for the entire cohort only among the subjects with an estimated GFR of 45 to 59 ml per minute per 1.73 m². In the analysis of the subgroup itself, as compared with the subjects with an estimated GFR of at least 60 ml per minute per 1.73 m², the subjects with an estimated GFR of 45 to 59 ml per minute per 1.73 m² had a similar adjusted hazard ratio for death (1.0; 95 percent confidence interval, 1.0 to 1.1) and hospitalization (1.0; 95 percent confidence interval, 1.0 to 1.0). The adjusted risk of cardiovascular events was also attenuated (1.2; 95 percent confidence interval, 1.1 to 1.3).

Table 2. Adjusted Hazard Ratio for Death from Any Cause, Cardiovascular Events, and Hospitalization among 1,120,295 Ambulatory Adults, According to the Estimated GFR.*

Estimated GFR	Death from Any Cause	Any Cardiovascular Event	Any Hospitalization
	adjusted hazard ratio (95 percent confidence interval)		
≥60 ml/min/1.73 m²†	1.00	1.00	1.00
45–59 ml/min/1.73 m²	1.2 (1.1–1.2)	1.4 (1.4–1.5)	1.1 (1.1–1.1)
30–44 ml/min/1.73 m²	1.8 (1.7–1.9)	2.0 (1.9–2.1)	1.5 (1.5–1.5)
15–29 ml/min/1.73 m²	3.2 (3.1–3.4)	2.8 (2.6–2.9)	2.1 (2.0–2.2)
<15 ml/min/1.73 m²	5.9 (5.4–6.5)	3.4 (3.1–3.8)	3.1 (3.0–3.3)

* The analyses were adjusted for age, sex, income, education, use or nonuse of dialysis, and the presence or absence of prior coronary heart disease, prior chronic heart failure, prior ischemic stroke or transient ischemic attack, prior peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, cancer, a serum albumin level of 3.5 g per deciliter or less, dementia, cirrhosis or chronic liver disease, chronic lung disease, documented proteinuria, and prior hospitalizations.

† This group served as the reference group.

DISCUSSION

Among a large, diverse population of adults, a reduced estimated GFR was associated with increased risks of death, cardiovascular events, and hospitalization that were independent of known risk factors, a history of cardiovascular disease, and the presence of documented proteinuria. Our study demonstrates that these graded risks of adverse events rose sharply for subjects with an estimated GFR of less than 45 ml per minute per 1.73 m² for each outcome examined both in the overall cohort and in subgroup analyses. Furthermore, in the cohort as a whole, the absolute rates of these outcomes were considerably higher than the risk of end-stage renal disease.

There has been rapidly growing interest in the relation between kidney disease and the risk of death and cardiovascular disease. With recognition that the presence of chronic kidney disease that does not necessitate dialysis is of considerable importance, several studies have examined the association of different cutoff values of serum creatinine with the risks of death from any cause, death from cardiovascular causes, and cardiovascular events, and most,[3,4,6-12,15] but not all,[5,13] of these studies have found increased risks with higher serum creatinine levels. Others have noted high rates of hospitalization among persons with elevated serum creatinine levels.[18] However, since serum creatinine levels are not linearly associated with GFR,[32] the use of predictive equations (the Cockcroft–Gault equation for creatinine clearance[33] and the MDRD equation for estimated GFR[19]) has been proposed as a more accurate means of estimating the GFR, with the MDRD equation having better predictive ability in certain populations.[20]

Relatively few studies have evaluated the estimated GFR and the risk of outcomes in the general population. In the Second National Health and Nutrition Examination Survey (NHANES II),[12] an estimated GFR of less than 70 ml per minute per 1.73 m² was associated with a 68 percent increase in the risk of death from any cause and a 51 percent increase in the risk of death from cardiovascular causes, as compared with an estimated GFR of at least 90 ml per minute per 1.73 m². In the Athero-

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sclerosis Risk in Communities Study,[17] an estimated GFR of 15 to 59 ml per minute per 1.73 m² at baseline was associated with a 38 percent increase in the risk of cardiovascular disease, as compared with an estimated GFR of 90 to 150 ml per minute per 1.73 m². Similar results were obtained in a cohort of older adults (at least 65 years of age)[16] for an estimated GFR of 15 to 59 ml per minute per 1.73 m², as compared with an estimated GFR of 90 to 130 ml per minute per 1.73 m². However, the NHANES I Epidemiologic Follow-up Study did not find a significant association between an estimated GFR of approximately 30 to 60 ml per minute per 1.73 m² and the risk of death from any cause or death from cardiovascular causes.[13] In addition, in the Framingham Heart Study, an elevated serum creatinine level — 1.5 to 3.0 mg per deciliter (133 to 265 μmol per liter) in men and 1.4 to 3.0 mg per deciliter (124 to 265 μmol per liter) in women — was associated with a significant risk of death among men but not women and was not associated with the risk of cardiovascular events in either sex.[5]

These studies were limited by the use of a single measurement of kidney function, the use of a broad range of definitions of diminished kidney function, and the inclusion of relatively small numbers of persons with kidney disease, thus limiting their statistical power to examine different levels of reduced GFR. Furthermore, although several studies used the MDRD equation to estimate GFR, serum creatinine measurements were not directly calibrated to the values of the MDRD laboratory, so the absolute threshold level of GFR associated with adverse outcomes cannot be known with confidence.

Our study further delineates the relation between the GFR and the risk of adverse events. We found nonlinear relations between the GFR and the risks of death, cardiovascular events, and hospitalization, with an increased risk associated with an estimated GFR of less than 60 ml per minute per 1.73 m², which further rose sharply when values dropped below 45 ml per minute per 1.73 m². We found that an estimated GFR of 15 to 29 ml per minute per 1.73 m² and an estimated GFR of less than 15 ml per minute per 1.73 m² in the absence of dialysis were associated with strikingly high age-adjusted mortality rates (11.4 and 14.1 per 100 person-years, respectively). These rates approach the rates among patients with treated end-stage renal disease.[1] Although the prevention of end-stage renal disease remains a very important goal in patients with kidney disease, more effective interventions are clearly needed to reduce the disproportionate cardiovascular and economic burden in this population.

Multiple possible explanations exist for the association between chronic kidney disease and increased risks of death and cardiovascular disease. We observed an increased prevalence of prior cardiovascular disease, known risk factors for cardiovascular events and death, and coexisting conditions with lower levels of the estimated GFR. However, a reduced estimated GFR was an independent and strong risk factor for adverse outcomes. Reduced kidney function is also associated with increased levels of inflammatory factors,[34,35] abnormal apolipoprotein levels,[34] elevated plasma homocysteine,[34] enhanced coagulability,[35] anemia,[36] left ventricular hypertrophy,[37] increased arterial calcification,[38] endothelial dysfunction,[39] and arterial stiffness.[40] Whether and how these and other factors interact to increase the risk of adverse outcomes remains unclear but are the focus of ongoing investigations.[41] Our large, ethnically diverse population is typical of patients receiving usual clinical care rather than referral populations, recruited cohorts, or clinical-trial participants, and thus, our results are probably more generalizable. The inclusion of large numbers of subjects with a spectrum of kidney disease also enabled us to make a more detailed evaluation of the effect of the level of the GFR on outcomes. Use of outpatient serum creatinine values that were directly calibrated to those of the MDRD core laboratory increased our confidence in the validity of the observed associations of absolute, not just relative, levels of the estimated GFR. Most subjects had serial estimates of the GFR in order to characterize kidney function over time as accurately as possible. We had complete records of deaths and hospitalizations among these subjects that occurred at health-plan and other facilities. Our study also shows that the use of a baseline estimate of the GFR alone may lead to the misattribution of events to a certain level of GFR measured in the distant past and to the subsequent attenuation of the true strength of the association between a reduced GFR and outcomes.

Our study had several limitations. As a study of subjects who received usual clinical care, estimates of the GFR were not available for the entire source population. For example, patients with a reduced GFR who did not use medical services would not have been included. However, over half of adult members of the health plan had serum creatinine

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measurements, which allowed for a robust assessment of the estimated GFR and outcomes among more than 1.1 million subjects. We did not have information on tobacco or alcohol use, diet, physical activity, other possible unmeasured confounders (e.g., body-mass index), or the severity of certain conditions (e.g., level of blood pressure or severity of diabetes). Nevertheless, residual confounding is unlikely to explain the large effect estimates observed for most categories of a reduced estimated GFR. Finally, since our study was conducted among insured adults in northern California, our results may not be completely generalizable to uninsured persons or persons in other geographic regions.

In conclusion, we found an independent, graded association between lower levels of the estimated GFR and the risks of death, cardiovascular events, and hospitalization. These risks were evident at an estimated GFR of less than 60 ml per minute per 1.73 m^2 and substantially increased with an estimated GFR of less than 45 ml per minute per 1.73 m^2. Our findings support the validity of the National Kidney Foundation staging system for chronic kidney disease[22] but suggest that the system could be further refined, since all persons with stage 3 chronic kidney disease (GFR, 30 to 59 ml per minute per 1.73 m^2) may not be at equal risk for each outcome. Our findings highlight the clinical and public health importance of chronic kidney disease that does not necessitate dialysis.

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APPENDIX

The following criteria and *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM), and *Current Procedural Terminology* (CPT) codes, if relevant, were used to define coexisting illnesses.

Condition	Criteria	ICD-9-CM	CPT Code*
Acute myocardial infarction	Primary discharge diagnosis in hospitalization databases	410	NA
Unstable and stable angina	Primary discharge diagnosis in hospitalization databases or physician-assigned diagnosis in ambulatory-visit database	411, 413	NA
Coronary artery disease	Primary discharge diagnosis in hospitalization databases or physician-assigned diagnosis in ambulatory-visit database	414.0, 414.8, 414.9	NA
Percutaneous coronary intervention	Procedural code in hospitalization and ambulatory-visit databases	36.01–36.02, 36.05, 36.06, 36.09	92980–92981, 92982, 92984–92996
Coronary-artery bypass surgery	Procedural code in hospitalization databases	36.10–36.17, 36.19	33510–33519, 33521–33523, 33533–33536
Ischemic stroke	Primary discharge diagnosis in hospitalization databases or physician-assigned diagnosis in emergency-department database	433.x1, 434.x1, 436.0	NA
Transient ischemic attack	Primary discharge diagnosis in hospitalization databases or physician-assigned diagnosis in emergency-department database	435	NA
Chronic heart failure	Primary discharge diagnosis in hospitalization databases	398.91, 402.01, 402.11, 402.91, 428.0, 428.1, 428.9	NA
Peripheral arterial disease	Primary discharge diagnosis or procedural code in hospitalization databases or physician-assigned diagnosis in ambulatory-visit database	440.0–440.9, 38.13, 38.14, 38.15, 38.16, 38.18, 39.22, 39.24, 39.25, 39.26, 39.28	35450, 35452, 35454, 35456, 35458, 35459, 35470–35475, 35879, 75962, 75964, 75966, 75968, 33322, 33335, 33860, 33870, 35511, 35516, 35518, 35521, 35531, 35533, 35536, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35560, 35563, 35565, 35566, 35571, 35582, 35583, 35585, 35587, 35612, 35616, 35621, 35623, 35631, 35636, 35641, 35646, 35650, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671

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Appendix (Continued).

Condition	Criteria	ICD-9-CM	CPT Code*
Diabetes mellitus	Validated health plan registry based on inpatient or outpatient diagnoses, antidiabetes therapies, laboratory results, and patient self-report[26]	See Selby et al.[26]	See Selby et al.[26]
Diagnosed hypertension	Two or more physician-assigned diagnoses in ambulatory-visit database or one outpatient diagnosis plus receipt of antihypertensive pharmacologic therapy found in pharmacy database	401–405	NA
Dyslipidemia	Physician-assigned clinical diagnosis in ambulatory database, record of filled prescriptions for lipid-lowering therapies in automated pharmacy databases within five years before index date, or lipid levels that met the cutoffs for elevated low-density lipoprotein and reduced high-density lipoprotein cholesterol identified in laboratory databases with the use of Adult Treatment Panel III guidelines[27]†	272.0, 272.2, 272.4	NA
Chronic lung disease	Primary discharge diagnosis of chronic obstructive pulmonary disease, chronic bronchitis, or asthma in hospitalization databases or physician-assigned diagnosis in ambulatory-visit databases	491.x, 492.x, 493.x, 496, 518.1, 518.2	NA
Chronic liver disease	Primary discharge diagnosis of cirrhosis or chronic liver disease in hospitalization database or physician-assigned diagnosis in ambulatory-visit database	571	NA
Dementia	Physician-assigned diagnosis of dementia or organic brain disease found in ambulatory-visit database	290, 294, 331	NA
Cancer (other than localized, nonmelanoma skin cancer)	Comprehensive health-plan registry linked to regional Surveillance, Epidemiology, and End Results data[24]	See Fireman et al.[24]	See Fireman et al.[24]

* NA denotes not applicable.
† Subjects could have met any or all of the criteria.

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ORIGINAL

Sodium chloride or Plasmalyte-148 evaluation in severe diabetic ketoacidosis (SCOPE-DKA): a cluster, crossover, randomized, controlled trial

Mahesh Ramanan[1,2,3,4*], Antony Attokaran[5], Lauren Murray[6], Neeraj Bhadange[7], David Stewart[8], Gokulnath Rajendran[9], Raju Pusapati[10], Melissa Petty[1], Peter Garrett[6], Peter Kruger[11], Sandra Peake[12], Laurent Billot[3] and Balasubramanian Venkatesh[3,13] on behalf of the SCOPE-DKA Collaborators and Queensland Critical Care Research Network (QCCRN)

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Abstract

Purpose: To determine whether treatment with Plasmalyte-148 (PL) compared to sodium chloride 0.9% (SC) results in faster resolution of diabetic ketoacidosis (DKA) and whether the acetate in PL potentiates ketosis.

Methods: We conducted a cluster, crossover, open-label, randomized, controlled Phase 2 trial at seven hospitals in adults admitted to intensive care unit (ICU) with severe DKA with hospital randomised to PL or SC as fluid therapy. The primary outcome, DKA resolution, was defined as a change in base excess to ≥ -3 mEq/L at 48 h.

Results: Ninety-three patients were enrolled with 90 patients included in the modified-intention-to-treat population (PL $n=48$, SC $n=42$). At 48 h, mean fluid administration was 6798 ± 4850 ml vs 6574 ± 3123 ml, median anion gap 6 mEq/L (IQR 5–7) vs 7 mEq/L (IQR 5–7) and median blood ketones 0.3 mmol/L (IQR 0.1–0.5) vs 0.3 (IQR 0.1–0.5) in the PL and SC groups. DKA resolution at 48 h occurred in 96% (PL) and 86% (SC) of patients; odds ratio 3.93 (95% CI 0.73–21.16, $p=0.111$). At 24 h, DKA resolution occurred in 69% (PL) and 36% (SC) of patients; odds ratio 4.24 (95% CI 1.68–10.72, $p=0.002$). The median ICU and hospital lengths of stay were 49 h (IQR 23–72) vs 55 h (IQR 41–80) and 81 h (IQR 58–137) vs 98 h (IQR 65–195) in the PL and SC groups.

Conclusion: Plasmalyte-148, compared to sodium chloride 0.9%, may lead to faster resolution of metabolic acidosis in patients with DKA without an increase in ketosis. These findings need confirmation in a large, Phase 3 trial.

Keywords: Diabetic ketoacidosis, Diabetes, Critical care, Fluid therapy, Plasmalyte-148, Sodium chloride

*Correspondence: Mahesh.ramanan@health.qld.gov.au
[1] Intensive Care Unit, Caboolture Hospital, McKean Street, Caboolture, QLD 4510, Australia
Full author information is available at the end of the article

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Introduction

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus described in patients with both type 1 and type 2 diabetes [1]. Intravenous fluid replacement and insulin therapy for reversal of ketosis and correction of hyperglycemia remain the cornerstones of therapy. Whilst there is general agreement about the dose and route of insulin administration, the choice of fluid therapy, in both DKA and critical illness in general, is debated [2–5].

Current international guidelines recommend sodium chloride 0.9% (SC) as the replacement fluid of choice [6–8]. Whilst SC is effective in restoring the circulating volume and improving tissue perfusion, its use in large volumes is associated with hyperchloremia [9], and in DKA is associated with non-anion gap metabolic acidosis [10–13] and prolonged lengths of stay in intensive care unit (ICU) [14] and hospital [15, 16].

Plasmalyte-148 (PL) is a buffered salt solution that contains lower chloride concentrations than SC and acetate and gluconate as additional anions. It has been evaluated in two small randomized trials, one each in pediatric [17] and adult patients [18] with DKA. The pediatric trial demonstrated no differences between the PL and SC groups in the development of acute kidney injury (the primary outcome) or other clinical outcomes. The adult trial demonstrated faster resolution of acidosis in the PL group. A secondary analysis of two other cluster randomized trials showed faster resolution of DKA with the use of balanced crystalloids (including PL and compound sodium lactate) compared to SC [19].

Whilst PL may be effective in DKA, its safety profile in patients with severe DKA has not been formally assessed. PL contains acetate at a concentration of 27 mmol/L [20]. Acetate is a precursor for acetoacetate, one of the ketone bodies. Acetoacetate is converted to beta-hydroxybutyrate, the predominant ketone body in DKA [21, 22]. In dogs, acetate infusions have been accompanied by increases in acetoacetate concentrations [23]. Liver mitochondrial fractions in rats convert acetate to acetoacetate [24]. In humans, there is evidence that acetate may contribute to ketogenesis, particularly in the setting of hemodialysis [25, 26]. Whether a similar metabolic step of clinically significant proportions occurs in patients with DKA has never been evaluated.

We designed the 'Sodium chloride or Plasmalyte-148 evaluation in severe diabetic ketoacidosis' (SCOPE-DKA) trial to test the hypothesis that in critically ill patients with severe DKA, PL would result in faster resolution of DKA than SC and will not increase ketone generation.

Take-home message

Plasmalyte-148 compared to sodium chloride 0.9%, as intravenous fluid therapy, may result in faster resolution of metabolic acidosis in adult patients with severe diabetic ketoacidosis

Plasmalyte-148, when used as intravenous fluid therapy for patients with diabetic ketoacidosis, does not result in an increase in ketosis

Methods

Study design and participants

The SCOPE-DKA trial was prospectively registered with the Australia New Zealand Clinical Trials Registry (ACTRN12618001622291) and reported here according to the CONSORT extension for cluster trials guidelines [27]. Ethics approval was granted by the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/2018/QRBW/43868) for this trial to be conducted at all participating sites with a full consent waiver.

SCOPE-DKA was a cluster, crossover, open-label, randomized, controlled trial comparing the use of PL and SC for patients with severe DKA conducted in seven Australian intensive care units (ICU) over a 13-months period including two 6-months intervention periods and a 1-month washout period in the middle. Each ICU was a single cluster, with all patients admitted with DKA to that ICU during the intervention periods potentially eligible for inclusion in the trial. After the first 6-months intervention period, there was a 1-month washout period during which patients were not recruited into the trial. As this trial was a cluster-randomized, crossover, design, where recruitment was conducted over a fixed time period, there was no pre-determined sample size. Trial conduct was overseen by an independent data safety monitoring committee (DSMC) who performed a safety review during the washout period on data from the first intervention period. Following DSMC's advice to continue recruitment, the sites then crossed over to the other fluid for the second intervention period.

All patients 16 years of age and over who presented to the emergency department (ED) or ICU at a participating site during either intervention period with severe DKA were eligible for recruitment. Severe DKA was defined as arterial pH $\leq$ 7.25 (or serum bicarbonate $\leq$ 15 mmol/L) and blood glucose $\geq$ 14 mmol/L and requirement for ICU admission in the judgement of the treating clinician [28]. Based on Australian data [29], which showed that the temporal rise in DKA ICU admissions was predominately in rural and metropolitan hospitals (as opposed to tertiary and private hospitals), all sites that were invited to participate in SCOPE-DKA were rural or metropolitan hospitals.

Patients were excluded if they were under 16 years of age, had previously been included in this trial, had a contraindication to either fluid or had a suspected diagnosis of the hyperosmotic hyperglycemic non-ketotic syndrome.

Randomisation

Participating sites were allocated using randomly generated computer tables in a 1:1 ratio to PL or SC for the first intervention period. All sites crossed over to the alternate allocation for the second intervention period. Allocation for the first intervention period was concealed from the sites until 1 week prior to commencement.

Procedures

All included patients received open-label PL or SC, depending on the fluid assigned to the site for the relevant intervention period, as part of their DKA therapy. The volume and rate of administration of fluids were guided by clinical and biochemical endpoints determined by the treating clinician. All other aspects of DKA therapy, such as insulin and electrolyte replacement, were managed as per local protocols. The only aspect of management stipulated by this trial was the fluid type. Study treatment commenced as soon as practical once the diagnosis was made and eligibility criteria were confirmed by ED staff. The intervention continued for 48 h from ICU admission. If patients were discharged from ICU within 48 h, fluid choice after ICU discharge was determined by the treating clinician on the wards. The study fluid was used for all resuscitation and intravenous maintenance purposes. Diluents for infusions, electrolyte replacement, dextrose-containing solutions for glucose control, albumin, and bicarbonate-containing fluids were able be administered for specific indications as per local protocols. The frequency of blood testing was at the discretion of the treating clinician.

Outcomes

The primary outcome was a change in base excess to ≥ -3 mEq/L at 48 h post-ICU admission. Sensitivity analyses for the primary outcome were: (1) change in base excess to ≥ -3 mEq/L at 24 h post-ICU admission and (2) fulfilment of American Diabetes Association (ADA) criteria for DKA resolution at 24 h post-ICU admission i.e., plasma glucose < 11.1 mmol/L and two of the following: plasma bicarbonate $\geq$ 15 mmol/L, venous pH > 7.3 and anion gap $\leq$ 12 mEq/L.

Secondary outcomes were ICU and hospital mortality and lengths of stay, the proportion of patients receiving organ support (invasive and non-invasive ventilation, acute renal replacement therapy) and cumulative urine output and fluid balance at 24, 48, and 72 h post-ICU admission. Other biochemical outcomes included serum sodium, potassium and chloride concentrations, pH, pCO_2, pO_2, base excess, anion gap, blood glucose (BGL) and ketone concentrations at 6, 12, 18, 24, 36, 48, and 72 h post-ICU admission or at the timepoint closest to these times.

Safety data included the proportion of patients with severe hypokalemia (serum potassium < 3 mmol/L), hypoglycemia (plasma glucose < 3.8 mmol/L), hypophosphatemia (serum phosphate < 0.7 mmol/L), hypocalcemia (ionized calcium < 1 mmol/L) and persistent ketosis (blood ketone concentration > 1.5 mmol/L) at 24 h post-ICU admission or any adverse events deemed by the treating clinician to be related to the administered study fluid.

Compliance with fluid allocation was defined as the proportion of the total fluid received by each patient that was consistent with the allocation. For example, if a patient in the PL group received 5000 ml of fluid overall, and 4000 ml of this was PL, compliance would be 80%. Compliance was assessed overall, as well as in the ED and ICU separately.

Biochemical analyses, including electrolytes and acid–base values, were measured using point-of-care blood gas analysers. Ketone concentrations were measured on capillary blood samples using point-of-care blood ketone analysers. These devices measure beta-hydroxybutyrate. All measurements were performed at the individual sites using locally available devices.

Statistical analysis

All outcomes were analyzed at an individual patient level on a modified intention-to-treat basis (i.e., patients with complete outcome data for the primary outcome) according to the fluid allocation, regardless of the type of fluid received.

Continuous variables were reported as the median and interquartile range (IQR) or mean and standard deviation (SD). Categorical variables were reported as frequencies and proportions. To adjust for cluster-level correlation, logistic mixed models were used with group allocation as a fixed effect and site as a random effect with patients nested within sites. Given the small expected sample size, we did not add a random cluster-period effect, thus assuming constant correlations within a site regardless of the period. Differences between groups were reported as odds ratio (OR) for categorical outcomes and mean difference for continuous outcomes, both with 95% confidence intervals (CI). Repeated measures mixed-effects models were constructed to assess the changes in the biochemical variables (pH, base excess, anion gap, bicarbonate, sodium, chloride, glucose and ketones) over time between the two groups. *P*-values have been reported for

the primary outcome but without a threshold for statistical significance given the trial was not powered to specifically investigate a between-group difference in the primary outcome.

All analyses were performed in Stata 13.0 (StataCorp, College Station, TX-USA).

Funding source

There was no specific funding source for SCOPE-DKA. This trial was performed using in-kind support from the participating sites.

Results

Patients

From September 2019 to September 2020, we enrolled 93 patients at 7 sites: 50 (54%) into the PL group and 43 (46%) into the SC group. Details of the recruitment are presented in Fig. 1. Individual sites recruited between 2 and 24 patients. One site commenced recruitment but was unable to continue recruitment for the entire duration of the trial due to unanticipated changes to local staffing and resourcing. The two patients recruited at this site were lost to follow-up and did not have any treatment or outcome data, therefore, they were not included in the analyses. There was one additional patient with missing data for the primary outcome, leaving a final modified-intention-to-treat-analysis cohort of 90 patients: 48 (53%) in the PL group and 42 (47%) in the SC group.

Patient baseline characteristics are presented in Table 1. Briefly, the age and sex distributions, body mass index and clinical observations at ED presentation were similar between the two groups. There were more patients with Type 1 diabetes (83% versus 67%), higher initial anion gap (32 mEq/L, IQR 24–35 versus 28 mEq/L, IQR 25–32) and higher initial blood ketone concentrations (6.2 mmol/L, IQR 5.6–7.7 versus 5.4 mmol/L, IQR 4.9–6.7) in the PL versus SC group.

Fluid types and volumes administered

The mean volume of fluid administered up to 48 h post-ICU admission in the PL and SC groups were 6798 ml (SD 4850) and 6574 ml (SD 3123) respectively (Supplemental Table S1).

Compliance with treatment allocation was 66% (IQR 38–85%) in the PL group and 100% (IQR 75–100%) in the SC group (Supplemental Table S1). There were seven patients (15%) in the PL group who received PL for ≥ 95% of their administered fluids compared to 23 patients (55%) in the SC group who received SC for ≥ 95% of their administered fluids.

Compliance with PL treatment allocation was greater in the ICU; 76% (IQR 41–95%) versus 50% (IQR 0–99%) in the ED.

Primary outcome

The primary outcome (base excess ≥ −3 mEq/L at 48 h post-ICU admission) was attained by 46 patients (96%) in the PL group and 36 patients (86%) in the SC group. After adjustment for site-level random effects in the mixed effects logistic regression model, the OR for attaining the primary outcome was 3.93 (95% CI 0.73–21.16, $p = 0.111$). In a post hoc analysis using repeated measures mixed-effects modelling, base excess was significantly higher in the PL group at 24 h (+3.6 mEq/L, 95% CI 1.1–6.2, $p = 0.005$) and 48 h (+3.5 mEq/L, 95% CI 0.4–6.7, $p = 0.026$) (Supplemental Table S2). In the pre-specified sensitivity analyses (Table 2), the adjusted OR was 4.24 (95% CI 1.68–10.72, $p = 0.002$) when base excess ≥ −3 mEq/L at 24 h post-ICU admission was used to define DKA resolution and 1.47 (95% CI 0.61–3.52, $p = 0.390$) using the ADA criteria.

Two additional post-hoc sensitivity analyses were performed with the addition of base excess at presentation and diabetes type as fixed effects given the baseline imbalance between the two groups for these two variables. Upon addition of base excess at presentation, the OR for the primary outcome was 4.15 (95% CI 0.77–22.34, $p = 0.097$). Upon addition of diabetes type, the OR was 3.15 (95% CI 0.52–18.96, $p = 0.211$). When both were added, the OR was 2.95 (95% CI 0.5–17.54, $p = 0.234$).

The median blood ketone concentration at 48 h was 0.3 mmol/L (IQR 0.1–0.5) and 0.3 mmol/L (IQR 0.1–0.5) in the PL and SC groups. The median anion gap at 48 h was 6 mEq/L (IQR 5–7) and 7 mEq/L (IQR 5–7) in the PL and SC groups, respectively. The median serum chloride concentrations at 48 h were 106.5 mmol/L (IQR 103–110) and 108 (IQR 104–113) in the PL and NS groups. In the repeated measures mixed-effects model, the PL group had significantly lower serum chloride concentrations at 24 h (−3.5 mmol/L, 95% CI −6.4 to −0.5, $p = 0.021$) and similar serum chloride concentrations at 48 h (−2.9 mmol/L, 95% CI −6.5 to 0.6, $p = 0.106$). The changes in blood ketone concentrations, anion gap and other biochemical results over the first 48 h are presented graphically in Figs. 2 and 3.

Insulin and electrolytes administered in 48 h

The median insulin infusion dose administered to patients in both groups was similar- 0.08 units/kg/h (IQR 0.06–0.12) in the PL group and 0.08 units/kg/h (IQR 0.05–0.12) in the SC group. The PL group received a median of 78 mmol (IQR 39–130) intravenous potassium replacement and the SC group received a median of 116 mmol (IQR 40–211). The corresponding values for phosphate replacement were 20 mmol (0–32) and 13 mmol (IQR 0–27).

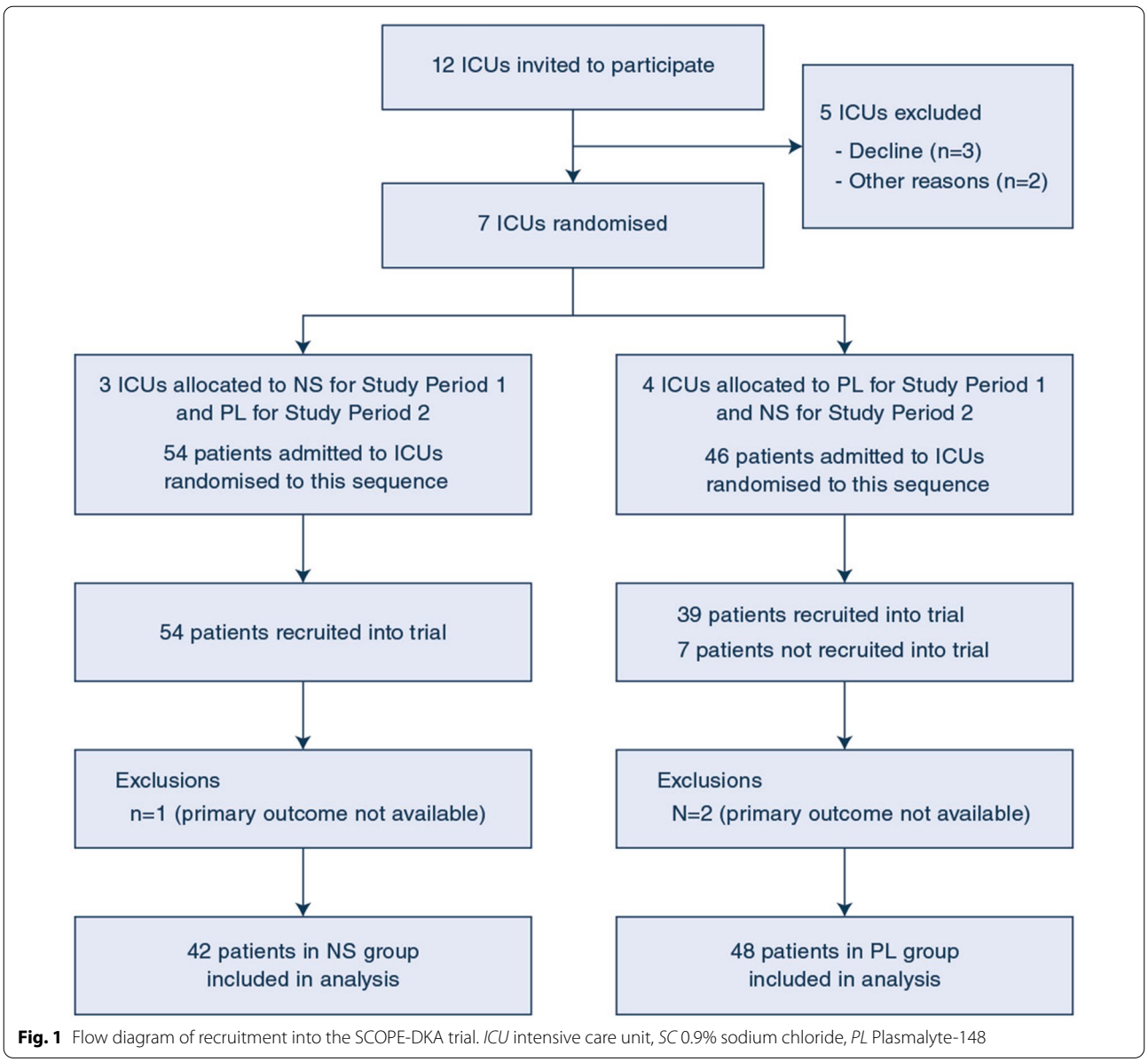


Fig. 1 Flow diagram of recruitment into the SCOPE-DKA trial. *ICU* intensive care unit, *SC* 0.9% sodium chloride, *PL* Plasmalyte-148

Clinical outcomes

The median ICU lengths of stay were 49 h (IQR 23–72) and 55 h (IQR 41–80) in the PL and SC groups. Hospital length of stay also tended to be shorter in the PL group; 81 h (IQR 58–137) versus 98 h (IQR 65–195) in the SC group. ICU readmission rates were 4% (2 of 48) in the PL group and 2% (1 of 42) in the SC group. Kaplan–Meier curves of time to ICU and hospital discharge are presented Supplemental Figures S1 and S2. One death occurred in the SC group in a patient who died from rhinocerebral mucormycosis.

Adverse events

Adverse events were similar between groups (Supplemental Table S3). Hypoglycemia occurred in 9 (19%) and 11 (26%) patients in the PL and SC groups, respectively. Hypophosphatemia occurred in 33 (69%) and 34 (81%) patients and persistent ketosis in 5 (10%) and 5 (12%) patients, respectively. Severe hypokalaemia occurred in 5 (10%) patients in the PL group and 7 (17%) in the SC group.

Missing data

Missing data ranged from 0 to 5% for the considered variables in the intention-to-treat analysis sample of 90 patients (Supplemental Table S4).

Table 1 Patient characteristics at ED admission

Characteristic	PL $n=48$	SC $n=42$
Age, years	36.7 (23.7–51.2)	38.1 (24.4–53.2)
Female sex	26 (54%)	24 (57%)
Diabetes type		
Type 1	40 (83%)	28 (67%)
Type 2	6 (13%)	9 (21%)
Newly diagnosed (not yet typed)	2 (4%)	5 (12%)
Previous DKA admissions	29 (60%)	25 (60%)
Body-mass index, kg/m^2	22.2 (19.1–26)	23.1 (20.6–26.7)
Clinical findings at presentation		
Heart rate, beats per minute	115 (100–125)	110 (92–125)
Respiratory rate, breaths per minute	26 (21–30)	22 (20–26)
Systolic blood pressure, mm Hg	124 (109–150)	118 (103–139)
Glasgow coma score	15 (13–15)	15 (13–15)
Laboratory values at presentation		
pH	6.99 (6.86–7.07)	7.02 (6.89–7.08)
Base excess, mEq/L		
≥ − 8	0 (0%)	0 (0%)
− 8.1 to − 16.0	3 (6%)	4 (10%)
− 16.1 to − 24.0	17 (35%)	19 (45%)
≤ − 24.1	28 (58%)	19 (45%)
Median base excess, mEq/L	− 25.2 (− 21.2 to − 28.7)	− 23.7 (− 21.2 to − 28.7)
Glucose, mmol/L	31.4 (19.9–41.6)	30.2 (23.8–44.7)
Sodium, mmol/L	136 (132–140)	135 (128–138)
Chloride, mmol/L	100 (95–106)	100 (94–105)
Blood ketones, mmol/L	6.2 (5.6–7.7)	5.4 (4.9–6.7)
Anion gap, mEq/L	32 (24–35)	28 (25–32)

Data are *n* (%) or median (interquartile range)

ED emergency department, *PL* Plasmalyte-148, *SC* 0.9% sodium chloride, *DKA* diabetic ketoacidosis

Table 2 Resolution of diabetic ketoacidosis

Outcome	PL $n=48$	SC $n=42$	Odds ratio (PL vs NS)	95% confidence interval	*p* values*
Primary outcome					
Base excess > − 3.0 mEq/L at 48 h	46 (96%)	36 (86%)	3.93	0.73–21.16	0.111
Pre-specified sensitivity analyses					
Base excess > − 3.0 mEq/L at 24 h	33 (69%)	15 (36%)	4.24	1.68–10.72	0.002
ADA criteria for DKA resolution at 24 h	29 (60%)	22 (52%)	1.47	0.61–3.52	0.390
Post-hoc sensitivity analyses					
Addition of base excess at presentation	46 (96%)	36 (86%)	4.15	0.77–22.34	0.097
Addition of diabetes type	46 (96%)	36 (86%)	3.15	0.52–18.96	0.211
Addition of both base excess at presentation and diabetes type	46 (96%)	36 (86%)	2.95	0.50–17.54	0.234

Data in columns 'PL' and NS' are *n* (%)

PL Plasmalyte-148, *SC* 0.9% sodium chloride, *ADA* American Diabetes Association, *DKA* diabetic ketoacidosis

**p* values: All results were generated from a mixed effects logistic regression model with treatment allocation (PL versus SC) as a fixed effect and site as a random effect. For the post-hoc sensitivity analyses, the specified fixed effect/s were added. The odds ratio for resolution of diabetic ketoacidosis in PL group compared to the SC group are presented, therefore, an odds ratio greater than 1 indicates an increase in resolution with PL treatment

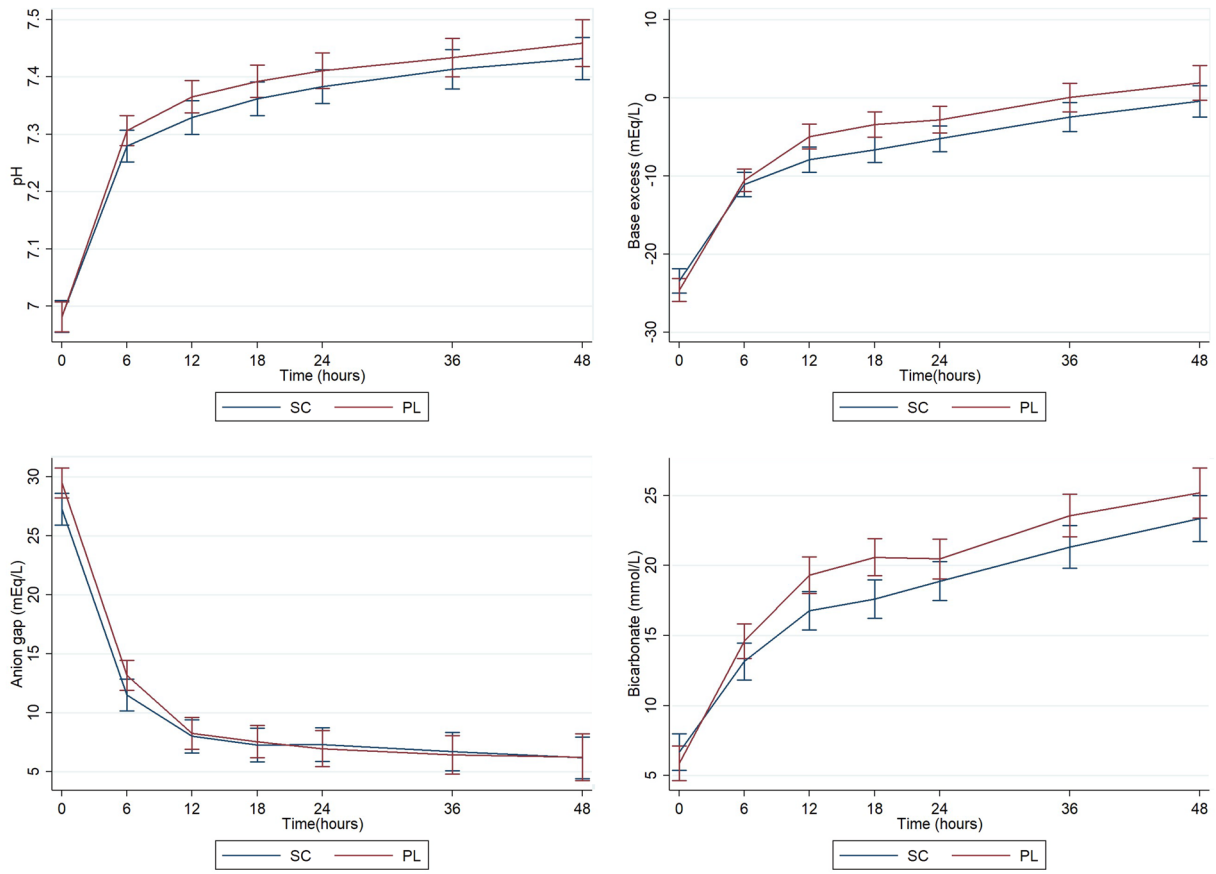


Fig. 2 Changes in pH, base excess, anion and bicarbonate during the first 48 h in the intensive care unit are shown here with 95% confidence intervals. Estimates presented here were generated using mixed-effects models to account for repeated measures. *SC* 0.9% sodium chloride, *PL* Plasmalyte-148

Discussion

Key findings

The SCOPE-DKA Phase 2 trial has demonstrated that treatment of patients with severe DKA with PL compared to SC may result in faster resolution of metabolic acidosis, accompanied by lower serum chloride concentrations, and without any increase in ketone generation. Clinical and safety outcomes were similar between the two groups.

Our trial evaluated the effect of two different crystalloid fluids on the rate of resolution of acidosis in patients with severe DKA. We adopted a cluster-crossover design because of the associated pragmatic benefits; including reduced setup and education costs, easier delivery of the trial intervention as a fluid choice was incorporated into hospital DKA guidelines at each site and higher recruitment rates due to consent waiver. We chose base excess as a primary outcome and specifically targeted a population of patients with severe DKA who are likely to be dehydrated and have high requirements for fluids. The trial was successful in enrolling the intended population. A high proportion of eligible patients received the trial intervention as planned, and few enrolled patients were lost to follow-up.

Our trial differs from previously published data in several respects. Previous RCTs investigating fluids in DKA have been small and only one has evaluated PL in adult patients. Results of our Phase 2 trial will inform the conduct of a large, well-powered, confirmatory trial in the future. Our results are in accord with a recent report of a subgroup analysis of adults with DKA in 2 large cluster randomized trials evaluating balanced crystalloids (both compound sodium lactate and PL) versus SC in ED and ICU patients [19]. Plasma ketone concentrations were not reported in that study.

Safety concerns

One of the significant concerns with the use of PL in DKA is the potential for acetate anions contained in PL to be converted to acetoacetate, one of the "ketone bodies" and

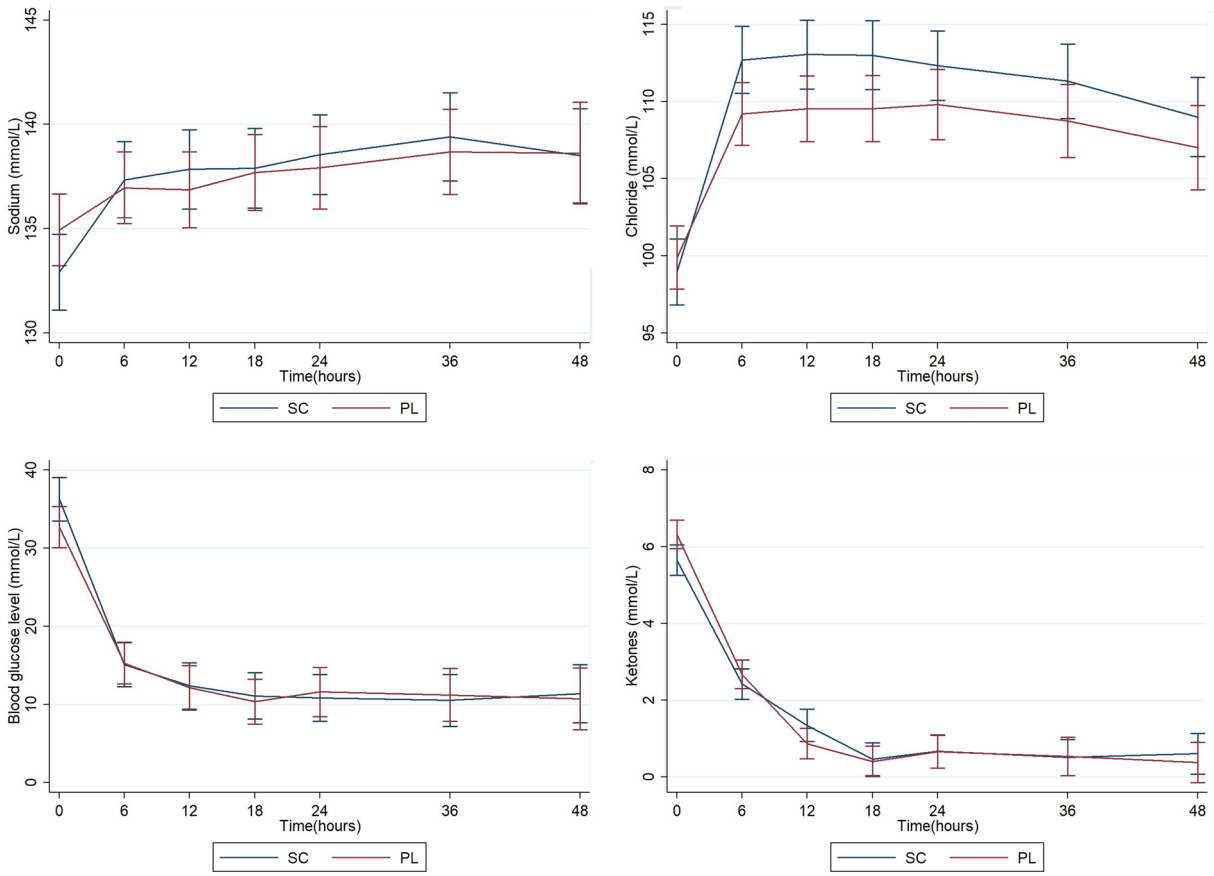


Fig. 3 Changes in sodium, chloride, blood glucose level and ketones during the first 48 h in the intensive care unit are shown here with 95% confidence intervals. Estimates presented here were generated using mixed-effects models to account for repeated measures. *SC* 0.9% sodium chloride, *PL* Plasmalyte-148

potentiate the ketosis. We did not observe an increase in ketosis, in fact, the rates were 14% at 24 h into the ICU admission in both groups. Resolution of DKA using multiple different definitions tended to be faster in the PL group, thus supporting our hypothesis that acetate in PL does not contribute to excess ketone generation in DKA. This is consistent with the finding that acetate infusions (4 mmol/kg over 1 h) in healthy volunteers resulted in only a small rise in plasma acetate concentrations and a metabolic alkalosis with acetate having a rapid plasma clearance of 2.31 L/min [30]. Comparatively, 1 L of PL-148 contains 27 mmol/L of acetate which is equivalent to 0.39 mmol/kg in a 70 kg individual.

The frequency of some adverse events, such as hypoglycemia and hypophosphatemia were also lower in the PL group.

Limitations

Our trial had limitations. As a Phase 2 trial not powered to detect differences in clinical outcomes, the clinical results can only be considered exploratory. While there was a separation between the groups in terms of the fluids administered, adherence to allocated fluids was not high in the PL group. There were substantial volumes of SC used, although if it influenced the clinical outcomes, it would tend to bias the results towards the null (Type-2 error) rather than leading to an erroneous conclusion of superiority (Type-1 error) for PL. As this trial allowed for usual local practices for drug dilution, often done using SC, it is likely that some of the non-compliance in the PL group can be explained by this. Additionally, compliance was better overall in ICU compared to ED, which may reflect greater familiarity with PL use amongst intensive care staff and better education of ICU compared to ED staff with regards to trial procedures.

Conclusion

In conclusion, for patients with severe DKA, treatment with PL compared to SC may result in faster resolution of metabolic acidosis. The use of PL was not associated with an increase in ketone generation.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-021-06480-5.

Author details
[1] Intensive Care Unit, Caboolture Hospital, McKean Street, Caboolture, QLD 4510, Australia. [2] Adult Intensive Care Services, The Prince Charles Hospital, Rode Road, Chermside, QLD 4032, Australia. [3] The George Institute for Global Health, University of New South Wales, Level 5/1 King Street, Newtown, NSW 2042, Australia. [4] School of Medicine, University of Queensland, Sir Fred Schonell Drive, St Lucia, QLD 4072, Australia. [5] Intensive Care Unit, Rockhampton Hospital, Canning Street, Rockhampton, QLD 4700, Australia. [6] Intensive Care Unit, Sunshine Coast University Hospital, Doherty Street, Birtinya, QLD 4575, Australia. [7] Intensive Care Unit, Ipswich Hospital, Chelmsford Avenue, Ipswich, QLD 4305, Australia. [8] Intensive Care Unit, Queen Elizabeth-2 Jubilee Hospital, Kessels Road, Coopers Plains, QLD 4108, Australia. [9] Intensive Care Unit, Mackay Base Hospital, Bridge Road, Mackay, QLD 4741, Australia. [10] Intensive Care Unit, Hervey Bay Hospital, Urraween Road, Pialba, QLD 4655, Australia. [11] Intensive Care Unit, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, QLD 4102, Australia. [12] Department of Intensive Care Medicine, The Queen Elizabeth Hospital, Woodville Road, Woodville South, South Australia 5011, Australia. [13] Intensive Care Unit, Wesley and Princess Alexandra Hospitals, Woolloongabba, QLD, Australia.

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Data Safety Monitoring Committee: Anthony Russell FRACP Director of Endocrinology, Princess Alexandra Hospital, Brisbane, Queensland, Australia Associate Professor, School of Medicine, University of Queensland, Brisbane, Queensland, Australia. Michael D'Emden FRACP Director of Endocrinology, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia. Kunwarjit Sangla FRACP Staff Specialist, Endocrinology, Rural Hospital Services Group, Queensland Health, Queensland, Australia.

Queensland Critical Care Research Network (QCCRN): The QCCRN was formed in June 2017 with a mission *"to foster a state-wide collaborative approach to critical care research with the goals of increasing research capacity in Queensland's Intensive Care Units and support high quality research output from local investigators with a focus on improving patient outcomes".* QCCRN is not open to commercial enterprise and access is restricted to individuals working non-commercially in the field of critical care research. Mahesh Ramanan is currently the Chair of QCCRN (term July 2019-June2021).

Author contributions
Conceptualisation: MR, PK, SP, LB and BV. Data curation: MR, AA. Formal analysis: MR, LB. Investigation: MR, AA, LM, NB, DS, GR, RP, MP, PG. Methodology: MR, LM, PK, SP, LB and BV. Project administration: MR, BV. Resources: MR, AA. Validation: MR, BV. Writing—original draft: MR. Writing—review and editing: All authors. Supervision: BV, SP.

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Availability of data and material
Deidentified data are available for sharing. To request data, please contact the corresponding author with a request. This will be reviewed by the trial management committee. Applications from investigators with the suitable academic capability to conduct the proposed work will be given consideration. Any proposal will require approval from the ethics committee which approved the conduct of this trial prior to sharing of any patient data. If a proposal is approved, a signed data transfer agreement will be required before data sharing.

Code availability
Not applicable.

Declarations

Conflicts of interest
The authors do not have any conflicts of interest or competing interests to declare.

Ethics approval (include appropriate approvals or waivers)
Ethics approval was granted by the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/2018/QRBW/43868) for this trial to be conducted at all participating sites with a full consent waiver.

Consent to participate
Full consent waiver was approved by the Ethics Committee.

Consent for publication
Not applicable.

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Médico y Cirujano

A

Leonardo Marín Restrepo

IDENTIFICADO CON: C.C.No 94 366 458 DE TULUA V.
QUIEN CUMPLIO SATISFACTORIAMENTE LOS REQUISITOS ACADEMICOS EXIGIDOS.
EN TESTIMONIO DE ELLO LE OTORGA EL PRESENTE

DIPLOMA

EN LA CIUDAD DE PEREIRA A LOS 7 DIAS DEL MES DE DICIEMBRE DE 1995
Y LO REFRENDA CON EL SELLO DE LA INSTITUCION

RECTOR

VICE-RECTOR ACADEMICO

DECANO

SECRETARIO GENERAL

DIRECTOR REGISTRO ACADEMICO

EL SUSCRITO NOTARIO UNICO DE JAMUNDI - VALLE - COLOMBIA
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15 SET. 1995
FRANCISCO JARAMILLO MORALES
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Augusto Leonardo Garcia
Notario Unico del Circulo de Jamundi

SECRETARIA DE EDUCACION DEPTAL
ANOTADO EN EL FOLIO No
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NOTARIA UNICA DE JAMUNDI
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18 ENE 1996
FRANCISCO JARAMILLO MORALES
NOTARIO
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Notario Unico del Circulo de Jamundi

LA UNIVERSIDAD NACIONAL DE COLOMBIA

FACULTAD DE

Medicina

TENIENDO EN CUENTA QUE

Leonardo Marin Restrepo

C.C. 94.366.458 de Tuluá (Valle)

CUMPLIO SATISFACTORIAMENTE
TODOS LOS REQUISITOS REGLAMENTARIOS DEL PROGRAMA
DE ESTUDIOS PARA GRADUADOS LE CONFIERE EL TITULO DE

Especialista en Medicina Interna

EN LA CIUDAD DE Valle de Bdn 13 de Abril DEL 2000

RECTOR DE LA UNIVERSIDAD

DECANO DE LA FACULTAD

SECRETARIO GENERAL DE LA UNIVERSIDAD

SECRETARIO DE LA FACULTAD

Folio: 20 Libro: 1
Facultad de Medicina
0010380

EL SUSCRITO NOTARIO VEINTIUNO
DEL CIRCULO DE CALI
CERTIFICO
QUE LA PRESENTE FOTOCOPIA CORRESPONDE
AL ORIGINAL DEL DOCUMENTO QUE HE TENIDO
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En Santiago de Cali 25 ABR. 2000
HOLDER HERNAN CARDONA M.
NOTARIO VEINTIUNO

LA PONTIFICIA UNIVERSIDAD JAVERIANA

PERSONERIA JURIDICA: RES. 73-12 DE DICIEMBRE 1.933 - MINGOBIERNO

EN ATENCION A QUE

LEONARDO MARIN RESTREPO

C.C. 94.366.458

HA CURSADO TODOS LOS ESTUDIOS Y CUMPLIDO LOS REQUISITOS ESTABLECIDOS POR LA UNIVERSIDAD Y LAS DISPOSICIONES LEGALES PARA UN GRADO UNIVERSITARIO

EN LA FACULTAD DE **MEDICINA**

LE OTORGA

EN NOMBRE DE LA REPUBLICA DE COLOMBIA

Y POR AUTORIZACION DEL MINISTERIO DE EDUCACION NACIONAL

EL TITULO DE **ESPECIALISTA EN NEFROLOGIA**

EN FE DE LO CUAL FIRMAMOS Y SELLAMOS ESTE DIPLOMA

NOSOTROS EL RECTOR LOS DECANOS Y EL SECRETARIO GENERAL DE LA UNIVERSIDAD

EXPEDIDO EN BOGOTA A LOS 21 DIAS DEL MES DE MARZO DEL AÑO 2002

RECTOR

SECRETARIO GENERAL

ASCOFAME

DECANO ACADEMICO

DECANO DEL MEDIO UNIVERSITARIO

DIRECTOR DE PROGRAMA

REPUBLICA DE COLOMBIA
NOTARIA QUINCE Dpto. del Valle del Cauca
CERTIFICA
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Cali, 03 ABR 2003
Ma. MERCEDES LALINDE O.
Notaria Quince de Cali

UNIVERSIDAD JAVERIANA COLOMBIA

Nº 2522

República de Colombia
Ministerio de Educación Nacional

Universidad del Valle

La Universidad del Valle

Confiere el Título de

Especialista en Medicina Crítica y Cuidado Intensivo

a

Leonardo Marin Restrepo

Identificado con c.c. **94366458**
En testimonio de ello le expide el presente Diploma,
en la ciudad de Santiago de Cali, Valle del Cauca,
a los 15 días del mes de diciembre de 2018

El Rector

El Decano

Registro al folio 713-21 del Libro 3 de Diplomas, a los 15 días del mes de diciembre de 2018

104758

Universidad del Valle

RECTORÍA

ACTA DE GRADO No 939

En la ciudad Santiago de Cali del Departamento del Valle del Cauca, de conformidad con lo dispuesto en la Resolución No 951 emanada de la Rectoría de la Universidad del Valle; el día 15 de Diciembre de 2018, en nombre de la República de Colombia y por autorización del Ministro de Educación Nacional, confiere el título de:

ESPECIALISTA EN MEDICINA CRÍTICA Y CUIDADO INTENSIVO
RG 54253 SNIES

a:

LEONARDO MARIN RESTREPO
Identificado con C.C. 94366458

El diploma correspondiente le será entregado en la fecha prevista en la Resolución No. 951 y anotado en el libro 3 Folio 713 Registro 21 de la Universidad del Valle.

(Fdo) Edgar Varela Barrios - Rector
(Fdo) Antonio Jose Echeverry Perez - Secretario General

Se firma en Santiago de Cali, el 15 de Diciembre de 2018

MARTA SOFÍA COTACIO TORRES
Jefa División de Admisiones y Registro Académico

ESTE DOCUMENTO NO REQUIERE AUTENTIFICACIÓN EN VIRTUD DEL DECRETO No 1024 DE 1982