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ANÁLISIS FARMACOCINÉTICO Y ESTRATEGIAS DE DOSIFICACIÓN DE AMICACINA EN PACIENTES CON HIPOALBUMINEMIA

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CERTIFICAN:

En calidad de directores de la Tesis cuyo título es **"*Análisis farmacocinético y estrategias de dosificación de amicacina en pacientes con hipoalbuminemia*"**, que la citada investigación ha sido realizada por la Graduada en Farmacia Dña. Eva Mª Sáez Fernández bajo su dirección y supervisión, reuniendo las condiciones necesarias para que pueda aspirar con este trabajo a la obtención del Título de Doctora en Farmacia y Salud.

Para que así conste, firman el presente certificado a 15 de Junio de 2020

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"El destino une y separa a la gente, pero no existe ninguna fuerza que sea tan grande que haga olvidar a las personas que, por algún motivo, algún día nos hicieron felices…"

El futuro tiene muchos nombres. Para los débiles es lo inalcanzable. Para los temerosos lo desconocido. Para los valientes es la oportunidad.

Víctor Hugo

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I. INTRODUCCIÓN

En los últimos años se han publicado diversos estudios que demuestran la influencia de la hipoalbuminemia en la morbi-mortalidad y duración de la estancia hospitalaria (1–5). Al ingreso la hipoalbuminemia puede estar presente hasta en un 30% de los pacientes, siendo considerado este parámetro por algunos investigadores como factor pronóstico de mortalidad a los 30 días tras el ingreso por proceso agudo (1,6). Aun considerando las comorbilidades existentes, la tasa de mortalidad en pacientes con hipoalbuminemia triplica su valor respecto a aquellos que presentan valores normales de esta proteína plasmática (1). Entre las múltiples complicaciones asociadas, cobra especial relevancia la disminución de la eficacia de distintos tratamientos debido a la modificación que la hipoalbuminemia puede provocar en las concentraciones de los fármacos en los distintos compartimentos del organismo. Por todos los aspectos anteriormente expuestos, la hipoalbuminemia, junto con otras variables fisiopatológicas, es un importante parámetro a considerar en la individualización posológica a fin de optimizar los tratamientos y alcanzar la máxima eficacia con el menor riesgo de toxicidad.

La aparición y propagación de infecciones causadas por bacterias multirresistentes o virus de nueva aparición (ej. SARS-CoV-2) constituye una de las amenazas actuales más graves para la salud pública, a la vez que uno de los retos más importantes de la medicina moderna a nivel mundial. El uso inapropiado e indiscriminado de tratamientos antibióticos contribuye de forma significativa a este fenómeno de gran impacto clínico, microbiológico y epidemiológico (7). De hecho, alrededor de 33.000 personas mueren cada año en Europa como consecuencia de infecciones hospitalarias debidas a bacterias resistentes, mientras que en España la cifra alcanza las 3.000 muertes anuales (7).

La selección de la estrategia farmacoterapéutica más adecuada a cada situación clínica particular a menudo se fundamenta en la experiencia clínica previa, las guías de tratamiento disponibles y la evolución clínica del paciente (8). La medicina personalizada, o medicina de precisión, constituye una estrategia ampliamente desarrollada en los últimos años y representa la adaptación del tratamiento farmacoterapéutico a las características individuales de cada paciente. En este contexto, la monitorización terapéutica de fármacos (TDM, Therapeutic Drug Monitoring), entendida como la determinación de la concentración de fármacos en fluidos

biológicos, junto con una adecuada interpretación de los mismos, constituye una herramienta primordial para la optimización de algunos tratamientos farmacológicos. El objetivo principal de la TDM consiste en mantener las concentraciones de fármaco dentro del margen terapéutico definido, aumentando la probabilidad de conseguir la máxima eficacia y seguridad del tratamiento. La TDM cobra especial interés en aquellos fármacos con estrecho margen terapéutico, elevada variabilidad inter e intra-individual, efecto farmacológico difícil de medir y buena correlación entre el efecto farmacológico y las concentraciones medidas (9). En el caso concreto de los aminoglucósidos, esta práctica ha demostrado ser coste-efectiva al proporcionar una reducción significativa en los efectos adversos y mortalidad (10).

Los modelos farmacocinéticos (PK) poblacionales permiten caracterizar la cinética de los fármacos en la población diana, mediante la estimación de parámetros PK medios así como de la cuantificación de la variabilidad de los mismos. Con herramientas de simulación basadas en modelos farmacocinéticos y farmacodinámicos (PKPD) previamente desarrollados en la población de interés, es posible realizar una estimación cuantitativa de la respuesta al tratamiento farmacológico e identificar los distintos factores (demográficos, fisiopatológicos, genéticos, ambientales, etc.) que potencialmente pueden influir en la variabilidad PK observada en vida real (8).

Los aminoglucósidos constituyen un grupo de antibióticos ampliamente utilizados desde hace varias décadas, siendo aún en la actualidad agentes de primera línea de tratamiento en una gran variedad de infecciones. El éxito continuado de estos antibióticos se atribuye a diversos factores, entre los que se encuentran su actividad bactericida, sinergismo con betalactámicos, gran eficacia clínica, baja tasa de resistencias y reducido coste.

Amicacina, derivado semisintético de kanamicina, es uno de los antibióticos aminoglucósidos más eficaces, ampliamente utilizado para el tratamiento de infecciones graves producidas por bacterias gram negativas, siendo un importante componente de la terapia empírica cuando aún no se conoce el microorganismo responsable de la infección. Su mecanismo de acción se basa en la unión a la subunidad 30S del ribosoma bacteriano, produciendo un complejo de iniciación 70S de carácter no funcional e interfiriendo en la síntesis proteica (11).

La mayoría de los antibióticos inhibidores de la síntesis de proteínas poseen actividad bacteriostática. Sin embargo, tanto los aminoglucósidos en general como la amicacina en particular se comportan como bactericidas (12). Este antibiótico posee actividad bactericida frente a distintas especies de bacilos gram negativos: *Pseudomonas*, *Escherichia Coli*, *Proteus*, *Providencia*, *Klebsiella*, *Enterobacter*, *Acinetobacter* o *Citrobacter freundii.* Además, la asociación de este aminoglucósido con antibióticos que actúan sobre la pared bacteriana (ej. betalactámicos o glucopéptidos) origina una acción sinérgica frente a diversos microorganismos, permitiendo su uso combinado en el tratamiento de algunas infecciones producidas por especies de cocos gram positivos tales como estafilococos productores y no productores de penicilinasa, incluyendo cepas meticilin-resistentes como *Staphylococcus aureus*, entre otros (11,13). Por otro lado, el uso de amicacina en monoterapia ha sido propuesto como una alternativa eficaz en aquellas infecciones sistémicas que tienen su origen en el tracto urinario (14).

Eficacia y toxicidad de amicacina

Desde un punto de vista farmacodinámico, los antibióticos se clasifican en tres grupos atendiendo a su patrón de actividad (15):

1. Actividad concentración-dependiente y efecto post-antibiótico (EPA) prolongado. En este grupo se encuentran los aminoglucósidos, fluoroquinolonas, metronidazol y daptomicina. Los índices PKPD relacionados con la eficacia del tratamiento en este grupo de antibióticos son dos: la relación Cmax/CMI (concentración máxima / concentración mínima inhibitoria) y la relación ABC/CMI (área bajo la curva de concentraciones-tiempo / CMI).
2. Actividad tiempo-dependiente y ligero EPA. Grupo en el que están incluidos los antibióticos betalactámicos, cuyo parámetro PKPD representativo es el tiempo que la concentración del antibiótico se mantiene superior a la CMI (%T>CMI).

3. Actividad tiempo-dependiente y EPA prolongado. Se incluyen en este grupo los antibióticos glucopéptidos (vancomicina y teicoplanina), linezolid o tigeciclina, cuyo índice PKPD característico es la relación ABC/CMI.

El EPA representa la capacidad del antibiótico para inhibir el crecimiento bacteriano una vez que las concentraciones del fármaco descienden por debajo de la CMI del microorganismo. En el caso de amicacina, el EPA tiene una duración variable comprendida entre 2 y 8 horas. Entre los múltiples mecanismos relacionados con el EPA, la inhibición de la expulsión del fármaco fuera de la célula, el incremento de la susceptibilidad de las bacterias a la acción de células del sistema inmune y en concreto, el tiempo necesario para la regeneración de los ácidos nucleicos y la síntesis de proteínas, son algunos de los relacionados con amicacina (16–21). Depende de diversos factores, entre los que se encuentran el agente causal de la infección, la potencia antibacteriana, las concentraciones del antibiótico o los mecanismos de defensa del paciente. La duración del EPA de los aminoglucósidos se encuentra íntimamente relacionada con la concentración máxima alcanzada (22,23).

En el año 1987 se estableció la importancia de la relación Cmax/CMI como índice PKPD relacionado con la eficacia del tratamiento con aminoglucósidos (24). Otro índice, introducido con posterioridad en la práctica clínica, es la relación ABC/CMI. Los índices Cmax/CMI y ABC/CMI están correlacionados, reflejando ambos la actividad bactericida concentración-dependiente (25–28). Más recientemente, se ha relacionado con la eficacia de los aminoglucósidos el parámetro %T>CMI, asociado a su vez con la actividad de los antibióticos tiempo-dependientes (25).

La relación Cmax/CMI convencionalmente asociada con la mejor respuesta clínica de amicacina está comprendida como mínimo entre 8 y 10 (29,30). Por otro lado, el objetivo terapéutico habitual de la relación ABC/CMI es ≥ 75 (26,28,31–34). No obstante, los objetivos para estos dos parámetros PKPD están en cierta medida relacionados con el patógeno a tratar y el esquema de antibioterapia a utilizar, por lo que será necesario valorar también la evolución clínica del paciente y/o la posibilidad de cambio de alternativa terapéutica en el caso de requerirse Cmax potencialmente tóxicas para alcanzar los valores indicados. El European

Committee on Antimicrobial Susceptibility Testing (EUCAST), en su última actualización (enero de 2020), mantiene en 8 mg/L el valor máximo de CMI para las bacterias sensibles a amicacina (*Enterobacteriaceas, Acinetobacter spp* y *Staphylococcus spp)* (35). Sin embargo, este valor asciende a 16 mg/L para *Pseudomonas spp*. (35). Con estos puntos de corte para la CMI, valores de Cmax ≥ 64 mg/L y ABC ≥ 600 mg·h/L deberían ser el objetivo terapéutico para las bacterias más sensibles, mientras que para el éxito del tratamiento de infecciones producidas por *Pseudomonas* deberían alcanzarse concentraciones de amicacina muy superiores, potencialmente tóxicas.

Aunque está establecido que la óptima relación ABC/CMI debe tener un valor mínimo de 75, en el tratamiento de pacientes inmunocompetentes o en terapia combinada con otros antibióticos el objetivo podría ser próximo a 50 mg/L. Sin embargo, en monoterapia o en el tratamiento de infecciones graves en el paciente crítico, puede ser necesario alcanzar un valor de ABC/CMI próximo a 100 para alcanzar una respuesta terapéutica adecuada (28)**.** Finalmente, es necesario resaltar que una relación Cmax/CMI adecuada no garantiza la eficacia del tratamiento con aminoglucósidos si la concentración del antibiótico no se mantiene superior a la CMI durante al menos el 60% del intervalo posológico (25,36,37).

Los efectos tóxicos de los aminoglucósidos constituyen la principal limitación de su utilización clínica, siendo la nefrotoxicidad y ototoxicidad las manifestaciones más frecuentes, seguidas de toxicidad neuromuscular. Por otra parte, no se ha podido demostrar la existencia de diferencias significativas en el grado de toxicidad de los tres aminoglucósidos más utilizados (gentamicina, tobramicina y amicacina). Determinados factores modifican el riesgo de toxicidad, tales como las enfermedades preexistentes, gravedad de la infección a tratar, la medicación concomitante o la predisposición genética (38). Además, está demostrado que la duración prolongada del tratamiento constituye un factor independiente del riesgo de toxicidad de estos antibióticos (39). Mientras que en determinados pacientes el efecto farmacológico puede manifestarse incluso a bajas concentraciones, los efectos tóxicos pueden aparecer con concentraciones dentro del margen terapéutico (9). Para amicacina se ha establecido una clara relación entre concentraciones mínimas (Cmin) elevadas (> 4 mg/L) y la aparición de nefrotoxicidad y pérdida

de células ciliadas y cocleares, con la consecuente pérdida de audición y equilibrio (23). Se estima que en torno a un 25% de los pacientes que reciben tratamiento con aminoglucósidos desarrollan toxicidad a nivel renal, caracterizada por su reversibilidad a lo largo del tiempo (23,39). Esta toxicidad ha sido tradicionalmente asociada al daño tubular renal y está relacionada tanto con una reducción del filtrado glomerular como con una reducción del flujo sanguíneo renal (39). Con menor frecuencia, alrededor del 20% de los pacientes que reciben tratamiento intravenoso con amicacina durante varios días desarrollan toxicidad a nivel coclear y vestibular, habitualmente de carácter irreversible (23,40).

Farmacocinética de amicacina

Amicacina se administra por vía intramuscular y mediante perfusión intravenosa intermitente, si bien es cierto que en ocasiones es utilizada a nivel tópico local (11,13). Aunque no tan extendida en la práctica clínica habitual como las vías de administración anteriormente mencionadas, existe también la posibilidad de administrar amicacina nebulizada o en forma de aerosol por vía inhalatoria para el tratamiento de infecciones de las vías respiratorias inferiores (41–45). La absorción tras la administración intramuscular es completa, alcanzándose la Cmax en sangre 30-90 minutos tras la administración, mientras que por vía intravenosa esta concentración se alcanza al finalizar la perfusión de amicacina. En la administración vía intravenosa se recomiendan infusiones de 15-30 minutos de duración y 30-60 minutos en el caso de administrar dosis elevadas (11).

La estructura química, basada en un aminoazúcar unido mediante un enlace glucosídico al aminociclitol 2-desoxiestreptamina, confiere a amicacina un carácter básico, catiónico y polar. Estas propiedades son el fundamento de su elevada solubilidad en agua y distribución en el espacio extravascular (favorecida en ambientes básicos) y relativa insolubilidad en lípidos y, por tanto, un transporte mínimo a través de las membranas biológicas (11).

El volumen de distribución de amicacina está comprendido entre 0,2 y 0,4 L/kg, limitándose, al igual que en otros antibióticos hidrosolubles, al espacio extravascular (11,46). En varios estudios se ha demostrado un incremento del volumen de distribución de amicacina en pacientes

con hipoalbuminemia, sepsis, shock séptico, embarazo, neumonía nosocomial grave, patologías hematológicas o pacientes quemados (11,31,47–51). Diferentes situaciones clínicas han sido asociadas con cambios en el volumen de distribución: alteraciones cardiovasculares con aparición de terceros espacios (administración de fluidos para contrarrestar la hipotensión con el consiguiente aumento del volumen intersticial), hipoalbuminemia (asociada a una disminución de la presión oncótica y extravasación capilar), caquexia (incremento en la relación agua corporal / peso), malnutrición o ascitis (49,52). En todas estas situaciones puede encontrarse incrementado el volumen de distribución de amicacina, con la consiguiente reducción de la Cmax alcanzada y, por tanto, posible reducción de la eficacia del tratamiento. Por otra parte, el envejecimiento está asociado con cambios fisiológicos como la reducción del filtrado glomerular y cambios en el porcentaje de agua y grasa corporal, pudiendo modificar el volumen de distribución y comportamiento PK de amicacina (48).

La eliminación de amicacina se realiza esencialmente mediante filtración glomerular sin metabolismo previo alguno. Una vez filtrada, un pequeño porcentaje de amicacina es reabsorbido por las células de los túbulos proximales, mecanismo responsable, en parte, de la toxicidad producida a dicho nivel (39,53). Así, en pacientes con alteraciones de la función renal o presión de filtración glomerular disminuida existe una disminución del aclaramiento renal, un mayor riesgo de acumulación del fármaco e incremento de la semivida, cuyo valor habitual está comprendido entre 2 y 3 horas (11). La eliminación renal juega un papel fundamental en la PK de los fármacos hidrosolubles como amicacina, pudiendo verse afectada por factores fisiológicos y/o patológicos como la edad y el sexo, insuficiencia renal, infección por el virus de la inmunodeficiencia humana (VIH), artritis reumatoide, coadministración de catecolaminas (ej. dopamina, adrenalina, noradrenalina) u otros fármacos vasoactivos o nefrotóxicos (ej. anfotericina) (25,31,47,52,54–64).

La selección del modelo PK que describa más adecuadamente la evolución del fármaco en el organismo debe basarse en las características cinéticas inherentes al mismo, así como en la información experimental y clínica disponible (65). La cinética de amicacina ha sido caracterizada por modelos bicompartimentales, pero el escaso número de muestras obtenidas

por paciente en la práctica clínica habitual supone una limitación para su aplicación rutinaria (48). Este hecho, junto con una muy reducida fase de distribución y unos resultados similares en cuanto a estimación de parámetros PK, justifica que el modelo PK utilizado habitualmente para la individualización posológica de amicacina administrada mediante perfusión intravenosa sea el monocompartimental (49). En este modelo, los cálculos que permiten determinar los parámetros que describen el perfil cinético de amicacina son relativamente sencillos, con la ventaja de necesitar un reducido número de muestras del paciente. Además, se considera al organismo como un sistema homogéneo, de manera que la evolución temporal de las concentraciones séricas representa adecuadamente la evolución en cualquier punto del mismo (65).

De forma similar al resto de antibióticos aminoglucósidos, amicacina se caracteriza por una elevada variabilidad intra e interindividual en sus parámetros PK debido a múltiples factores fisiopatológicos o clínicos (peso, edad, estado de la función renal, diagnóstico, comorbilidades, etc.) (66,67). Teniendo en cuenta estos factores, se han definido distintas poblaciones de pacientes que presentan parámetros PK similares de amicacina como el paciente crítico, hematológico o quemado (25,31,47–52,54–61,68–70). Las tablas 1 y 2 recogen distintos modelos cinéticos de amicacina, tanto monocompartimentales como bicompartimentales, desarrollados en diversas poblaciones entre las que destacan los pacientes críticos y aquellos con sepsis.

Tabla 1. Características de la población incluida y el tratamiento en los principales modelos farmacocinéticos poblacionales de amicacina en adultos

Referencia	Población				Tratamiento y muestreo	
	N (hombres)	Edad (años) *	Albúmina (g/dL) *	Pacientes	Dosis de amicacina	Muestras (n)
Burdet 2015 (31)	60 (47)	61.5 [28-84]	1.9 [1.4-4.4]	Críticos	11-28 mg/kg/24h	291
Matar 2013 (54)	56 (32)	57.4 [19-90] $^{\Delta}$	-	Críticos	500 mg/12h	331
Jang 2011 (60)	197 (113)	61.0 ± 17.5	-	Medicina general y críticos	125-1000 mg/24h	698
Delattre 2010 (55)	88 (57)	65.0 [22-89]	1.8 [0.8-4.9]	Sepsis	25 mg/kg/24h	507
Lugo-Goytia 2000 (56)	42 (ND)	59 ± 15	ND	Sepsis	7.5-30 mg/kg/8-24h	ND
Joubert 1999 (68)	14 (ND)	52.7 ± 20.2	-	Críticos	600-1350 mg/24h	744
Romano 1999 (47)	134 (77)	53.0 ± 16.4	-	Hematológicos	18.5 ± 5.5 mg/kg/24h $^{\spadesuit}$	3.2 ± 1.9 $^{\spadesuit}$
Romano 1998 (52)	120 (73)	52.9 ± 18.5	-	Críticos	15.6 ± 6.2 mg/kg/24h $^{\spadesuit}$	4.2 ± 2.7 $^{\spadesuit}$
Tod1998 (57)	57 (35)	51.0 ± 16.0	ND	Hematológicos	7.5 mg/kg/12h ó 20 mg/kg/24h	278
Lugo 1997 (61)	73 (ND)	60.0 ± 12.0 $^{\Omega}$ 57.8 ± 8.0 †	-	Sepsis	7.5-30 mg/kg/24h	ND
Lugo 1997 (59)	30 (17)	50.0 ± 15.0	2.4 ± 0.6	Sepsis	7.5 mg/kg $^{\blacklozenge}$	ND
Debord 1995 (58)	40 (30)	51.8 ± 18.2	-	Críticos	2.2-31.4 mg/kg/24h	212
Maire 1994 (69)	50 (ND) 50 (ND)	62 (±ND) 80 (±ND)	- -	Medicina general Geriatría	ND ND	124 277
Debord 1992 (70)	40 (ND)	51 [18-77] $^{\Delta}$	-	Críticos	7.5 mg/kg/24h	7 (ND) $^{\spadesuit}$

ND, no disponible.
* Valores expresados como media ± desviación estándar o mediana [rango].
$^{\Delta}$ Valores expresados como media [rango].
$^{\spadesuit}$ Valores expresados como media ± desviación estándar por paciente.
$^{\Omega}$ Pacientes sin cirrosis.
† Pacientes con cirrosis.
$^{\blacklozenge}$ Intervalo posológico ajustado mediante monitorización farmacocinética.

Tabla 2. Principales modelos farmacocinéticos poblacionales de amicacina en adultos

Referencia	Modelo		Covariables evaluadas			Covariables modelo final		Parámetros estimados * (VII, CV %)			
	Modelo estructural	Software	Demográficos	Datos clínicos y bioquímicos	Co-medicación	CL	Vd	CL (L/h)	V_1 (L)	Q (L/h)	V_2 (L)
Burdet 2015 (31)	Bicompartimental	Monolix	Edad, peso, sexo	Albúmina, bilirrubina total, CL_{CR}, edema, PaO_2/FiO_2, PEEP, SAPS II, shock, SOFA	-	CL_{CR}	PaO_2/FiO_2, peso	4.3 (31)	15.9 (22)	12.1 (27)	21.4 (47)
Matar 2013 (54)	Bicompartimental	USC PACK	Altura, edad, peso, sexo	CL_{CR}	-	CL_{CR}	-	5.08 (ND) $^{\Delta}$	16.7 (38)	36.9 (ND) $^{\Delta}$	25.8 (ND) $^{\Delta}$
Jang 2011 (60)	Monocompartimental	NONMEM	Edad, peso, sexo	CL_{CR}, diagnóstico (cirrosis hepática, colecistitis, diabetes mellitus, hipertensión, infección del tracto urinario, neumonia, sepsis,), unidad de ingreso (UCI – no UCI)	-	CL_{CR}, unidad de ingreso	Colecistitis, peso	2.8 (30)	18.0 (ND)	-	-
Delattre 2010 (55)	Bicompartimental	NONMEM	Edad, peso, sexo	Albúmina, ALT, APACHE II, AST, bilirrubina total, CL_{CR}, creatinina, FA, GGT, PEEP, proteína C reactiva, proteínas totales, tiempo de protrombina, tiempo de tromboplastina parcial activada, shock séptico, SOFA, urea, ventilación mecánica	Catecolaminas, cefepima, ceftazidima, coloides, cristaloides, meropenem, piperacilina	CL_{CR}	-	0.77 (59)	19.2 (39)	4.4 (17)	9.4 (44)
Lugo-Goytia **2000** (56)	Monocompartimental	USC PACK	Altura, edad, sexo	Albúmina, APACHE II, CL_{CR}, consumo de oxígeno, gasto cardíaco, PEEP	Catecolaminas	Catecolaminas, CL_{CR}, PEEP	APACHE II	3.85 (41)	31.7 (29)	-	-
Joubert 1999 (68)	Bicompartimental	NONMEM	-	CL_{CR}	-	CL_{CR}	-	-	17.1 (22.2)	5.22 (104)	-
Romano 1999 (47)	Monocompartimental	NONMEM	Edad, peso, sexo	CL_{CR}, diagnóstico, ECOG, hiperhidratación, hipoalbu minemia, neutropenia, nº de semanas post-quimioterapia, trasplante de medula ósea autólogo/alogénico, tratamiento antineoplásico	Anfotericina B, nutrición parenteral, vancomicina	LMA, CL_{CR}, diagnóstico,	Hipoalbumi nemia, peso	No LMA 5.53 (29) LMA 6.63 (29)	Normoalbúmina 23.98 (26) Hipoalbúmina 31.17 (26)	-	-
Romano 1998 (52)	Monocompartimental	NONMEM	Edad, peso, sexo	CL_{CR}, diagnóstico, día de tratamiento con amicacina, hospital	Nutrición parenteral	CL_{CR}, trauma	Peso, sepsis	No trauma 4.5 (28.2) Trauma 5.5 (28.2)	No sepsis 27.1 (23.2) Sepsis 33.6 (23.2)	-	-

Tabla 2. Principales modelos farmacocinéticos poblacionales de amicacina en adultos (continuación)

Referencia	Modelo		Covariables evaluadas			Covariables modelo final		Parámetros estimados * (VII, CV %)			
	Modelo estructural	Software	Demográficos	Datos clínicos y bioquímicos	Co-medicación	CL	Vd	CL (L/h)	V_1 (L)	Q (L/h)	V_2 (L)
Tod 1998 (57)	Bicompartimental	NONMEM	Edad, peso, sexo	Albúmina, CL_{CR}, creatinina, duración de la infusión, duración del tratamiento, leucocitos, neutrofilos, régimen de dosificación,	-	Creatinina, edad, peso, sexo	-	Hombre 3.82 (21) Mujer 3.40 (21)	8.92 (15)	4.43 (30)	11.4 (25)
Lugo 1997 (61)	Monocompartimental	USC PACK	Altura, edad, peso, sexo	Cirrosis, creatinina, régimen de dosificación, sepsis	-	Cirrosis	Cirrosis	-	No cirrhosis 31.0 (ND) Cirrosis 41.5 (ND)	-	-
Lugo 1997 (59)	Monocompartimental	PCNonlin	Edad, peso	Albúmina, ALT, APACHE II, CL_{CR}, consumo de oxígeno, índice cardiaco, PaO_2/FiO_2, PEEP, urea, ventilación mecánica	Catecolaminas, dopamina	Catecolaminas, CL_{CR}, PEEP	Albúmina, peso, relación de extracción de oxígeno	3.6 (34)	32.0 (35)	-	-
Debord 1995 (58)	Monocompartimental	USC PACK	-	CL_{CR}	-	CL_{CR}	-	4.5 (69)	25.6 (28)	-	-
Maire 1994 (69)	Monocompartimental	NONMEM USC PACK	Peso	CL_{CR}	-	CL_{CR}	Peso	NONMEM 2.74 (70) NPEM 3.76 (46) NPML 3.77 (57)	NONMEM 19.6 (28) NPEM 22.3 (33) NPML 21.4 (36)	-	-
Debord 1992 (70)	Monocompartimental	USC PACK	-	-	-	-	-	-	0.4 L/kg (ND)	-	-
	Bicompartimental	USC PACK	-	-	-	-	-	-	0.36 L/kg (ND)	0.013 (ND) $^{\Delta}$ L/kg h	1.08 (ND) $^{\Delta}$ L/kg

ALT, alanina aminotransferasa; APACHE, Acute Physiology and Chronic Health Evaluation; AST, aspartato aminotransferasa; CL, aclaramiento total; CLCR, aclaramiento de creatinina; CV, coeficiente de variación; ECOG, Eastern Cooperative Oncology Group score; FA, fosfatasa alcalina; GGT, gamma-glutamil transferasa; VII, variabilidad interindividual; LMA, leucemia mieloblástica aguda, ND, no disponible; PaO2/FiO2, relación entre la presión parcial de oxígeno en sangre arterial y la fracción de oxígeno inspirado; PEEP, positive end-expiratory pressure; Q, aclaramiento intercompartimental; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; UCI, unidad de cuidados intensivos; Vd, volumen de distribución; V1 o V2, volumen de distribución de los compartimentos central y periférico respectivamente; Peso, peso corporal total expresado en kilogramos.

*Valores expresados en forma de media.

Δ Parámetros calculados a partir de las microconstantes indicadas en los modelos farmacocinéticos: k12, constante de transferencia de primer orden desde el compartimento central al periférico; k21, constante de transferencia de primer orden desde el compartimento periférico al central; Kslope, componente renal de la constante de eliminación.

Dosificación de amicacina

La dosis de amicacina aprobada por la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) para administración intravenosa, en adultos y niños mayores de 12 años, es de 15 mg/kg/día (13). Sin embargo, los distintos factores que pueden modificar las propiedades PKPD de este antibiótico aconsejan la utilización de dosis individualizadas en función de las características del paciente.

El régimen convencional para la dosificación de amicacina consiste en dividir la dosis total diaria en 2-3 dosis equivalentes entre sí y administrarlas a intervalos de tiempo regulares (13). Para bacterias con una CMI relativamente baja el objetivo terapéutico para la relación Cmax/CMI se alcanza fácilmente mediante la administración de dosis estandarizadas de amicacina en regímenes de dosificación convencionales. Sin embargo, en infecciones causadas por bacterias altamente resistentes será necesario recurrir a diferentes estrategias de dosificación. Desde los años 1990, se ha extendido en la práctica clínica la administración de amicacina con régimen de dosis única diaria o ampliación de intervalo, pareciendo ofrecer mejores resultados clínicos y microbiológicos sin una mayor incidencia de toxicidad asociada (71,72). Esta modalidad consiste en administrar la dosis diaria total en una única dosis o incluso más espaciada (cada 36 ó 48 h) (13). Apoyándose en el marcado EPA de amicacina frente a bacterias gram negativas, esta estrategia permite alcanzar una mayor eficacia como resultado del aumento de la Cmax. Así mismo, persigue una reducción de la toxicidad mediante la disminución de la Cmin, ya que el antibiótico se elimina antes de la administración de la siguiente dosis y se reduce su acumulación. La elección del régimen de administración más adecuado dependerá de los múltiples factores modificadores de la PK de amicacina que presente el paciente.

La concentración diana terapéutica del tratamiento se ve modificada en función de la estrategia de dosificación elegida. Así, en regímenes de dosificación convencional la Cmax propuesta para conseguir la eficacia terapéutica está comprendida entre 20 y 30 mg/L, mientras que en regímenes de ampliación de intervalo esta concentración se encuentra entre 45 y 60 mg/L (25).

Además de maximizar la eficacia, el objetivo terapéutico de los tratamientos con amicacina también incluye la minimización de su toxicidad. Aunque no se ha podido establecer una relación directa entre las concentraciones de amicacina y la aparición de efectos adversos, la Cmin debe ser siempre inferior a 4 mg/L con el fin de disminuir la probabilidad de aparición de éstos (25,66). En el régimen de dosificación con ampliación del intervalo, la concentración antes de administrar la siguiente dosis, esto es la Cmin, casi siempre es indetectable, minimizándose teóricamente la toxicidad.

La influencia de factores que pueden modificar la PK de amicacina, como el peso corporal, la albúmina, la función renal, la edad, el tratamiento concomitante con otros fármacos o nutricional parenteral, entre otros, ha sido estudiada con el objetivo de optimizar los regímenes de dosificación de amicacina (25,31,47,52,54–58,60,61,64,68). El empleo de dosis estandarizadas de antibióticos para el tratamiento de infecciones bacterianas constituye una práctica habitual. La recomendación de administrar 15-20 mg/kg/día de amicacina en una única dosis diaria ha sido mayoritariamente aceptada, ajustándose la dosis únicamente a la función renal o la edad del paciente. Sin embargo, algunas de las últimas recomendaciones de dosificación de antimicrobianos recogidas por el EUCAST o la guía de dosificación del Queensland Health System han postulado la necesidad de administrar dosis de amicacina elevadas, hasta 30 mg/kg/día, para conseguir un tratamiento efectivo (35,73).

Las distintas guías y recomendaciones de dosificación establecen la dosis de amicacina según el peso corporal total, peso corporal ideal o peso corporal ajustado del paciente en función de si el paciente presenta obesidad o no, sin tener en cuenta cada uno de los rangos incluidos en la clasificación del índice de masa corporal (IMC). Atendiendo a este último parámetro, podrían existir diferencias significativas de dosificación tanto en el paciente no obeso como en el obeso, que se harían más notables en los valores extremos de la clasificación, es decir, en pacientes de bajo peso (IMC < 18,5 kg/m^2) y en pacientes con obesidad grado 3 (IMC > 40 kg/m^2).

Un factor presente en las guías de dosificación de amicacina es la función renal del paciente. El argumento en este caso se basa no tanto en la clasificación de los distintos rangos de función renal, casi unánime en las distintas guías, sino en el método utilizado para su valoración, dando

lugar a diferencias que podrían resultar significativas para la elección de la dosis a administrar (35,73–76). En la práctica clínica, el filtrado glomerular estimado a partir de la creatinina sérica del paciente es el parámetro más comúnmente empleado para valorar la función renal. Es, además, el más frecuentemente utilizado en el ajuste posológico de fármacos eliminados principalmente por el riñón, como amicacina (77). Desde su introducción en clínica, la fórmula de Cockcroft-Gault con peso corporal total ha sido el estándar de referencia para el cálculo del aclaramiento de creatinina. Más recientemente se han desarrollado múltiples ecuaciones, siendo las más comunes: Modification of Diet in Renal Disease (MDRD-4), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), revised Lund-Malmö (rLM), Berlin Initiative Study (BIS) o Full Age Spectrum (FAS) (78–81). Sin embargo, es bien conocido el hecho de que estas ecuaciones que emplean la creatinina para estimar el filtrado glomerular pueden dar lugar a resultados discordantes (82). Es preciso destacar que no todas las ecuaciones se basan en los mismos parámetros para estimar la función renal ni fueron validadas en grupos de población equivalentes de edad y/o función renal (79–81,83–86). A pesar de que en los últimos años se han publicado distintos estudios comparativos de las ecuaciones de filtrado glomerular descritas en la literatura, no existe consenso en la actualidad sobre la ecuación más representativa de la función renal, proponiéndose en la mayoría de los casos Cockcroft-Gault como la ecuación que proporciona mejores resultados en pacientes ancianos y con insuficiencia renal (62,67,87–93).

Otras variables como la albúmina, con efecto regulador del volumen de distribución, el tratamiento concomitante con otros fármacos y la administración de soporte nutricional, no son tenidos en cuenta a la hora de realizar las recomendaciones de dosificación, lo cual tiene un efecto potencial sobre la eficacia y/o toxicidad del tratamiento con amicacina.

La estrategia terapéutica óptima para amicacina debe incluir la dosificación inicial más adecuada a las características del paciente. Sin embargo, la existencia de recomendaciones discordantes para la dosificación estándar de amicacina genera incertidumbre en la prescripción. Por otra parte, es necesario identificar aquellos factores y situaciones clínicas que requieran una dosificación adaptada. El peso de dosificación a utilizar (peso corporal total, peso ideal o peso ajustado), la ecuación más adecuada para valorar la función renal del paciente, así como los

factores que modifican la cinética de amicacina y puedan condicionar su dosificación, necesitan ser esclarecidos a fin de proponer guías seguras para la dosificación inicial de amicacina.

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II. OBJETIVOS

1. Evaluar, mediante metodología fármaco-estadística, la capacidad predictiva de las principales ecuaciones de estimación de la función renal para describir la eliminación renal de amicacina en la práctica clínica habitual.
2. Caracterizar la farmacocinética de amicacina en pacientes con hipoalbuminemia mediante una aproximación poblacional y evaluar la capacidad descriptiva y predictiva del modelo poblacional desarrollado.
3. Desarrollar una aplicación interactiva, basada en el modelo farmacocinético poblacional propuesto, para la optimización de los regímenes de dosificación inicial de amicacina.
4. Evaluar comparativamente la eficacia y seguridad de las recomendaciones internacionales de dosificación de amicacina.
5. Desarrollar una aplicación interactiva para la construcción de nomogramas de dosificación de amicacina.
6. Evaluar el impacto de factores intrínsecos en la eficacia y seguridad de los regímenes de dosificación de amicacina.

III. TRABAJO EXPERIMENTAL

III.1. EVALUATION OF RENAL FUNCTION EQUATIONS TO PREDICT AMIKACIN CLEARANCE

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RESUMEN

Objetivo: Evaluar la capacidad predictiva de ocho ecuaciones de estimación de la función renal para describir la eliminación de amicacina en una población estándar con un amplio rango de edad.

Métodos: Estudio retrospectivo realizado con pacientes adultos hospitalizados en tratamiento con amicacina y monitorizados en el laboratorio de farmacocinética del Servicio de Farmacia. La función renal fue calculada mediante las ecuaciones de Cockcroft-Gault (peso corporal total, ajustado e ideal), MDRD-4, CKD-EPI, rLM, BIS1, y FAS. Se seleccionó un modelo monocompartimental con eliminación de primer orden, incluyendo la variabilidad interindividual en el aclaramiento y el volumen de distribución y el error residual combinado como modelo estructural. Se realizó un análisis fármaco-estadístico siguiendo una metodología de efectos mixtos no lineales con NONMEM v.7.3.

Resultados: Se incluyeron 198 pacientes (61 años [18-93]) y 566 concentraciones plasmáticas de amicacina. Todas las ecuaciones de filtrado glomerular estimado y de aclaramiento de creatinina evaluadas describieron adecuadamente los datos. La relación lineal entre el aclaramiento y el filtrado glomerular estimado según la ecuación revisada de Lund-Malmö (rLM) mostró una mejora estadísticamente significativa en el ajuste de los datos. rLM debe ser evaluado cuidadosamente para el ajuste de dosis de amicacina en insuficiencia renal.

Conclusiones: La ecuación rLM y CKD-EPI mostraron una capacidad predictiva superior de la eliminación de amicacina en comparación con las alternativas evaluadas.

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ORIGINAL RESEARCH

Evaluation of renal function equations to predict amikacin clearance

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ABSTRACT

Objective: To evaluate the predictive performance of eight renal function equations to describe amikacin elimination in a large standard population with a wide range of age.

Methods: Retrospective study of adult hospitalized patients treated with amikacin and monitored in the clinical pharmacokinetics laboratory of a pharmacy service. Renal function was calculated as Cockcroft-Gault with total, adjusted and ideal body weight, MDRD-4, CKD-EPI, rLM, BIS1, and FAS. One compartment model with first-order elimination, including interindividual variability on clearance and volume of distribution and combined residual error model was selected as a base structural model. A pharmaco-statistical analysis was performed following a non-linear mixed effects modeling approach (NONMEM 7.3 software).

Results: 198 patients (61 years [18–93]) and 566 measured amikacin plasma concentrations were included. All the estimated glomerular filtration rate and creatinine clearance equations evaluated described properly the data. The linear relationship between clearance and glomerular filtration rate based on rLM showed a statistically significant improvement in the fit of the data. rLM must be evaluated carefully in renal failure for amikacin dose adjustment.

Conclusions: Revised Lund-Malmö (rLM) and CKD-EPI showed the superior predictive performance of amikacin drug elimination comparing to all the alternative metrics evaluated.

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KEYWORDS
Amikacin; aminoglycosides; eGFR; glomerular filtration rate; pharmacokinetics; renal elimination

1. Introduction

Renal elimination plays a key role in the pharmacokinetics (PK) and pharmacodynamics (PD) of water-soluble drugs and for most of the metabolites [1]. This process can be affected in a large extent for several physiopathological situations including, but not limited to, renal dysfunction, HIV infection, renal transplant, rheumatoid arthritis, age, sex or drug interactions [2]. In addition, changes in the volume of distribution (V) due to capillary leak and modified protein binding are important kinetic changes derived from renal disease influencing the elimination process. All these sources of drug elimination variability highlight the importance of accurately quantify the renal elimination for drugs mainly excreted by this pathway, especially when dose adjustment based on renal elimination is highly recommended (i.e. drugs with narrow therapeutic index).

Estimated glomerular filtration rate (eGFR) is the most extensive metric commonly used in clinical setting to predict renal function for drugs mainly eliminated by the kidney pathway and needing dosing individualization [3]. Different authors have recently performed several comparative studies of the different eGFR equations analyzing the advantages and disadvantages of these equations. However, there is no unanimous consensus on the best eGFR equation to be applied in the clinical routine [1,4–10]. Since the 1970s, the gold standard for creatinine clearance (CL_{CR}) estimation in clinical practice was the Cockcroft-Gault by total body weight equation (CGT). More recently, alternative metrics to evaluate the renal function such as Modification of Diet in Renal Disease (MDRD-4), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Revised Lund-Malmö (rLM), Berlin Initiative Study (BIS) or Full Age Spectrum (FAS), among others, have been performed [11–14]. However, it is well established that the available serum creatinine-based equations for estimation of kidney function through the eGFR may provide discrepant results [15].

Aminoglycosides constitute an antibiotic group with a narrow therapeutic index eliminated primarily by the kidneys. Many studies have reported a positive linear correlation between several aminoglycosides total clearance (CL) and CL_{CR} or eGFR from equations based on serum creatinine [15–20], commonly applied for dose adjustment in clinical practice.

The aim of the present research was to evaluate the predictive performance of eight renal function metrics to describe drug elimination using specific pharmaco-statistical methodology and amikacin as a model drug in a large standard population with a wide range of age from a clinical setting.

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Preliminary results of this research were presented as a poster in the 1st Global Congress of Pharmacy Faculties, Innovation in Pharmacy: Advances and Perspectives (IPAP2018), on September 2018 in Salamanca, Spain. *These authors contributed equally to this work

Supplemental data for this article can be accessed here.

Article highlights

- A population pharmacokinetic approach has been used to evaluate eight renal function metrics of amikacin clearance
- rLM values were more reliable than alternative equations in a wide range of age
- rLM provided a better estimation of amikacin clearance than alternative renal function metrics
- Dose-adjustment based on eGFR must be evaluated carefully in kidney failure

2. Patients and methods

2.1. Ethics

The study was approved by the local Biomedical Ethics Committee after evaluation of compliance with ethical standards and good clinical practice.

2.2. Study design

This was a retrospective study performed with data of adult hospitalized patients, treated with amikacin and routinely monitored in the clinical pharmacokinetics laboratory of the Pharmacy Service from January 2012 to December 2013.

2.3. Patients and data collection

All adult patients hospitalized receiving amikacin and monitored during the period of the study with at least one detectable plasma concentration of amikacin were eligible for inclusion in this study. Patients undergoing renal replacement therapies or without PK, demographic or clinic information were excluded from the analysis. The following information were recorded for each patient: age, gender, race, weight, height, serum albumin, creatinine and urea, sampling time, dosing regimen, hospital unit, reason for hospital admission, diagnostic and comorbid disease status.

Empirical loading dose and posterior dose adjustments were selected to reach target concentrations according to the type of dosage regimen, conventional or extended interval.

The usual sampling times were 1 h after the end of the infusion (conventional dosage regimen) or 8 h after the end of the infusion (extended interval dosage regimen), as well as a through concentration.

2.4. Laboratory tests

The serum creatinine was measured using an enzymatic method (Jaffé, Roche/Hitachi cobas c). This method is traceable to the isotope dilution mass spectrometry reference for creatinine (IDMS). Amikacin plasma concentrations were measured using a particle-enhanced turbidimetric inhibition immunoassay (PETINIA, ARCHITECT c4000, Abbot Laboratories). The method was successfully validated following the FDA recommendations included in the Q2B Validation of Analytical Procedures: Methodology guidance [21].

2.5. Renal function evaluation

Amikacin PK was initially described by a pharmaco-statistical model based on an open linear one-compartment disposition model as previously reported in the literature. The population PK model was parameterized in terms of volume of distribution (V, L/kg) and total clearance (CL, L/h). Interindividual variability assuming log-normal distribution was included on CL and V. A proportional error model was used to describe the unknown residual variability [22].

The base model described above was the starting point for further evaluation of the following CL_{CR} and eGFR equations: Cockcroft-Gault using total, ideal and adjusted body weight (CGT, CGI and CGA, respectively), MDRD-4, CKD-EPI, rLM, BIS1, and FAS. Following EMA and FDA recommendations for Kidney Disease/Improving Global Outcomes, non-indexed eGFR values (mL/min) were considered in this study for MDRD, CKD-EPI, rLM, BIS1 and FAS Equations [1] . CGA was applied to patients with a body mass index (BMI) higher than 30 kg/m^2 (CGT for BMI ≤ 30). The CL_{CR} and eGFR equations are presented in Table 1.

Table 1. Renal function equations.

Formula	Equation	Ref.
Cockcroft-Gault (CG)		
- CG total body weight [mL/min]	$CGT = (140 - age) \times \left[TBW/(72 \times Cr)\right] \times 0.85^{sex}$	[23]
- CG adjusted body weight [mL/min]	$CGA = (140 - age) \times \left[ABW/(72 \times Cr)\right] \times 0.85^{sex}$	[24]
- CG ideal body weight [mL/min]	$CGI = (140 - age) \times \left[IBW/(72 \times Cr)\right] \times 0.85^{sex}$	[24]
Modification of Diet in Renal Disease (MDRD4) [mL/min/1.73m^2]	$MDRD4 = 175 \times Cr^{-1.154} \times age^{-0.203} \times 0.742^{sex} \times 1.212^{race}$	[14]
Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)		
- CKD-EPI women [mL/min/1.73m^2]	$CKD-EPI = 144 \times \left(Cr/0.7\right)^{Crfw} \times 0.993^{age} \times 1.159^{race}$	[25]
- CKD-EPI men [mL/min/1.73m^2]	$CKD-EPI = 141 \times \left(Cr/0.9\right)^{Crfm} \times 0.993^{age} \times 1.159^{race}$	[25]
Revised Lund-Malmö (rLM) [mL/min/1.73m^2]	$rLM = e^{X-0.0158\times age+0.438\times ln(age)}$	[13]
Berlin Initiative Study (BIS1) [mL/min/1.73m^2]	$BIS1 = 3,736 \times Cr^{-0.87} \times age^{-0.95} \times 0.82^{sex}$	[26]
Full Age Spectrum (FAS) [mL/min/1.73m^2]	$FAS = \left[107.3/\left(Cr/Q\right)\right] \times \left(0.988^{age-40}\right)^{Fage}$	[12]

Ref, reference; age (years); TBW, total body weight (kg); sex, 1 for women and 0 for men; ; Cr, serum creatinine (mg/dL); ABW, adjusted body weight (kg); IBW, ideal body weight (kg); race, 1 for black and 0 for not black; Crfw, creatinine factor women: -0.329 when Cr ≤ 0.7 mg/dl and -1.209 when Cr > 0.7 mg/dl; Crfm, creatinine factor men:-0.411 when Cr ≤ 0.9 mg/dl and -1.209 when Cr > 0.9 mg/dl; Q, constant: 0.70 mg/dL for women and 0.90 mg/dL for men; Fage, FAS age: 0 for 2 < age < 40 years and 1 for age > 40 years. X: (female and Cr < 150 µmol/L, X = 2.50 + 0.0121 x (150 - Cr)), (female and Cr ≥ 150 µmol/L, X = 2.50 − 0.926 x ln (Cr/150)), (male and Cr < 180 µmol/L, X = 2.56 + 0.00968 x (180 - Cr)), (male and Cr ≥ 180 µmol/L, X = 2.56 − 0.926 x ln(Cr/180)).

The eight renal function metrics were evaluated as a covariate on the renal clearance of amikacin following a linear or non-linear relationship as described in Equation 1 and Equation 2, respectively.

$$CL = CLnr + CLr \times \left(eGFR/\overline{eGFR}\right) \quad (1)$$

$$CL = CLnr + \left(eGFR/\overline{eGFR}\right)^{CLrp} \quad (2)$$

where CLr is the slope of the renal clearance as a linear relationship for a typical subject, CLnr is the non-renal clearance, eGFR is the estimated glomerular filtration rate expressed in mL/min (see Table 1), $\overline{eGFR}$ is the arithmetic mean of the eGFR evaluated; CLrp is the exponent of the renal clearance as a power relationship for a typical subject.

An exploratory analysis of the linear relationship between amikacin CL and the different CL_{CR} and eGFR evaluated was carried out together with a linear regression of each relationship calculating the squared root and p-value of the analysis.

Bias and accuracy of the individual amikacin plasma concentrations predictions were evaluated [27]. Bias was defined as the mean of the differences between the estimated (individual prediction) and the measured amikacin concentrations. Accuracy was calculated as the absolute difference between the measured and the individual predicted amikacin concentration and expressed as a percentage of the measured concentration (|[obs-ipred]/obs|x100). Bias and accuracy were evaluated in subgroups of age (18–29, 30–69 and ≥70 years), weight (<65, 65–73 and ≥74 kg) and chronic kidney disease classification (15–29, 30–59, 60–89 and ≥ 90 mL/min/1.73 m^2) and expressed as mean and 95% confidence interval.

The impact of very low creatinine values was evaluated either truncating the eGFR to 150 mL/min or excluding serum creatinine values lower than 0.63 mg/dL and 0.48 mg/dL for male and female, respectively.

The population PK analysis for both, the linear and non-linear relationships between CL and the corresponding renal function metric, was performed following a non-linear mixed effect modeling approach (NONMEM® version 7.3, Icon Development Solutions, Ellicott City, MD, USA) [28]. The first order conditional estimation method with interaction (FOCEI) was applied for parameter estimation. The log-likelihood ratio test assuming a χ^2 distribution with a statistical significance of 5% together with the goodness-of-fit of the scatterplot of observed versus population and individual predictions were used for model selection and evaluation of CL_{CR} and eGFR equations in the population PK analysis. No further model building was considered, a part of renal function metric evaluation.

Deterministic simulations of the concentration-time profile with the models including the CL_{CR} or the eGFR metric following a linear relationship for a patient of 70 kg receiving 15 mg/kg of amikacin over 30-min intravenous (IV) infusion were carried out to investigate the difference in drug exposure in three different renal function scenarios: a) kidney failure (eGFR = 10 mL/min), b) moderate failure (eGFR = 50 mL/min) and c) normal function (eGFR = 120 mL/min).

Stochastic simulations (n = 1000) with the final model were carried out with a typical subject (70 kg) receiving 20 mg/kg of amikacin over 30 min IV infusion to investigate the relevance of the best renal function metric selected compared to the base model (not including renal function metric on CL). Data visualization and all other statistical analysis such as the exploratory analysis of the population PK model development were performed in R version 3.3.1 or higher (Comprehensive R Network, http://cran.r-project.org/) [29].

3. Results

A total of 566 amikacin concentrations were quantified in 198 patients (n = 113 males) who received 375 to 3000 mg/day of amikacin infused during 30–60 min. Hematological malignancy was the most frequent defined diagnostic (39.4%) followed by other oncological malignancies (19.7%), sepsis/septic shock (16.2%) and critically ill patients (patients hospitalized in intensive care unit without sepsis/septic shock) (7.1%). The median age was 61 [18–93] years and the median serum creatinine was 0.70 [0.2–3] mg/dL. Most of the subjects presented a normal renal function or mild renal impairment (76%). Values calculated with the CKD-EPI and rLM equations showed a more homogenous distribution with lack of extreme high values compared with the alternative metrics (Figure 1). Baseline characteristics of the study population are provided in Table 2.

Exploratory analysis of the linear relationship between the eight renal function metrics evaluated and amikacin clearance estimated with the base model is shown in Figure 2. All the equations presented high correlation (p-value<0.001) with CL,

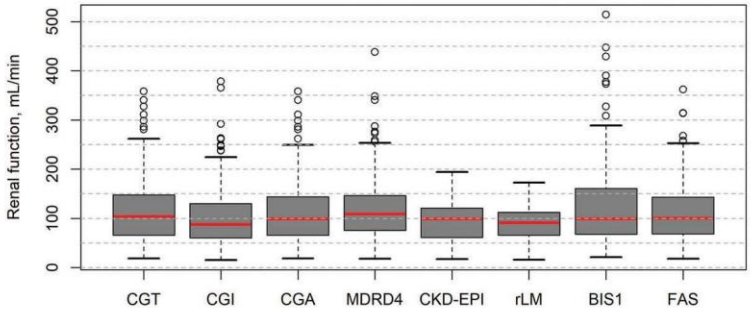

Figure 1. Baseline estimated renal function distribution. CGT, Cockcroft–Gault Total body weight; CGI, Cockcroft–Gault Ideal body weight; CGA, Cockcroft–Gault Adjusted body weight; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; rLM, Revised Lund-Malmö; BIS, Berlin Initiative Study; FAS, Full Age Spectrum; All the renal function metrics are expressed in mL/min; red solid line, median; open circles, outliers.

Table 2. Baseline characteristics of study population (n = 198).

	Mean	SD	Median	Min	Max
Age (years)	59.6	18.2	61.0	18.0	93
Total body weight (kg)	69.9	15.3	70.0	43.0	190
Ideal body weight (kg)	60.8	9.8	61.2	39.2	85
Adjusted body weight (kg)	64.5	10.2	63.8	40.7	109
Albumin (g/dL)	2.88	0.61	2.90	1.20	4.90
Body mass index (kg/m^2)	25.3	5.1	24.4	16.2	72
Body surface area (m^2)	1.77	0.20	1.77	1.31	2.68
Serum Creatinine (mg/dL)	0.80	0.41	0.69	0.21	2.59
Urea (mg/dL)	40.1	30.6	31.0	6.0	185
CGT (mL/min)	115.5	67.6	103.7	18.1	358
CGA (mL/min)	111.7	63.8	99.2	18.1	358
CGI (mL/min)	101.9	62.3	88.0	15.0	378
MDRD-4 (mL/min)	118.2	64.6	108.9	17.7	438
CKD-EPI (mL/min)	94.1	38.6	98.8	16.9	194
rLM (mL/min)	89.4	33.5	91.4	15.9	172
BIS1(mL/min)	123.7	83.7	99.1	21.0	514
FAS (mL/min)	111.1	60.5	100.2	18.0	362
	Frequency		**Percentage (%)**		
Sex					
Male	113		57.1		
Female	85		42.9		
Diagnostic					
Sepsis/Septic shock	32		16.2		
Critic	14		7.1		
Haematological malignancy	78		39.4		
Oncology	39		19.7		
Others (including surgery)	35		17.7		
Chronic Kidney Disease Classification [†]					
Normal (≥ 90 mL/min)	117		59		
Mild (60–89 mL/min)	34		17.2		
Moderate (30–59 mL/min)	45		22.7		
Severe (15–29 mL/min)	2		1.0		

SD, standard deviation; Min, minimum value; Max, maximum value; CGT, Cockcroft-Gault equation using total body weight; CGA, Cockcroft-Gault equation using adjusted body weight; CGI, Cockcroft-Gault equation using ideal body weight; MDRD-4, Modification of Diet in Renal Disease 4-variable equation; rLM, Revised Lund-Malmö equation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; BIS1, Berlin Initiative Study equation; FAS, Full Age Spectrum equation.

[†]Staging based on Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling [30].

being rLM, CKD-EPI, and CGT the *a priori* most likely relationships (r^2 equal to 0.49, 0.45 and 0.42, respectively).

The pharmaco-statistical analysis performed showed an overall statistical significance superiority of the linear relationships over the non-linear ones. Figure 3 shows the differences among the model-based linear relationships evaluated.

Including eGFR calculated with rLM on CL following a linear relationship (equation 1) provided the best fit to the data comparing to all the other renal function metrics evaluated, thus confirming the preliminary results obtained in the exploratory analysis. Intercept of the relationship was estimated to 0 implying the absence of non-renal elimination calculated with rLM equation. The PK parameters estimated with all the models evaluated, including population value, variability and their corresponding precision, are shown in Supplementary Table 1. The PK parameters of the final model were described as follows:

$$CL(L/h) = 5.15 \times eGFR/89 \quad (3)$$

$$V(L/kg) = 0.42 \times TBW \quad (4)$$

where CL is the amikacin clearance, eGFR is the estimated glomerular filtration rate calculated with rLM equation expressed in mL/min, V is the volume of distribution expressed in L/kg and TBW is the total body weight expressed in kg.

All parameters in the final model were estimated with adequate precision and absence of bias (residual standard error lower than 20% and shrinkages lower than 50%). The goodness-of-fit plots showed satisfactory prediction, both at population and individual levels together with the absence of bias (Supplementary Figure 1).

Amikacin model-based bias and accuracy across the different groups of age, weight and Chronic Kidney Disease Classification (CKDC) were relatively adequate using the eight renal function equations. In general, CKD-EPI and rLM showed better accuracy in young adults (18–29 years) and normal CKDC (eGFR≥90 mL/min) and a reduced accuracy for severe CKDC subsects (GFR≤60 mL/min). Absence of pronounce bias was shown with all the

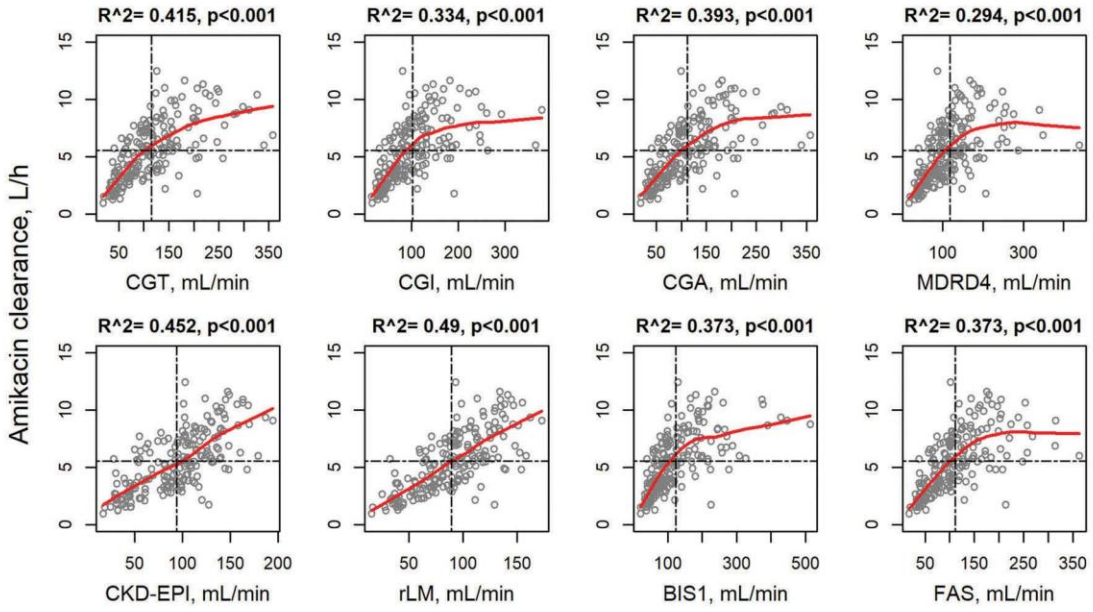

Figure 2. Relationship between amikacin clearance and renal function metrics evaluated. CGT, Cockcroft–Gault Total body weight; CGI, Cockcroft–Gault Ideal body weight; CGA, Cockcroft–Gault Adjusted body weight; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; rLM, Revised Lund-Malmö; BIS, Berlin Initiative Study; FAS, Full Age Spectrum; R^2 and p (p-value) are the results of a linear model regression; red solid line, trend line (lowess, locally weighted scatterplot smoothing).

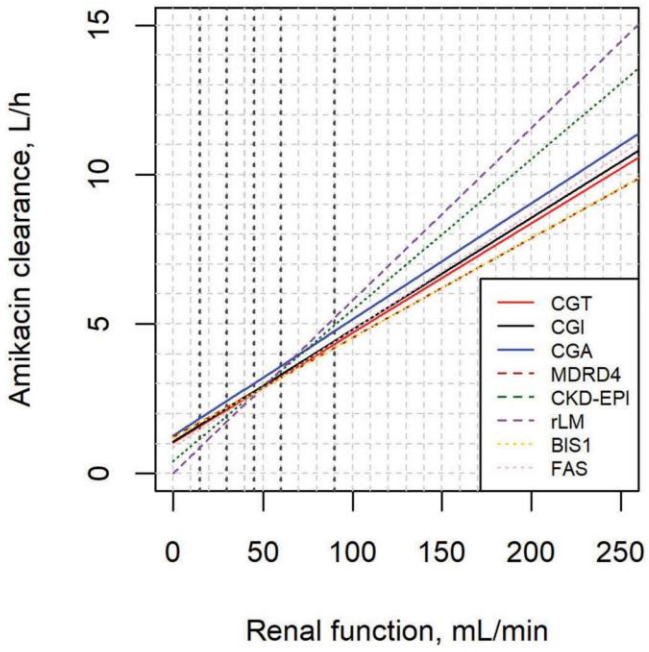

Figure 3. Model-based linear relationship between amikacin clearance and estimated glomerular filtration rate equations. CGT, Cockcroft–Gault Total body weight; CGI, Cockcroft–Gault Ideal body weight; CGA, Cockcroft–Gault Adjusted body weight; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; rLM, Revised Lund-Malmö; BIS, Berlin Initiative Study; FAS, Full Age Spectrum; renal function can be creatinine clearance values (CGT, CGI, CGA) or estimated glomerular filtration rate (MDRD, CKD-EPI, BIS1, FAS).

values within −1.7 and 0.9. Mean and 95% confidence interval of the bias and accuracy for the amikacin concentrations based on the individual predictions taking into account the different renal function equations evaluated stratified by age, weight, and CKDC are shown in Supplementary Table 2.

Differences across model performance of the renal function equations evaluated were significantly reduced when the renal

elimination value, CL_{CR} or eGFR, was truncated to 150 mL/min being rLM superior among the others. In addition, a similar performance of CGT, rLM, and FAS was observed when the very low serum creatinine values were excluded from the analysis (Supplementary Table 3).

The deterministic simulations of the typical concentration-time profile of amikacin evaluated showed no major differences across the different CL_{CR} and eGFR models and scenarios except for the through concentration using rLM and CKD-EPI in kidney failure with a two-fold higher exposure compared with the alternative equations (Figure 4).

The stochastic simulations of the concentration-time profile for a typical subject of 70 kg receiving a standard amikacin infusion, 20 mg/kg over 30 min, are shown in Figure 5. These simulations demonstrate the important reduction of amikacin CL variability, 53% reduction, explained by the rLM inclusion on the elimination parameter following a linear relationship reflecting adequately the variability of the data.

4. Discussion

The importance of renal function for drug dosing adjustments, combined with the difficulty of obtaining an accurate eGFR estimation by simple methods, has motivated during the last decades the search for equations that reliably and accurately describe eGFR. Several authors have evaluated the appropriateness of CL_{CR} and eGFR from the classical equations, such as Jellife or Cockcroft-Gault (CG), to the most recent ones, such as BIS1 and FAS equations, among others [11,12]. Renal function elimination is the most important source of PK variability influencing the PD and dose adjustment requirements of drugs mainly renally eliminated such as amikacin. Therefore, the accurate estimation of a metric to characterize the elimination by the kidney has been historically of great interest for these drugs.

Several authors have studied the adequacy of different eGFR equations as a main driver of amikacin renal elimination and other drugs eliminated mainly by the kidneys, not

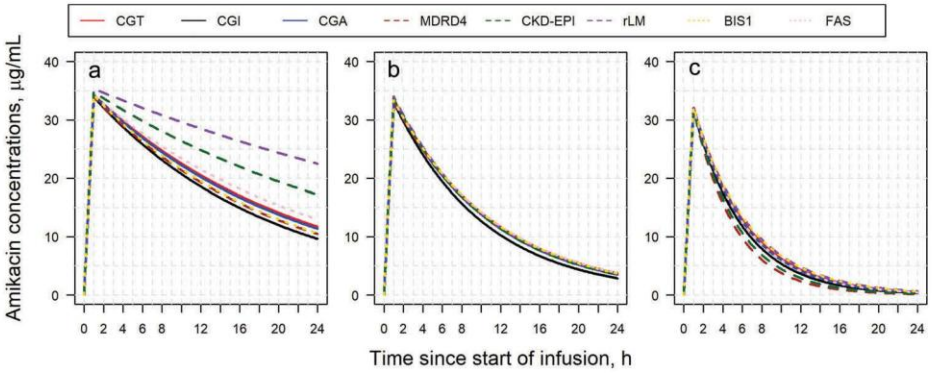

Figure 4. Deterministic simulations with the final pharmacokinetic model of a subject of 70 kg receiving 15 mg/kg of amikacin over 30 min in A) Kidney failure (eGFR = 10 mL/min), B) Moderate failure (eGFR = 50 mL/min) and C) Normal renal function (eGFR = 120 mL/min). CGT, Cockcroft–Gault Total body weight; CGI, Cockcroft–Gault Ideal body weight; CGA, Cockcroft–Gault Adjusted body weight; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; rLM, Revised Lund-Malmö; BIS, Berlin Initiative Study; FAS, Full Age Spectrum. All the renal function metrics are expressed in mL/min. Lines represent the median concentration-time profile of amikacin plasma concentration in the studied population when renal function is calculated with each of the eight different equations.

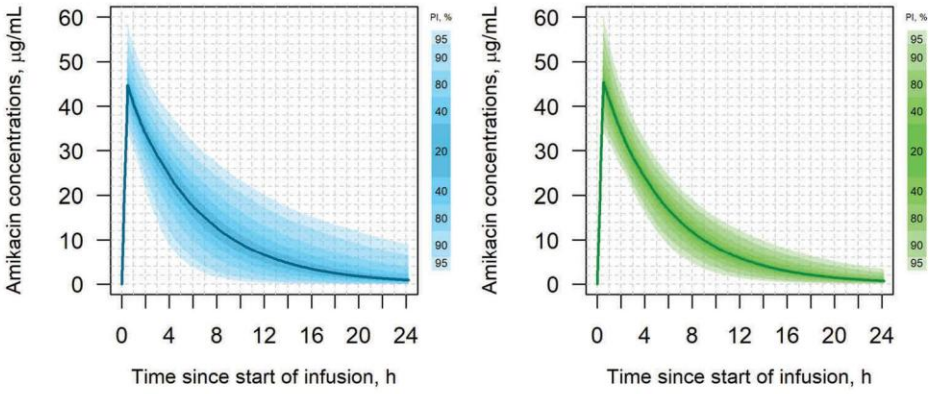

Figure 5. Stochastic simulations with base and final model for 1000 typical subjects of 70 kg and 89 mL/min of glomerular filtration rate calculated with revised Lund-Malmö (rLM) infused with 20 mg/kg of amikacin over 30 min. The final model includes rLM in the total clearance of amikacin as a linear relationship. Left panel (blue), base model; right panel (green), final model; Solid line represents the concentration-time profile of amikacin plasma concentration for the median subject (eGFR and weight); Shaded represents the dispersion of amikacin concentrations due to the interindividual variability of the pharmacokinetic parameters expressed as prediction interval bands (PI), i.e. PI 80 includes 80% of the 1000 concentrations simulated at each time point.

reaching a harmonious conclusion. In the last years, MDRD and CDK-EPI have been proposed to improve the decision-making of dose adjustment in different populations based on a more accurate estimation of eGFR over the alternatives [10,31–33]. However, several authors have suggested that the classical CGT equation provides better results for dose adjustment in elderly and impaired renal function patients among other equations [5,6,8] which has been confirmed in our studied population (Supplementary Table 2). In addition, new equations, such as FAS, developed in a full age range have been recently proposed in an effort to solve these limitations [12]. Therefore, there is no consensus on the most accurate renal function metric and each equation can show a better predictive ability regarding the population studied [1]. Furthermore, other studies support that the best clinical descriptor of renal function for the PK modeling of aminoglycosides in patients with kidney dysfunction has been questioned [6,10].

Our work includes most of the eGFR equations used in clinical settings together with more recent proposed equations such as rLM, BIS1 or FAS. In addition, the analysis has been carried out in a large clinical population of hospitalized patients with wide inclusion criteria, in order to evaluate which equation could fit the amikacin plasma concentrations best, in a wide range of age of a standard clinical population instead of a specific one. Moreover, a pharmaco-statistical methodology has been applied in order to evaluate qualitative and quantitatively the contribution of each renal function equation to the renal CL of amikacin.

Drug dosing has received international attention in the last years and the US Food and Drug Administration (FDA) is currently discussing which creatinine-based equation should be used for dose adjustment of drugs whose elimination depends on kidney functions [3]. Nowadays, CGT equation has been used as gold standard for dose adaptation [8]. However, our findings show that rLM and CKD-EPI equations can estimate eGFR accurately across the whole range of age, weight, and CKDC evaluated being able to support a correct dose adjustment of amikacin. Nonetheless, a better accuracy in amikacin concentrations model-based predicted with CGT was shown compared to rLM and CKD-EPI which must be taken into account for dose adjustment in patients with renal failure (GFR<60 mL/min).

The current analysis has been carried out applying a non-linear mixed effects modeling approach which allow to quantify the differences between the PK models evaluated. This pharmaco-statistical methodology allowed to quantify the reduction in amikacin PK variability. The interindividual variability of amikacin CL, including eGFR obtained with rLM, was reduced by 53%, thus translating in a lower uncertainty around the CL and reducing the potential bias of dose regimen adjustment. The final model can also be applied for deterministic and stochastic model-based simulations purposes in order to evaluate alternative amikacin dosing regimens based on rLM. However, additional variables and prognostic factors would be needed to perform more precise simulations, which was not the aim of the present work.

Some authors have highlighted that extremely small values of serum creatinine are not truly physiological, and that the linearity between CL and CL_{CR} above 150 mL/min was lost [34]. CKD-EPI and rLM equations introduced a mathematical twist to compensate overestimation of eGFR at very low values of serum creatinine (Figure 2). Then, the overall better performance of CKD-EPI and rLM over the alternative equations could be due to the higher proportion of patients with normal renal status (GFR>90 mL/min). However, rLM was also superior than the other renal function equations when eGFR values were truncated to 150 mL/min and similar to CGT and FAS when very low serum creatinine values were excluded from the analysis. However, there was a scarce number of severe renal impairment patients included in this population which could modify the linear relationships influencing predictions of the extreme values on both sides of the relationship suggesting that these values of eGFR must be evaluated carefully (Figure 2). Moreover, in kidney failure (eGFR<15 mL/min) significant differences between amikacin through concentrations are expected taking into account CKD-EPI and rLM comparing with the other renal function metrics evaluated as shown in Figure 4. These results may lead to different dose recommendations using rLM or CKD-EPI. However, this approach should be examined carefully considering that no kidney failure patients were included in this research and CGT has been used as the gold standard metric for dose adjustment in extreme low CL_{CR} values [6]. This fact is also supported by the better accuracy of amikacin plasma concentrations using CGT equation in patients with CL_{CR}<60 mL/min compared to the alternative equations, especially for CKD-EPI and rLM (Supplementary Table 2).

Plasma samples were very sparse as they were collected for therapeutic drug monitoring, which could bias the PK parameters. However, the estimated error (<20%), the shrinkage (<50%) of the PK parameters estimated and the goodness-of-fit plot showed a proper prediction of the model. In addition, the typical amikacin CL value obtained in our study, 5.15 L/h, is in accordance with the values expected (4.64–7.69 L/h). In the other hand, the high values of volume of distribution obtained (28.3 L) comparing to previous reported (15.1–27.3 L) could be explained by the large proportion of hypoalbuminemic patients [20,22,35,36].

Specific populations where significant PK differences have been shown, such as pediatric, burned or end-stage renal disease patients, were not included in this analysis. Several eGFR equations such as CKD-EPI, MDRD-4 have been validated between 18 and 70 years old in contrast with BIS1 which is valid only in elderly patients. Values of amikacin CL calculated taking into account BIS1 showed statistical differences between subjects younger than 70 years (CL = 155 mL/min) comparing to subjects older than 70 years (CL = 64 mL/min) (p-value<0.001). These differences support that BIS1 equation is not valid for patients younger than 70 years. In the other hand, only FAS and rLM equations were developed in a full range of age (2–97 and 26–85 years, respectively). However, FAS did not show a better prediction of the data than rLM, probably due to the more homogenous distribution of values provided by the rLM equation comparing with FAS (Figure 1) and also to a more similar developed population (>18 years). In addition, CKD-EPI has been proposed to largely overestimate the drug clearance in young

adults (18–29 years) [37]. In contrast, CKD-EPI and rLM showed better accuracy in young adults and no large overestimation was showed in our analysis. This result must be interpreted carefully as the analysis is based on amikacin concentration predictions instead the true amikacin clearance (i.e. iohexol clearance).

The study has been performed with amikacin, a standard drug mostly renally eliminated, in a very large spectrum of age and renal disease status. Broader population including additional drugs renally eliminated (i.e. gentamicin, vancomycin, digoxin, etc.) together with additional covariates evaluation and kidney failure subjects (eGFR<15mL/min) are suggested as potential improvements of the statistical power and conclusions of the current analysis.

In summary, the current research presents a population PK approach to evaluate the best renal function metric to describe amikacin elimination in a clinical routine population with a wide range of age (18–93 years). Linear relationships of CL_{CR} and eGFR on the total CL of amikacin showed better results than non-linear ones, being rLM the equation providing the best results in a clinical routine population. The inclusion of eGFR obtained with rLM in the model reduced by 53% the CL variability, highlighting the strong impact of renal status in dose adjustment for drugs mostly renally eliminated. Model-based dose recommendation taking into account rLM must be evaluated carefully in renal failure patients where CGT showed better accuracy on the model-based amikacin predictions.

5. Conclusions

The pharmaco-statistical methodology used in this research allowed to quantitatively evaluate the predictive performance of amikacin elimination through eight renal function equations applied in clinical practice. Our findings show that rLM and CKD-EPI equations can provide a better estimation of renal function than classical and alternative metrics such as CGT or MDRD, thus supporting a more precise dose adjustment of drugs mainly eliminated through the kidney.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Author contribution statement

Miss Eva María Saéz Fernández and Mr Jonás Samuel Pérez-Blanco were the principal researchers of this study and both contribute as first authors. Miss Eva María Saéz Fernández and Mr Jonás Samuel Pérez-Blanco performed the analysis and interpretation of the data. Eva María Sáez Fernández, Jonás Samuel Pérez-Blanco, Ana Martín-Suárez, José M Lanao and M Victoria Calvo have materially participated in the research and in the preparation and revision of this article. All authors approve the current version of the manuscript to be published and agree to be accountable for all aspects of the work.

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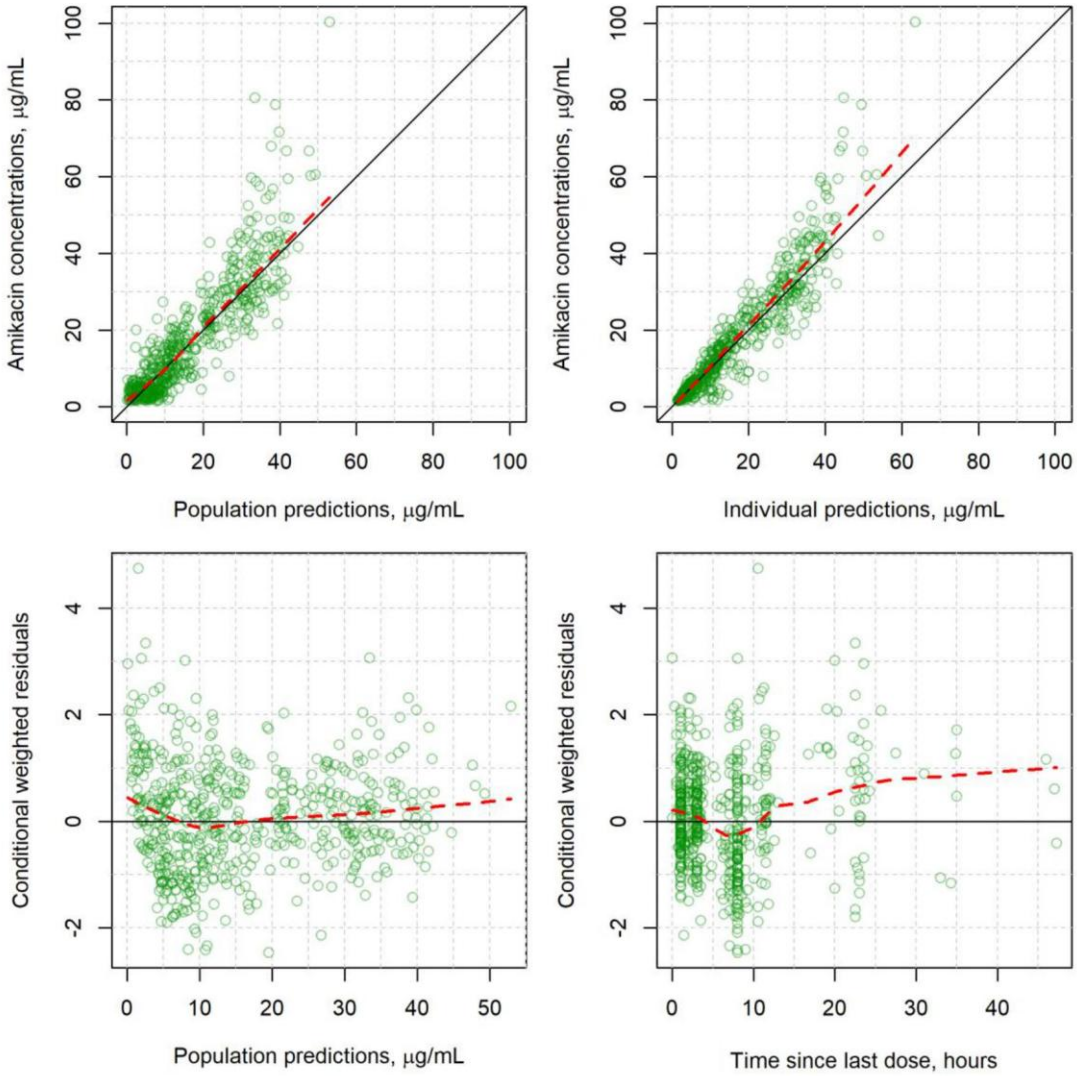
Supplementary Figure 1. Goodness-of-fit of the base and the final pharmacokinetic model



Goodness-of-fit of the base and the final pharmacokinetic model; open circles, observations/predictions; solid black lines, identity lines; red dashed lines, trend line (lowess, locally weighted scatterplot smoothing).

Supplementary Table 1. Population pharmacokinetic parameters of the models evaluated

Linear relationship: CL = CLnr + CLr x (eGFR/ $\overline{eGFR}$)									
	Base model	**CGT**	**CGA**	**CGI**	**MDRD4**	**CKD-EPI**	**rLM**	**BIS1**	**FAS**
OFV	2682.3	2531.1	2542.3	2557.9	2583.0	2501.8	2463.6	2546.1	2540.3
OFV diff with base model	0.0	-151.2	-140.0	-124.4	-99.3	-180.5	-218.7	-136.2	-142.0
CLnr, L/h	4.83 (4.3)	1.03 (26.7)	1.06 (27.9)	1.26 (25.1)	1.21 (30.6)	0.405 (47.9)	0.0* (0)	1.19 (27.7)	0.876 (31.6)
V, L/kg	0.427 (3.4)	0.427 (3.7)	0.428 (3.6)	0.43 (3.6)	0.432 (3.7)	0.425 (3.5)	0.42 (3.4)	0.428 (3.6)	0.429 (3.6)
CLr	0	4.26 (8)	4.2 (8.6)	3.97 (9.6)	4.2 (11)	4.76 (5.2)	5.15 (2.4)	4.15 (9.9)	5.02 (7.8)
CVCL, % (RSE, %)	60.8 (5.1)	32.2 (6.8)	33.4 (6.7)	35.1 (6.2)	36.8 (6.1)	30 (8.2)	28.3 (8)	35.1 (6)	32.8 (6.7)
CVV, % (RSE, %)	17.8 (18.8)	20.2 (14.7)	20.4 (15)	20.2 (15.6)	21.1 (15)	19 (16.4)	18.8 (17.3)	19.7 (15.4)	20.6 (15)
RUV, % (RSE, %)	32 (6.3)	32.9 (6.7)	32.9 (6.7)	33.1 (6.9)	33.3 (6.9)	32.9 (6.5)	32.1 (6.7)	32.8 (6.7)	33.1 (6.8)
Non-linear relationship: CL = CLnr + (eGFR/$\overline{eGFR}$)^CLrp									
	Base model	**CGT**	**CGA**	**CGI**	**MDRD4**	**CKD-EPI**	**rLM**	**BIS1**	**FAS**
OFV	2682.3	2633.3	2637.8	2639.1	2651.6	2599.5	2579.8	2633.7	2646.0
OFV diff with base model	0.0	-49.0	-44.5	-43.2	-30.7	-82.8	-102.5	-48.6	-36.3
CLnr, L/h	4.83 (4.3)	3.64 (6.1)	3.65 (6.3)	3.66 (5.9)	3.78 (6)	3.35 (6.7)	3.29 (5.9)	3.66 (5.8)	3.81 (5.1)
V, L/kg	0.427 (3.4)	0.427 (3.4)	0.427 (3.4)	0.428 (3.4)	0.427 (5)	0.424 (3.4)	0.423 (3.4)	0.427 (3.4)	0.428 (3.2)
CLrp	(0)	1.3 (38.8)	1.23 (46.1)	1.19 (37.4)	0.976 (52.4)	2.76 (21.3)	3.16 (12.9)	1.25 (31.8)	1.15 (46.6)
CVCL, % (RSE, %)	60.8 (5.1)	47.4 (7.6)	48.3 (7.6)	48.7 (6.5)	52.1 (19.1)	42.2 (6.9)	40.7 (6.5)	47.8 (6.5)	50.1 (5.5)
CVV, % (RSE, %)	17.8 (18.8)	19.8 (15)	19.5 (16.1)	19.1 (16.3)	18.9 (16.9)	19.9 (14.5)	19.2 (15.3)	19.1 (16.5)	19.1 (17.1)
RUV, % (RSE, %)	32 (6.3)	32.4 (6.4)	32.4 (6.3)	32.4 (6.3)	32.3 (11.6)	32.4 (6.5)	32.1 (6.5)	32.4 (6.30)	32.4 (5.7)

Estimated glomerular filtration rate (eGFR) and creatinine clearance equations are defined in table 1; CGT, Cockcroft-Gault Total body weight; CGA, Cockcroft-Gault Adjusted body weight; CGI, Cockcroft-Gault Ideal body weight; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; rLM, Revised Lund-Malmö; BIS1, Berlin Initiative Study; FAS, Full Age Spectrum; OFV, objective function value (-2 log likelihood); OFV diff, objective function value difference; CLnr, non-renal clearance; V, volume of distribution; CLr, slope of renal clearance as linear relationship; CV, coefficient of variation (log-normal distribution); RSE, residual standard error; RUV, residual unknown variability (proportional); rLM*, * fixed to 0 (boundary issues in estimation step; value close to lower boundary, 0); CLrp, power of renal clearance as power relationship. Base model is duplicated to facilitate the comparison of the results.

Supplementary Table 2. Amikacin model-based bias and precision stratified by group of age, weight and chronic kidney disease classification

Bias, µg/mL (mean [95% CI])	**n**	**CGT**	**CGA**	**CGI**	**MDRD4**	**CKD-EPI**	**rLM**	**BIS1**	**FAS**
Age (years)									
18 – 29	61	0.6 [-1.1 – 2.3]	0.5 [-1.1 – 2.2]	0.5 [-1.2 – 2.2]	0.9 [-0.8 – 2.7]	0.3 [-1.2 – 1.8]	0.5 [-1.0 – 2.0]	0.0 [-1.7 – 1.7]	0.7 [-1.0 – 2.4]
30 – 69	336	-1.3 [-1.9 – -0.7]	-1.3 [-1.9 – -0.7]	-1.3 [-1.9 – -0.7]	-1.2 [-1.8 – -0.6]	-1.2 [-1.8 – -0.6]	-1.2 [-1.8 – -0.6]	-1.2 [-1.8 – -0.6]	-1.3 [-1.9 – -0.7]
≥ 70	169	-1.1 [-1.9 – -0.3]	-1.1 [-1.9 – -0.3]	-1.1 [-1.9 – -0.3]	-1.4 [-2.2 – -0.6]	-1.1 [-1.9 – -0.3]	-1.1 [-1.9 – -0.3]	-1.1 [-1.8 – -0.3]	-1.1 [-1.9 – -0.3]
Total Body Weight (kg)									
< 65	166	-0.7 [-1.5 – 0.1]	-0.8 [-1.6 – 0.0]	-1.0 [-1.8 – -0.2]	-1.0 [-1.8 – -0.2]	-0.8 [-1.6 – 0.1]	-0.7 [-1.5 – 0.1]	-0.9 [-1.7 – -0.1]	-0.9 [-1.7 – -0.1]
65 – 73	196	-1.1 [-1.8 – -0.4]	-1.2 [-1.9 – -0.5]	-1.2 [-1.9 – -0.5]	-1.2 [-1.9 – -0.5]	-1.1 [-1.9 – -0.4]	-1.1 [-1.8 – -0.4]	-1.2 [-1.9 – -0.5]	-1.2 [-1.9 – -0.5]
≥ 74	204	-1.1 [-2.0 – -0.2]	-1.0 [-1.9 – -0.1]	-0.9 [-1.8 – 0.0]	-0.9 [-1.8 – 0.0]	-1.1 [-2.0 – -0.3]	-1.2 [-2.0 – -0.3]	-1.1 [-1.9 – -0.2]	-1.0 [-1.9 – -0.1]
Chronic Kidney Disease (mL/min/1.73m^2)*									
15 – 29	22	-0.6 [-2.1 – 0.9]	-0.7 [-2.1 – 0.8]	-0.7 [-2.2 – 0.8]	-0.7 [-2.2 – 0.8]	0.2 [-1.4 – 1.8]	0.5 [-1.2 – 2.1]	-0.7 [-2.2 – 0.8]	-0.5 [-2.1 – 1.0]
30 – 59	98	-1.6 [-2.8 – -0.3]	-1.6 [-2.8 – -0.3]	-1.7 [-2.9 – -0.4]	-1.6 [-2.9 – -0.4]	-0.9 [-2.2 – 0.4]	-1.4 [-2.6 – -0.1]	-1.7 [-2.9 – -0.4]	-1.5 [-2.7 – -0.3]
60 – 89	77	-1.2 [-2.2 – -0.3]	-1.3 [-2.2 – -0.4]	-1.3 [-2.2 – -0.4]	-1.5 [-2.4 – -0.6]	-1.6 [-2.5 – -0.7]	-1.5 [-2.4 – -0.5]	-1.3 [-2.2 – -0.4]	-1.3 [-2.3 – -0.4]
≥ 90	369	-0.8 [-1.4 – -0.2]	-0.8 [-1.4 – -0.2]	-0.8 [-1.4 – -0.2]	-0.8 [-1.4 – -0.2]	-1.0 [-1.6 – -0.4]	-0.9 [-1.4 – -0.3]	-0.8 [-1.4 – -0.3]	-0.9 [-1.4 – -0.3]
Accuracy, % (mean [95% CI])	**n**	**CGT**	**CGA**	**CGI**	**MDRD4**	**CKD-EPI**	**rLM**	**BIS1**	**FAS**
Age (years)									
18 – 29	61	68.1 [34.0 – 102.2]	68.0 [33.9 – 102.1]	69.1 [35.2 – 103.0]	73.6 [36.7 – 110.5]	53.8 [28.7 – 78.8]	54.7 [27.6 – 81.7]	65.4 [34.1 – 96.8]	69.8 [35.1 – 104.4]
30 – 69	336	25.2 [18.9 – 31.5]	25.3 [18.9 – 31.6]	25.8 [19.3 – 32.4]	26.2 [18.8 – 33.6]	24.5 [20.4 – 28.5]	23.5 [19.6 – 27.4]	24.8 [19.1 – 30.5]	25.5 [19.0 – 32.1]
≥ 70	169	19.8 [16.3 – 23.4]	19.8 [16.2 – 23.3]	19.4 [16.0 – 22.8]	20.2 [16.5 – 23.8]	21.6 [17.3 – 25.9]	20.4 [17.0 – 23.9]	19.1 [15.8 – 22.4]	20.0 [16.4 – 23.6]
Total Body Weight (kg)									
< 65	166	18.6 [14.7 – 22.4]	18.4 [14.6 – 22.1]	18.5 [14.9 – 22.2]	18.7 [14.9 – 22.4]	19.5 [15.5 – 23.5]	19.0 [15.4 – 22.6]	18.6 [15.0 – 22.1]	18.3 [14.7 – 22.0]
65 – 73	196	25.0 [18.5 – 31.6]	24.8 [18.2 – 31.3]	25.0 [18.6 – 31.4]	25.6 [18.7 – 32.5]	26.0 [20.2 – 31.7]	24.5 [19.0 – 30.0]	24.4 [18.3 – 30.5]	25.3 [18.7 – 31.8]
≥ 74	204	39.2 [25.9 – 52.5]	39.6 [26.3 – 52.9]	40.2 [26.6 – 53.9]	42.1 [26.9 – 57.3]	33.5 [24.8 – 42.1]	32.9 [23.9 – 41.9]	37.6 [25.6 – 49.7]	40.3 [26.5 – 54.0]
Chronic Kidney Disease (mL/min/1.73m^2)*									
15 – 29	22	21.4 [11.9 – 30.8]	21.0 [11.6 – 30.5]	22.2 [11.5 – 32.9]	22.2 [11.5 – 33.0]	25.9 [11.8 – 39.9]	27.5 [13.5 – 41.4]	21.3 [11.6 – 31.0]	22.3 [11.6 – 33.0]
30 – 59	98	21.3 [16.2 – 26.3]	21.2 [16.2 – 26.2]	20.9 [15.9 – 25.8]	21.4 [16.1 – 26.7]	26.7 [18.8 – 34.7]	22.4 [16.9 – 27.9]	20.2 [15.5 – 24.9]	21.5 [16.3 – 26.8]
60 – 89	77	16.3 [12.8 – 19.7]	16.4 [12.9 – 20.0]	16.4 [12.9 – 20.0]	16.8 [13.4 – 20.2]	17.7 [14.1 – 21.2]	16.7 [13.2 – 20.3]	16.2 [12.7 – 19.6]	16.5 [13.0 – 20.1]
≥ 90	369	33.0 [24.8 – 41.2]	33.0 [24.8 – 41.2]	33.6 [25.2 – 41.9]	34.8 [25.5 – 44.0]	28.7 [23.3 – 34.2]	28.7 [23.0 – 34.4]	32.1 [24.6 – 39.6]	33.4 [25.0 – 41.8]

Estimated glomerular filtration rate (eGFR) and creatinine clearance equations are defined in table 1; n, number of amikacin concentrations; CGT, Cockcroft-Gault Total body weight; CGA, Cockcroft-Gault Adjusted body weight; CGI, Cockcroft-Gault Ideal body weight; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; rLM, Revised Lund-Malmö; BIS1, Berlin Initiative Study; FAS, Full Age Spectrum; CI, confidence interval assuming normal distribution; * eGFR calculated with CKD-EPI equation, Staging based on Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling [30].

Supplementary Table 3. Performance of creatinine-based renal function equations of amikacin based on objective function values (OFV).

OFV	CGT	CGA	CGI	MDRD4	CKD-EPI	rLM	BIS1	FAS
Linear relationship	2531.1	2542.3	2557.9	2583.0	2501.8	2463.6	2546.1	2540.3
Non-linear relationship	2633.3	2637.8	2639.1	2651.6	2599.5	2579.8	2633.7	2646.0
Truncated 150 mL/min	2472.0	2476.2	2488.0	2506.3	2484.1	2455.5	2475.2	2473.7
Subset by creatinine*	1652.7	1657.2	1666.1	1683.2	1684.3	1654.5	1662.3	1652.1

Estimated glomerular filtration rate (eGFR) and creatinine clearance equations are defined in table 1; CGT, Cockcroft-Gault Total body weight; CGA, Cockcroft-Gault Adjusted body weight; CGI, Cockcroft-Gault Ideal body weight; MDRD4, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; rLM, Revised Lund-Malmö; BIS1, Berlin Initiative Study; FAS, Full Age Spectrum; OFV, objective function value (-2 log likelihood); Linear relationship: CL = CLnr + CLr x (eGFR/ $\overline{eGFR}$); Non-linear relationship: CL = CLnr + (eGFR/$\overline{eGFR}$)^CLrp; Subset by creatinine*, Analysis performed in a subset population with creatinine higher than 0.63 mg/dL or 0.48 mg/dL in male and female, respectively (377 samples taking into account over the total 566)

III.2. AMIKACIN INITIAL DOSAGE IN PATIENTS WITH HYPOALBUMINAEMIA: AN INTERACTIVE TOOL BASED ON A POPULATION PHARMACOKINETIC APPROACH

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RESUMEN

Objetivo: Caracterizar la farmacocinética poblacional de amicacina en pacientes con hipoalbuminemia y desarrollar una aplicación interactiva, basada en el modelo poblacional resultante, para la dosificación inicial de amicacina.

Métodos: Se desarrolló un modelo farmacocinético poblacional siguiendo una metodología de efectos mixtos no lineales (NONMEM) con las concentraciones plasmáticas de amicacina obtenidas en la práctica clínica (75% pacientes con hipoalbuminemia). Para la evaluación del modelo se utilizaron gráficos de bondad de ajuste, valor mínimo de la función objetivo, gráfico visual de predicción corregido por la predicción (pcVPC), bootstrap, así como la precisión y el sesgo de los parámetros estimados. Se desarrolló una herramienta de simulación interactiva en R (Shiny and R Markdown). La relación Cmax/CMI, el tiempo por encima de la CMI y el cociente ABC/CMI fueron utilizados para la optimización de la dosis inicial recomendada de amicacina. Se calculó la probabilidad de alcanzar el objetivo terapéutico para la dosis recomendada.

Resultados: El modelo que mejor describió las 873 concentraciones plasmáticas de amicacina disponibles en 294 pacientes (población del modelo y validación externa) fue un modelo monocompatimental con eliminación de primer orden. Los parámetros farmacocinéticos de amicacina estimados en la población estudiada fueron CL (L/h) = (0,525 + 4,78 x CKD-EPI/98) x $0,77^{vancomicina}$ y V (L) = 26,3 x (albúmina/2.9)$^{-0.51}$ x [1+0.006 x (peso - 70)], donde CKD-EPI se calculó mediante la ecuación Chronic Kidney Disease Epidemiology Collaboration. AMKdose es una aplicación interactiva, basada en el modelo desarrollado, útil para la optimización de la dosis inicial recomendada de amicacina mediante el uso de información individual del paciente y microbiológica junto con criterios farmacocinéticos/farmacodinámicos predefinidos.

Conclusiones: La albúmina sérica, el peso corporal total, la tasa de filtrado glomerular estimado (calculado con la ecuación CKD-EPI) y el tratamiento concomitante con vancomicina mostraron un impacto significativo en la farmacocinética de amicacina. Se ha desarrollado una

herramienta interactiva para la selección de la dosis inicial de amicacina, disponible *online* de forma gratuita. AMKdose puede resultar útil para seleccionar la dosis inicial de amicacina cuando aún no se dispone de información farmacocinética individual.

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Amikacin initial dosage in patients with hypoalbuminaemia: an interactive tool based on a population pharmacokinetic approach

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Objectives: To characterize amikacin population pharmacokinetics in patients with hypoalbuminaemia and to develop a model-based interactive application for amikacin initial dosage.

Methods: A population pharmacokinetic model was developed using a non-linear mixed-effects modelling approach (NONMEM) with amikacin concentration–time data collected from clinical practice (75% hypoalbuminaemic patients). Goodness-of-fit plots, minimum objective function value, prediction-corrected visual predictive check, bootstrapping, precision and bias of parameter estimates were used for model evaluation. An interactive model-based simulation tool was developed in R (Shiny and R Markdown). C_{max}/MIC ratio, time above MIC and AUC/MIC were used for optimizing amikacin initial dose recommendation. Probabilities of reaching targets were calculated for the dosage proposed.

Results: A one-compartment model with first-order linear elimination best described the 873 amikacin plasma concentrations available from 294 subjects (model development and external validation groups). Estimated amikacin population pharmacokinetic parameters were CL (L/h) = $0.525+4.78 \times$ (CKD-EPI/98) $\times$ ($0.77 \times$ vancomycin) and V (L) = $26.3 \times (\text{albumin}/2.9)^{-0.51} \times [1+0.006 \times (\text{weight} - 70)]$, where CKD-EPI is calculated with the Chronic Kidney Disease Epidemiology Collaboration equation. AMKdose is a useful interactive model-based application for *a priori* optimization of amikacin dosage, using individual patient and microbiological information together with predefined pharmacokinetic/pharmacodynamic (PKPD) targets.

Conclusions: Serum albumin, total bodyweight, estimated glomerular filtration rate (using the CKD-EPI equation) and co-medication with vancomycin showed a significant impact on amikacin pharmacokinetics. A powerful interactive initial dose-finding tool has been developed and is freely available online. AMKdose could be useful for guiding initial amikacin dose selection before any individual pharmacokinetic information is available.

Introduction

Albumin concentration modifications may alter drug distribution, modifying protein binding and volume of distribution (V). Hypoalbuminaemia might produce a decrease in oncotic pressure, with a shift in body water composition from the intravascular to the extravascular space.[1–3] Drug exposure, especially for hydrophilic drugs, can be impacted by these modifications, leading to dose-adjustment requirements for drugs with a narrow therapeutic index in order to ensure treatment efficacy and safety. Patients with sepsis, septic shock and burns, among others, commonly present hypoalbuminaemia with an increased V, requiring higher doses than the standard ones needed to reach the proposed pharmacodynamic (PD) predictors of clinical efficacy.[1,4,5] In addition, the mortality risk associated with these pathologies is extremely high and early and appropriate infection control is a priority in the management of these patients.[6]

Amikacin is one of the most effective aminoglycoside antibiotics used for the treatment of severe infections caused by aerobic Gram-negative bacilli and MDR pathogens such as *Pseudomonas aeruginosa*.[7,8] Like most other aminoglycosides, amikacin exhibits a large intra- and inter-individual pharmacokinetic (PK) variability together with a narrow therapeutic index.[2] Amikacin PK have been widely studied in specific populations such as patients with renal

impairment, burns and haematological malignancies and critically ill or cystic fibrosis patients to improve amikacin dosing regimens.[1–5,7,9–17] Disease status may contribute to PK modifications, mainly clearance (CL) and *V*, which may decrease the probability of achieving the desired maximum concentration (C_{max}) or area under the concentration–time curve (AUC).[17] The proposed aetiology for an increase in *V* observed in specific populations includes leaky capillaries, aggressive fluid resuscitation, cachexia, protein malnutrition, ascites or congestive heart failure. The decrease of observed CL in critically ill patients has been ascribed to organ failure.[1,12] Increased CL has been observed in patients with burns, haematological malignancies and cystic fibrosis.[3,5,16,17] Thus, when severe infections are present, it is crucial to ensure adequate drug exposure from the beginning of treatment in order to maximize clinical response.

The most accepted relevant PKPD predictive parameters of clinical response to amikacin treatment are: (i) a ratio between the C_{max} and the MIC of >8–10 for efficacy; and (ii) a trough concentration lower than 5–10 mg/L due to toxicity, mainly nephrotoxicity (usually transient) and ototoxicity (irreversible).[1,4,7–10,18–20] Some authors have suggested a ratio between the AUC and MIC greater than 75–90 or the %*T*>MIC within a dosing interval ≥60% as alternative predictive metrics for amikacin therapeutic success.[11,13]

Initial amikacin dosage has been extensively discussed since extended dosing intervals (≥24 h) were suggested to improve antibiotic treatments. Higher doses than the standard 15 mg/kg once daily have been proposed in specific populations.[6,9,21] However, there is no agreement regarding the optimal initial amikacin dose regimen. Additional data are required to produce evidence-based guidelines for amikacin dosing to maximize its therapeutic outcomes.[22]

Dose optimization and application of population pharmacokinetic (PopPK) analysis may require advanced knowledge in pharmacostatistics, programming and clinical pharmacology and can be seen as a hurdle in clinical practice. In contrast, using R with the Shiny and R Markdown packages has the potential to integrate all this information in a user-friendly interface.[23] However, to the best of our knowledge, there seem to be very few available dose-finding tools filling the gap between research and clinical practice.[24,25]

The objectives of the present study were to characterize the PK of amikacin in patients with hypoalbuminaemia and to develop an interactive model-based application for optimizing amikacin initial dosing regimens.

Materials and methods

Ethics

This study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. It was approved by the local biomedical ethics committee of the health area after evaluation of compliance with ethical standards and good clinical practice (CEIC Ref 16/04). This was a retrospective observational study performed with hospitalized adult patients, receiving IV treatment with amikacin and routinely monitored in the clinical PK laboratory of the Pharmacy Service.

Study population and data collection

Amikacin dose was infused over 30 min or 1 h. Blood samples were obtained at the following times: (i) 1 and 8 h after the IV amikacin infusion, in patients receiving once-daily dosage regimens; and (ii) immediately before and 2 h after the infusion, when amikacin was administered with a conventional two- or three-times-daily dosage regimen. Additional samples could be collected following clinical requirements. Blood samples were collected without separator gel and only plasma samples without haemolysis were analysed. In order to avoid inactivation of amikacin *in vitro*, samples from patients receiving β-lactam antibiotics were analysed immediately, otherwise they were stored frozen until the analysis. All adult hospitalized patients with at least one detectable plasma concentration of amikacin were eligible for inclusion into the study. Patients undergoing renal replacement therapies or without the minimum PK information were excluded from the study.

The following patient information was recorded: amikacin dosing regimen, sampling time, age, total bodyweight, BMI, serum albumin, serum proteins, creatinine, total bilirubin, estimated glomerular filtration rate (eGFR), gender, concomitant treatments (β-lactam antibiotics, vancomycin and vasoactive drugs), total parenteral nutrition and diagnosis.

Additional patients, in a third proportion of the development dataset, were selected to perform an external validation of the final model developed.

Bioanalytical method

Serum creatinine was measured using an enzymatic method (Jaffé, Roche/Hitachi Cobas c) traceable to the isotope dilution MS (IDMS) reference for creatinine. Amikacin plasma concentrations were measured using a particle-enhanced turbidimetric inhibition immunoassay (PETINIA) (ARCHITECT c4000, Abbott Laboratories) using the amikacin reagent kit 6L35-20 (MULTIGENT; Abbott Diagnostics). The method was successfully validated following the FDA recommendations included in the Q2B Validation of Analytical Procedures: Methodology guidance.[26] The method had a lower limit of quantification (LLOQ) of 1.64 mg/L and an upper limit of quantification of 50 mg/L (overall precision <4%). Specimens with amikacin values exceeding 50.0 mg/L were manually diluted with saline serum before the reanalysis, following the manual instructions of the manufacturer.[27] According to the information from this manual, interference from bilirubin, triglycerides, haemoglobin or rheumatoid factor in the samples analysed was not present.

Population PK model development

A non-linear mixed-effects modelling approach using the first-order conditional estimation (FOCE) method with interaction was used to develop the model using NONMEM® version 7.4.0 (Icon Development Solutions, Ellicott City, MD, USA).[28] Data visualization and statistical analyses were carried out in R version 3.3.1 or higher (R Core Team, Vienna, Austria).[29]

Amikacin PK was initially described by an open linear one-compartment disposition model. The PopPK model was parameterized in terms of *V* and CL. The eGFR, calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, was used as the descriptor of amikacin renal elimination. Thus, amikacin CL was expressed as a linear function of CKD-EPI (Equation 1) based on previous evaluation.[30]

$$CL_{pop} = CL_{nr} + CL_r \times eGFR / \overline{eGFR} \quad (1)$$

where CL_{pop} (L/h) is the CL of the typical subject; CL_{nr} (L/h) is the non-renal CL; eGFR is the eGFR calculated using the CKD-EPI equation (mL/min); $\overline{eGFR}$ is the median of the eGFR (mL/min); and CL_r (L/h) is the renal CL of amikacin that quantifies the proportional increase in renal CL with the eGFR/$\overline{eGFR}$ ratio.

The inter-individual variability (IIV) of the PK parameters was assumed to follow a log-normal distribution and, consequently, an exponential error model was used (Equation 2):

$$P_{ji} = Ppop_j \times e^{\eta_i} \quad (2)$$

where P_{ji} is the jth PK parameter (i.e. CL or V) for the individual i; $Ppop_j$ is the jth population or typical estimated PK parameter (i.e. CL or V) and η_i is the inter-individual random effect. The η values were assumed to be independently and identically distributed with a mean of 0 and a variance of ω^2 : $\eta \sim N(0, \omega^2)$.

Residual unknown variability (RUV) was evaluated using an additive, proportional or combined (additive and proportional, Equation 3) error model:

$$C_{ij} = \hat{C}_{ij} \times (1 + \varepsilon_{1ij}) + \varepsilon_{2ij} \quad (3)$$

where C_{ij} is the jth measured serum concentration in individual i, $\hat{C}_{ij}$ is the model-predicted jth value in individual i and ε_{ij} is the residual random error for measurement j in individual i. ε_{1ij} is the proportional component and ε_{2ij} is the additive component of the residual random error. The ε values were assumed to be independently and identically distributed with a mean of 0 and variance of σ^2: $\varepsilon \sim N(0, \sigma^2)$.

The magnitudes of IIV and RUV were expressed approximately as a coefficient of variation (CV, %). Correlation between random parameters and inter-occasion variability (IOV) was graphically explored and evaluated.

After selecting the basic model, potential relationships between estimated individual PK parameters and physiological meaningful variables were explored graphically. Linear regressions of the relationships between the IIV of the PK parameters and continuous covariates were evaluated as well as analysis of variance (ANOVA) for categorical covariates. Only covariates showing statistical significance ($P < 0.05$) were considered as potentially clinically relevant and were further tested one by one following a stepwise covariate methodology (forward P value < 0.01; backward P value < 0.001). In addition, the most physiologically plausible covariate was selected among highly correlated ones (i.e. weight and height).

Model diagnostics and evaluation

To identify the best model to adequately describe amikacin concentration–time data, a series of structural and stochastic models were evaluated. For each model, the improvement in the fit was assessed by the likelihood ratio test ($P < 0.01$) (objective function value, OFV) together with the reduction in the IIV and residual variability. The precision of parameter estimates (residual standard error, RSE), the examination of diagnostic plots and predictive checks as well as shrinkage on parameters were also considered.[31]

Goodness-of-fit plots, including scatterplots of observed versus population- and individual-predicted concentrations and scatterplots of conditional weighted residuals (CWRES) versus population-predicted concentrations and versus time and prediction-corrected visual predictive checks (pcVPC) for both the development and the external validation data together with a bootstrap analysis were used to evaluate the PopPK model performance.[32,33] The pcVPC was performed for the original datasets and presented the 5th, 50th and 95th percentiles of the observed amikacin plasma concentrations, as well as the 5th, 50th and 95th percentiles together with their 95% CI for the corresponding model-based predicted concentrations computed for each bin across time and replicates. A total of 1000 replicates of the original development dataset were generated. A bootstrap resampling method was used to evaluate the stability of the final model and the precision of parameter estimates. A 1000-sample bootstrap was conducted where the median and 95% CI were obtained and compared for each PK parameter estimated.

AMKdose: interactive dose-finding tool for optimizing initial amikacin dosage

An interactive R-based application, AMKdose, implementing the final PopPK model was developed to investigate the influence of patients' characteristics on the expected amikacin efficacy.[23] AMKdose was mainly developed through Shiny and R Markdown packages (RStudio, Boston, MA, USA). Amikacin PKPD targets and the cut-off selected to drive the initial dosage selection were: (i) C_{max} 10-fold higher than the MIC; (ii) %T>MIC (% of dosing interval) >60%; and (iii) AUC/MIC ≥ 80.

AMKdose was divided into three independent interactive sections:

A. PK analysis: the minimum dose of amikacin (mg/kg) to reach the three PKPD targets previously defined is selected by the application for a defined subject. Patient information (i.e. weight and albumin concentration) and treatment information (i.e. amikacin infusion time, dose interval, vancomycin co-medication and MIC) together with PKPD targets cut-off can be modified. Stochastic simulations are carried out for the selected dose and a probabilistic concentration–time profile is displayed. Valuable PKPD results are available in the summary tab of this section (AUC, C_{max}, C_{max}/MIC etc.).
B. Simulation: model-based stochastic simulations based on dosage and patient information specified are performed. Amikacin concentration–time profile together with the PTA are displayed. Maximum effective MIC for the defined scenario is calculated based on reaching at least 90% of PTA for the three PKPD targets evaluated. A summary table with the PKPD targets results is also displayed.
C. Dose exploration: deterministic and stochastic model-based simulations are carried out with the dosage and patient information provided (i.e. eGFR), for all the possible combinations of the two main continuous variables identified. The three PKPD target values calculated are displayed for each combination, together with the PTA for each target.

Automated reports generated with R Markdown were implemented in 'PK analysis' and 'Simulation' sections of AMKdose. Additional information regarding the structure of the model and simulation settings were provided in the application ('readme tab').

Results

Demographic and clinical data

Demographic and physiological characteristics of the 294 patients, 215 considered for model development, included in the study are shown in Table 1. Most of the patients of the development group ($n = 149$, 69%) received an extended-interval regimen (≥24 h), with an initial mean dose of 16.4 (range: 6.5–27.3) mg/kg/day infused IV over 30–60 min. Three-quarters of the patients presented hypoalbuminaemia (albumin <3.5 g/dL). Most of the patients considered for PopPK model development had normal renal function with a median eGFR (CKD-EPI) of 98 (range: 17–194) mL/min and a median age of 61 (range: 18–93) years. Haematological malignancy was the most frequently defined diagnosis (41%) followed by other oncological malignancies (20%), sepsis/septic shock (15%) and critically ill patients (6%). Similar baseline patient characteristics were observed in the external validation group (Table 1).

PK model analysis and evaluation

A total of 623 amikacin plasma concentrations, 2.90±1.84 (mean±SD) per patient, were best described by a one-compartment linear model. A combined proportional (23.7%) and additive (3.95 mg/L) error model was used to describe the RUV. A total of 250 additional amikacin concentrations, 3.16±2.02 (mean±SD) per patient, were used for external model validation. A

Table 1. Baseline characteristics of study population

	Development group		External validation group	
Characteristic	all ($n = 215$)	hypoalbuminaemia ($n = 161$)	all ($n = 79$)	hypoalbuminaemia ($n = 59$)
Continuous, median (range)				
dose (mg/day)	1000 (250–2000)	1000 (250–1800)	1000 (350–2000)	1000 (350–2000)
age (years)	61.0 (18.0–93)	63.0 (18.0–93)	60 (18.0–92)	63 (30.0–92)
total bodyweight (kg)	70.0 (43.0–190)	69.9 (43.0–190)	70.0 (40.0–116)	70.0 (47.0–116)
BMI (kg/m^2)	24.4 (16.2–72)	24.7 (16.2–72)	24.5 (15.5–45.3)	24.5 (18.8–45.3)
albumin (g/dL)	2.9 (1.2–5)	2.7 (1.2–3)	3.1 (1.9–4.2)	3.0 (1.9–3.4)
protein (g/dL)	5.9 (4.20–8)	5.6 (4.2–7.7)	5.7 (3.7–9.6)	5.6 (3.7–9.6)
total bilirubin (mg/dL)	0.6 (0.1–8)	0.6 (0.1–7)	0.5 (0.2–3.6)	0.5 (0.2–3.6)
eGFR (mL/min)	98.0 (16.9–194)	97.1 (16.9–194)	94.5 (29.4–174.5)	87.4 (29.4–153.7)
Categorical, *n* (%)				
gender				
male	124 (57.7)	87 (54.0)	35 (44.3)	28 (47.5)
female	91 (42.3)	74 (46.0)	44 (55.7)	31 (52.5)
co-medication				
β-lactam	200 (93.0)	154 (95.7)	74 (93.7)	56 (94.9)
vancomycin	21 (9.8)	16 (9.9)	12 (15.2)	9 (15.3)
vasoactives[a]	22 (10.2)	20 (12.4)	3 (3.8)	3 (5.1)
total parenteral nutrition	23 (10.7)	21 (13.0)	1 (1.3)	1 (1.7)
diagnosis				
haematological malignancy	89 (41.4)	63 (39.1)	51 (64.6)	36 (61.0)
oncology	43 (20.0)	37 (23.0)	12 (15.2)	8 (13.6)
sepsis/septic shock	33 (15.3)	26 (16.1)	7 (8.9)	7 (11.9)
critically ill	13 (6.0)	11 (6.8)	2 (2.5)	2 (3.4)
others (including surgery)	37 (17.2)	24 (14.9)	7 (8.9)	6 (10.2)
chronic kidney disease, eGFR (mL/min)[b]				
>150	50 (23.3)	35 (21.7)	4 (5.1)	2 (3.4)
normal (90–150)	78 (36.3)	58 (36.0)	40 (50.6)	27 (45.8)
mild (60–89)	39 (18.1)	29 (18.0)	16 (20.3)	11 (18.6)
moderate (30–59)	46 (21.4)	37 (23.0)	18 (22.8)	18 (30.5)
severe (15–29)	2 (0.9)	2 (1.2)	1 (1.3)	1 (1.7)

[a]Dopamine, norepinephrine or nitroglycerin.
[b]Classification based on guidance for industry PK in patients with impaired renal function: study design, data analysis, and impact on dosing and labelling.[49] eGFR was calculated with the CKD-EPI equation; hypoalbuminaemia, albumin <3.5 g/dL.

summary of amikacin initial dosing and observations collected is shown in Table 2.

The base model included *a priori* CKD-EPI in amikacin CL following a linear relationship. The order of covariate inclusion and magnitude of decrease of OFV (dOFV) with respect to the previous model was: (i) serum albumin on *V* (dOFV = −20.94); (ii) concomitant administration of vancomycin on CL (dOFV = −13.53); and (iii) total bodyweight on CL (dOFV = −11.40). Age showed a potential influence on CL, but not with the statistical significance selected ($P < 0.001$). Albumin concentration and weight showed influence on the *V* of amikacin, reducing 27% of the IIV of this parameter. The PK parameter estimates of the final model, together with the internal validation results (bootstrap), are summarized in Table 3.

Goodness-of-fit plots of the final PopPK model showed the lack of structural bias and good population and individual model-based predictions compared with the observed data in both the development group and the external validation group (Figure 1). The pcVPC showed an adequate description of the amikacin concentration–time course and its associated variability after infusion administration in the model-development patients (Figure 2) and in the external evaluation ones (Figure S1, available as Supplementary data at *JAC* Online). All PK parameters estimated were within the calculated 95% CI of the bootstrap analysis (Table 3). Reliability and robustness of the parameter estimates were acceptable, with a high proportion of bootstrap samples able to converge successfully (82%).

AMKdose

A user-friendly web application, AMKdose, has been developed and it is freely available at http://shiny.cumulo.usal.es/amkdose/. This interactive application allows easy integration of patient, microorganism (MIC) and treatment information, together with Monte Carlo simulation based on the amikacin PopPK model developed and clinical targets to evaluate different amikacin initial dosages and their probability of treatment success.

Table 2. Summary of amikacin initial dosing and observations collected

	Development group		External validation group	
Characteristic	all ($n = 215$)	hypoalbuminaemia[a] ($n = 161$)	all ($n = 79$)	hypoalbuminaemia[a] ($n = 59$)
Conventional administration, *n* (%)				
<10 mg/kg q8h	7 (3.3)	5 (3.1)	1 (1.3)	1 (1.7)
<10 mg/kg q12h	53 (24.7)	42 (26.1)	17 (21.5)	13 (22.0)
10–15 mg/kg q6h	1 (0.5)	1 (0.6)	0 (0)	0 (0)
10–15 mg/kg q12h	3 (1.4)	2 (1.2)	1 (1.3)	0 (0)
>15–20 mg/kg q12h	2 (0.9)	1 (0.6)	0 (0)	0 (0)
Extended interval, *n* (%)				
<10 mg/kg q24h	5 (2.3)	4 (2.5)	1 (1.3)	1 (1.7)
10–15 mg/kg q24h	37 (17.2)	28 (17.4)	13 (16.5)	10 (16.9)
10–15 mg/kg q36h	1 (0.5)	0 (0)	0 (0)	0 (0)
>15–20 mg/kg q24h	82 (38.1)	61 (37.9)	33 (41.8)	25 (42.4)
>15–20 mg/kg q36h	1 (0.5)	1 (0.6)	0 (0)	0 (0)
>20–25 mg/kg q24h	22 (10.2)	15 (9.3)	13 (16.5)	9 (15.3)
>20–25 mg/kg q36h	1 (0.5)	1 (0.6)	0 (0)	0 (0)
Amikacin observations stratified by time since end of infusion (h), *n* (%)				
0–2	186 (29.9)	149 (29.9)	79 (31.6)	59 (29.4)
>2–8	284 (45.6)	228 (45.8)	57 (22.8)	47 (23.4)
>8–12	87 (14.0)	70 (14.1)	92 (36.8)	74 (36.8)
>12–24	51 (8.2)	41 (8.2)	18 (7.2)	17 (8.5)
>24	15 (2.4)	10 (2.0)	4 (1.6)	4 (2.0)

[a]Hypoalbuminaemia, albumin <3.5 g/dL.

Table 3. PK parameter and bootstrap estimates for the final model

Parameter	Parameter estimates	RSE (%)	Shrinkage (%)	Bootstrap median ($n = 1000$)[a]	95% CI
CL_{nr} (L/h)	0.525	43.0	—	0.506	0.129–0.996
CL_{eGFR} (L/h)	4.78	5.8	—	4.78	4.27–5.29
CL_{VANCO} (L/h)	−0.226	40.1	—	−0.223	−0.380 to −0.014
*V*pop (L)	26.3	2.4	—	26.3	24.9–27.6
V_{ALB} (L)	−0.517	21.5	—	−0.513	−0.733 to −0.309
V_{TBW} (L)	0.00609	31.0	—	0.00606	0.00239–0.00980
IIV CL (CV%)	28.3	8.8	18.0	28.1	22.9–33.0
IIV *V* (CV%)	10.4	30.1	68.0	10.4	2.94–14.9
RUVprop (CV%)	23.7	7.1	14.0	23.7	19.5–27.4
RUVadd (mg/L)	1.99	3.5	3.7	1.97	1.32–2.43

$CL = (CL_{nr} + CL_{eGFR} \times \text{CKD-EPI}/98) \times (1 + CL_{VANCO})^{VANCO}$.

$V = Vpop \times \left(\frac{ALB}{2.9}\right)^{V_{ALB}} \times [1 + V_{TBW} \times (TBW - 70)]$.

ALB, albumin (g/dL); TBW, total bodyweight (kg); CL_{VANCO}, magnitude of the effect of vancomycin on CL; eGFR, estimated by the CKD-EPI equation (mL/min); RUVadd, additive error of residual variability; RUVprop, proportional error of residual variability; V_{ALB}, magnitude of the effect of albumin on *V*; *V*pop, *V* of the typical subject (ALB = 2.9 g/dL, TBW = 70 kg); V_{TBW}, magnitude of the effect of TBW on *V*; VANCO, 0 for co-medication without vancomycin, 1 for co-medication with vancomycin.

[a]178 runs with estimates near a boundary were skipped when calculating the bootstrap results.

Additionally, automated reports in Word and HTML format can be generated and downloaded from AMKdose. Examples of 'PK analysis' and 'Simulation' screens from the AMKdose application are shown in Figures 3 and 4, respectively. Dose exploration was designed to evaluate the three PKPD targets of a specific dosage (dose and time of infusion) for a defined patient (eGFR and vancomycin co-medication) and a specific infection (MIC) through all possible combinations of weight and albumin concentration (Figure 5). Considering the interactive capacity of the AMKdose application, we strongly encourage the reader to explore the online tool to better understand the features implemented.

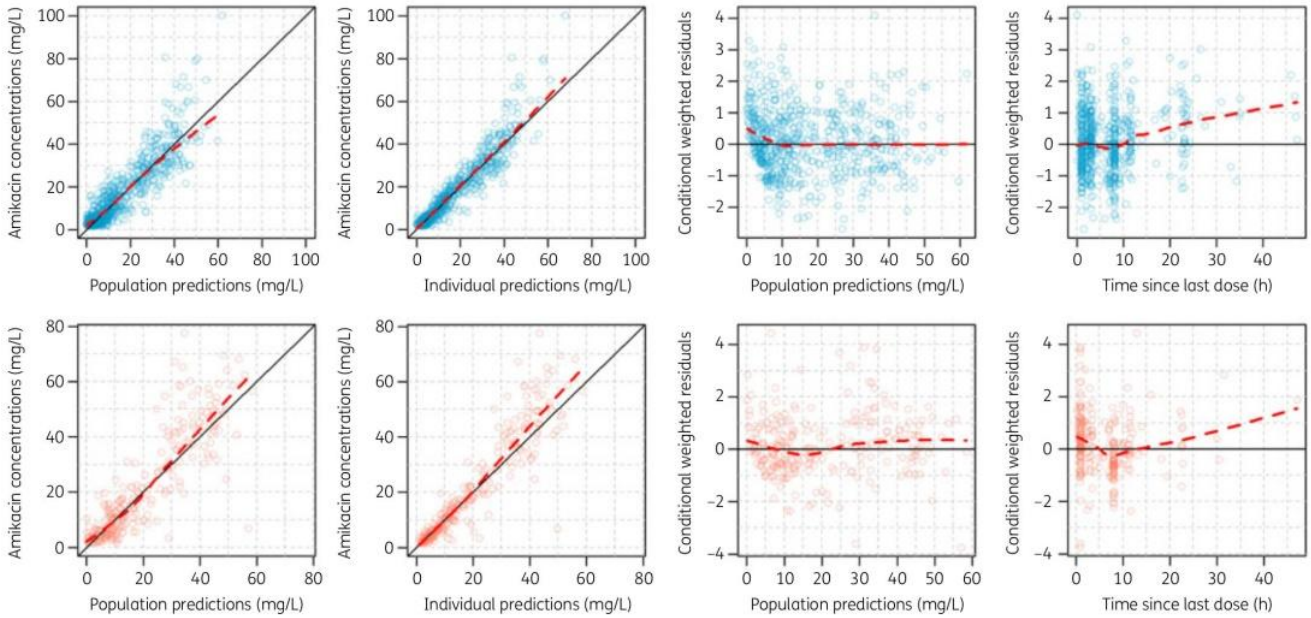

Figure 1. Goodness-of-fit of the final amikacin population PK model in the development group (upper panel) and the external validation group (lower panel). Open circles, amikacin concentrations; solid black lines, identity lines; red dashed lines, trend lines (LOWESS, locally weighted scatterplot smoothing). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

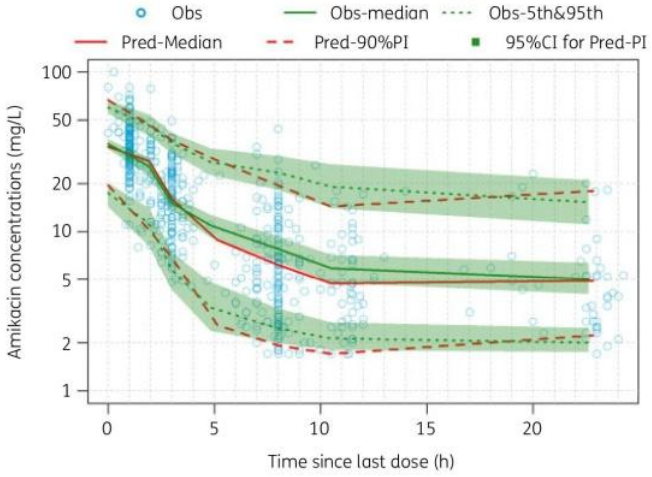

Figure 2. pcVPC for the concentration–time after-dose profiles of amikacin (development dataset). Blue open circles, amikacin observations (Obs); red solid line, 50th percentile of the Obs; red dashed lines, 5th and 95th percentiles of the Obs; green solid line, 50th percentile of the model-based predicted amikacin concentrations (Pred); green dashed lines, 5th and 95th percentile of the Pred (90% prediction interval, PI); green-shaded area, 95% CI for the 5th, 50th and 95th percentiles of the Pred. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Discussion

Several PopPK models have been developed for aminoglycosides in special populations, including patients with burns and critically ill or septic patients.[2,5,9,12,13,34] In addition, significant differences in model performance have been shown for amikacin.[15] Amikacin PopPK parameters estimated in our population, CL = 5.3 L/h and V = 26.3 L, are aligned with previous values reported in the literature for critically ill patients (2.8–6.3 L/h and 9.4–41.5 L for CL and V, respectively).[1,2,9,12–14] The model developed performs appropriately to describe both the individual amikacin concentrations and the PK variability observed. PK parameters were estimated with adequate precision and absence of bias, allowing the model to be used for predictive model-based simulation purposes. In addition, the final model has been successfully clinically validated with an external dataset, supporting its adequacy in the routine clinical setting.

The Cockcroft–Gault by total bodyweight equation has been applied over the last four decades as the gold standard to calculate renal function capacity in clinical practice. However, recent studies have pointed out that the CKD-EPI and revised Lund–Malmö (rLM) equations achieved better performance in adult subjects with no acute renal impairment (eGFR > 30mL/min).[30,35] Although the CKD-EPI equation was included in the model due to the vast experience with it in clinical practice, no major differences would be expected in the case that rLM had been chosen. Our PopPK model, developed in a population mostly with albumin deficiency, identified CKD-EPI and co-administration of vancomycin as significant covariates of amikacin CL. Increased plasma trough concentrations, concomitant administration with vancomycin and the duration of treatment can contribute to the nephrotoxicity caused by amikacin together with nephrotoxic agents and renal impairment status.[36]

A decreased production of albumin has been described in malnutrition, hepatic disease, acute-phase response (stress, injury, critical illness etc.), ageing and malignancies.[37] Hypoalbuminaemia may produce generalized oedema through

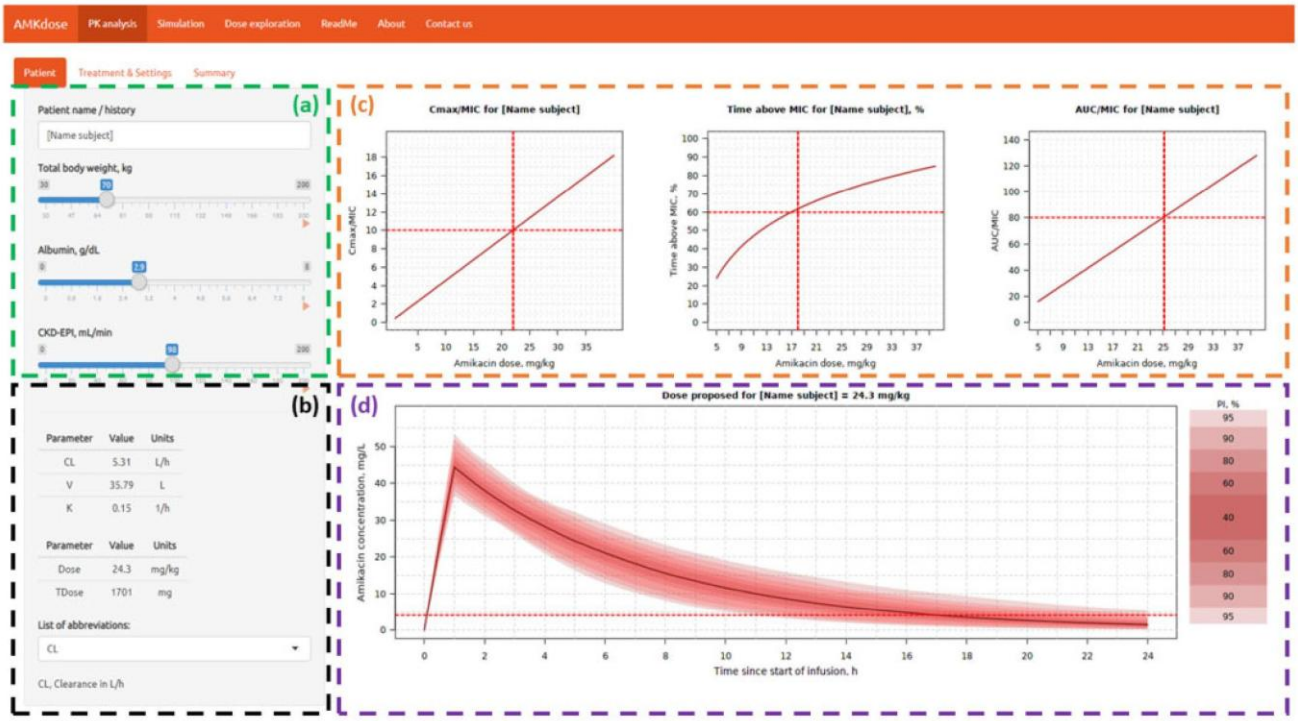

Figure 3. PK analysis section of AMKdose application. (a) Patient input information. (b) PK parameters for patient input values, amikacin dose selected to reach the three efficacy targets and list of abbreviations. (c) Efficacy targets: C_{max}/MIC, %*T*>MIC and AUC/MIC versus amikacin dose (mg/kg), respectively; vertical lines represent the dose needed to reach the target effective value (horizontal lines). (d) Stochastic simulation with the PK parameters calculated for the individual characteristics described in (a) for the dose selected (b). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

the reduction in oncotic pressure generating an accumulation of extracellular water. With hydrophilic drugs, such as amikacin, the increase in the extracellular water induces an increase in the apparent *V*, associated with hypoproteinaemia, as observed in the population included in this research.[37,38] Albumin concentration and weight showed a relevant impact on the *V* of amikacin in accordance with the results obtained by Romano *et al.*[3] in patients diagnosed with haematological malignancies.

Ageing has been associated with physiological changes such as reduction in eGFR, changes in body water and fat content. These modifications can alter amikacin *V*, thus modifying the PK properties of this drug in the elderly.[4] In the present study, changes in *V* were not significantly associated with age but were explained by changes in total bodyweight and serum albumin, which can also change with age.

Initial amikacin dosing regimens have been extensively discussed since aminoglycoside dosing was shifted from divided daily dosing to once-daily dosing (extended interval) in order to optimize the treatment efficacy/safety profile.[39] Several studies showed that empirical doses ≥25–30 mg/kg/day achieved higher C_{max}/MIC ratios with no higher incidence of nephrotoxicity, suggesting that the standard regimen (15 mg/kg/day) could be insufficient to reach recommended C_{max}.[6,9,21] In contrast, Kato *et al.*[40] proposed a 15 mg/kg once-daily dose of amikacin to be sufficient to achieve the PD target (C_{max}/MIC) with lower toxicity incidence for infections with MIC ≤4 mg/L. Therefore, there is currently no consensus regarding the optimal initial dose of amikacin. In addition, agents altering nucleic acid or protein synthesis, such as fluoroquinolones and aminoglycosides, show a prolonged post-antibiotic effect against any susceptible bacteria, as it takes considerably longer for the organism to regenerate these elements compared with cell wall components. Therefore, longer dose intervals (≥24 h) are possible without compromising treatment efficacy.[41–44] Zazo *et al.*[13] pointed out that an adequate C_{max}/MIC ratio does not guarantee therapeutic efficacy of aminoglycoside therapy if a %*T*>MIC of >60% is not reached. This threshold has been suggested by several other authors.[45,46] Moreover, previous studies were based on a single PKPD target and did not take into account individual patient information for dosing recommendations. In the current study, an interactive and flexible web-based application is proposed to individualize amikacin initial dosage based on a PopPK model together with individual patient information and including several PD targets to help increase the likelihood of treatment success. *A priori* drug dosage optimization with a lack of individual PK information can have a relevant impact in improving the probability of success in dose selection based on the target concentration intervention (TCI) approach. AMKdose is a powerful and easy-to-use model-based interactive application, freely available for research and clinical purposes. This innovative dose-finding tool allows better identification of the optimal initial amikacin dose to reach the well-established PKPD targets by

Figure 4. Simulation section of AMKdose application. (a) Patient and treatment input information. (b) Left plot, amikacin concentration–time profile for the stochastic simulations defined in the input panel (a); horizontal red line, MIC; (b) right plot, PTA for the three efficacy targets defined. (c) Numeric results of the simulations and list of abbreviations displayed on the screen. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

including individual patient and infection information (weight, albumin concentration, MIC, etc.).

The PopPK model of amikacin was developed in adult patients with no renal failure, which may be a limitation of this application. In addition, co-medication with other antimicrobial agents (meropenem, piperacillin, tigecycline, quinolones, etc.) or vasoactive drugs (dopamine, norepinephrine and nitroglycerin) can significantly modify amikacin PK. The three PKPD targets selected (C_{max}/MIC, %*T*>MIC and AUC/MIC) have been considered with equal relevance in this work. However, the impact on treatment success of each target can be variable in different clinical situations. In addition, definition of the optimal cut-off value for each target is still under discussion. Therefore, the cut-off values that need to be reached for each PKPD target can be modified in all the AMKdose sections. Additional information regarding the contribution of each target to the improvement of the clinical outcome would positively contribute to enhance the dose-decision algorithm currently implemented in the presented application. AMKdose has not been clinically validated. Therefore, it is also desirable to perform a prospective clinical validation of the *a priori* dosage application described in the current study, not only focusing on PKPD target achievement, but also on clinical treatment outcome (i.e. leucocyte counts, C-reactive protein, fever etc.). Moreover, the type of infection could be of high interest to improve the dose selection as it has been correlated with the grade of microbiological eradication rate (i.e. lung infections, MDR pathogens etc.).[47] The current research results are based on a retrospective study in a specific population (adults without severe renal failure) and amikacin measurements mostly within 24 h after the end of administration, which must be pointed out as the main limitations. Accordingly, updating the amikacin PopPK model in a wider population including, but not limited to, paediatrics and severely decreased renal function (eGFR < 30 mL/min) patients is proposed as the next step of this research. Moreover, validating the AMKdose application prospectively in patients undergoing amikacin treatment and routine therapeutic drug monitoring (TDM) is also planned to improve the developed simulation tool for initial amikacin dosage selection.

TDM has been successfully applied to amikacin, improving antibacterial treatments over the last few decades, becoming standard clinical practice due to the favourable efficacy/toxicity balance.[48] Accordingly, individual PK information, such as plasma concentration, together with a maximum *a posteriori* probability (MAP) Bayesian approach, can improve the estimation of the individual PK parameters and subsequently allow the individualization of the maintenance dose of amikacin. However, the key goal of this work was to improve the initial amikacin dosage, in order to give the appropriate dose as early as possible and thus maximize the probability of treatment success and infection control. The initial amikacin dosage is proposed with no individual PK information and based on the PopPK model developed and the patient information identified as impacting PK. In addition, AMKdose is a flexible *a priori* dose-finding tool useful for multiple bacteria and severe infections.

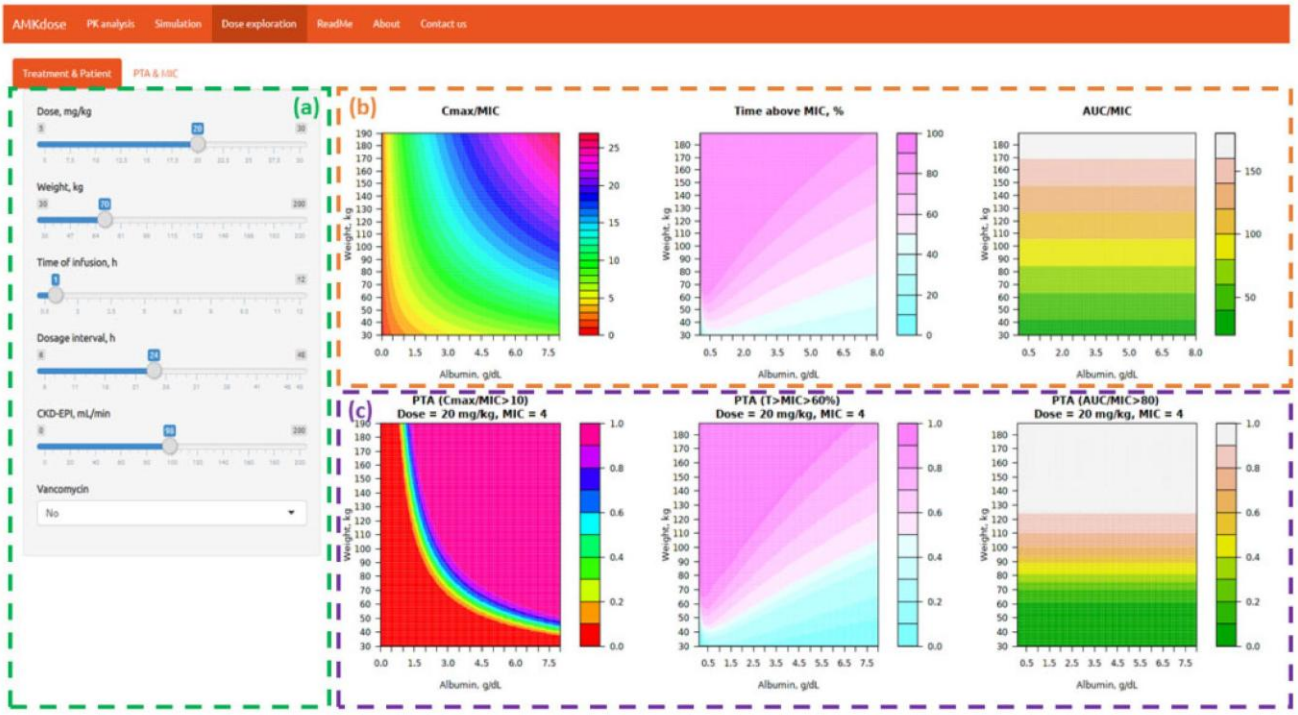

Figure 5. Dose exploration section of AMKdose application. (a) Patient input information. (b) Deterministic simulations for weight and albumin combinations of the efficacy targets: C_{max}/MIC, %*T*>MIC and AUC/MIC, respectively. (c) PTA of the efficacy targets as described in (b) for the values defined in the PTA and MIC tab and displayed in the title. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

In conclusion, we identified serum albumin, total bodyweight, eGFR (CKD-EPI) and co-medication with vancomycin as factors explaining part of the PK variability observed for amikacin. Under amikacin extended-interval administration (≥24 h), patients with hypoalbuminaemia presenting an increased *V* would require higher-than-standard doses to achieve amikacin PKPD targets. A powerful interactive model-based application has been developed, AMKdose, and is freely available online to optimize amikacin first-dose selection. AMKdose can be useful for individualizing amikacin initial dosage, helping to maximize treatment success as early as possible before any individual PK information is available.

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This study was carried out as part of our routine work.

Transparency declarations

J.S.P-B. was the main developer of AMKdose. J.S.P-B. and E.M.S.F. were the principal researchers of this study and both contributed as first authors. The remaining authors have none to declare.

Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online.

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Supplementary data

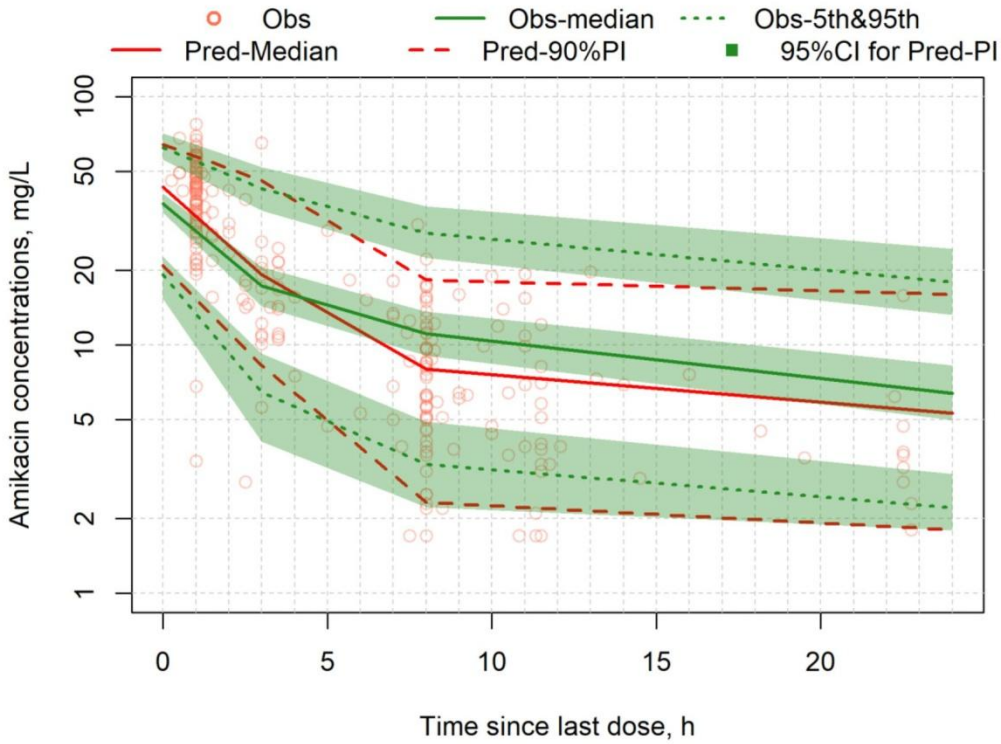

Figure S1. Prediction-corrected visual predictive check (pcVPC) for the concentration-time after-dose profiles of amikacin (external validation group). Orange open circles, amikacin observations (Obs); red solid line, 50th percentile of the Obs; red dashed lines, 5th and 95th percentiles of the Obs; green solid line, 50th percentile of the model-based amikacin predicted concentrations (Pred); green dashed lines, 5th and 95th percentile of the Pred (90% prediction interval, PI); green-shaded area, 95% confidence interval (CI) for the 5th, 50th and 95th percentiles of the Pred. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

III.3. EVALUATION OF CURRENT AMIKACIN DOSING RECOMMENDATIONS AGAINST MODEL-INFORMED PRECISION DOSING NOMOGRAMS: THE ROLE OF ALBUMIN

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RESUMEN

Objetivo: i) Evaluar la eficacia y seguridad de las recomendaciones internacionales de dosificación de amicacina, ii) desarrollar una aplicación interactiva para la construcción de nomogramas de dosificación de amicacina basada en criterios farmacocinéticos/farmacodinámicos (PKPD) y iii) evaluar el impacto de factores intrínsecos en la eficacia y seguridad de los regímenes de dosificación de amicacina.

Métodos: La eficacia y toxicidad de las principales recomendaciones de dosificación de amicacina (EUCAST, Mensa, Queensland, Sanford y UpToDate) fueron evaluadas mediante la aplicación de criterios PKPD. La probabilidad de alcanzar el objetivo terapéutico para las distintas recomendaciones fue calculada mediante simulaciones de Monte Carlo. Cmax/CMI ≥ 10 y %T>CMI ≥ 60% del intervalo de dosificación junto con Cmin < 4 mg/L en el estado estacionario, fueron los parámetros de eficacia y toxicidad seleccionados, respectivamente. Se desarrolló una aplicación interactiva para la construcción de nomogramas en R (Shiny and R Markdown).

Resultados: Las recomendaciones de EUCAST y Queensland mostraron una eficacia superior asociada a potenciales problemas de toxicidad en pacientes con insuficiencia renal que podrían agravarse en situación de hipoalbuminemia. AMKnom, es una aplicación interactiva útil para la construcción de nomogramas de dosificación de amicacina. Los resultados obtenidos han puesto de manifiesto que, a las dosis recomendadas, cuanto mayor sea la albúmina, mayor será la probabilidad de alcanzar el objetivo terapéutico Cmax/CMI seleccionado; sin embargo, la probabilidad de alcanzar los objetivos %T>CMI y Cmin será menor.

Conclusiones: EUCAST y Queensland mostraron los mejores resultados de eficacia asociados a potenciales problemas de toxicidad. La aplicación interactiva AMKnom ha sido desarrollada para la construcción de nomogramas de dosificación y está disponible online de forma gratuita. Dado el significativo impacto de la albúmina en la eficacia y seguridad del tratamiento con

amicacina, se requieren estudios adicionales para la optimización de los regímenes de dosificación con especial atención a los valores séricos de albúmina.

Introduction

Amikacin is one of the most effective aminoglycoside antibiotics used against severe gram-negative bacterial infections and initial empirical antimicrobial treatments. It is commonly administered with β-lactam antibiotics to extend the antimicrobial activity spectrum against multidrug-resistant pathogens such us *Pseudomonas aeruginosa.* [1,2] Optimizing amikacin treatments has been recently proposed by clinicians due to the increase of resistance to alternative antibiotic drugs. [3]

Amikacin treatment success, in terms of bacterial killing and clinical response, has been mainly associated with reaching a ratio between the maximum serum concentration (Cmax) and the minimum inhibitory concentration (MIC) (Cmax/MIC) ≥ 8-10 with recommended Cmax target values of 40-64 mg/L. [4–10] A ratio between the area under the concentration-time curve (AUC) and the MIC (AUC/MIC) ≥ 70 (up to 80-100 in amikacin monotherapy or in critically ill patients with high-bacterial burden infections) and concentrations exceeding the MIC (%T>MIC) of at least 60% of the dosing interval, have also been proposed as predictive efficacy pharmacokinetic/pharmacodynamic (PKPD) criteria. [4,6,11] Despite AUC/MIC is highly correlated with Cmax/MIC, it has been more commonly applied for vancomycin and fluoroquinolones while an insufficient %T>MIC has been associated with an increase in the likelihood of resistance development and treatment failure in β-lactams or amikacin. [4,11,12] On the other hand, nephrotoxicity and ototoxicity continue to be a major concern associated with the clinical use of amikacin. Target values of through concentrations (Cmin) < 4 mg/L have been proposed to reduce the risk of developing toxicity. [11,13]

Amikacin is characterized by a narrow therapeutic index and a large intra and interindividual PK variability associated with differences in renal function, bodyweight, albumin or age, among others (Appendix 1). [13–28] However, the quantitative impact of some physiological factors, especially serum albumin concentrations, on amikacin exposure, efficacy and safety is still unclear.

Amikacin was approved at doses of 15 mg/kg/day divided as 2 or 3 equal doses administered at equivalent intervals or a single daily dose under normal renal function. [29] Since 1990s, the once-

daily or extended interval dose regimen has been globally adopted improving microbiological and clinical outcomes without greater incidence of associated toxicities. [30,31] Enhanced concentration-related bacterial killing, increased postantibiotic effect (PAE) of 0.5-8 hours and decreased adaptive bacteria resistance, represent clinical advantages of once-daily dosing regimen. [1,30] Although several studies have shown amikacin extended interval dose regimen is as effective, with lower risk of toxicity, than multiple-dose regimens, it should be used with caution in specific populations. [13,30,32]

The "one-dose-fits all" treatment strategy is a common practice in antibiotic drugs. Amikacin 15-20 mg/kg/day once-daily has been lately adopted for most of antibiotic treatments only eventually adjusted based on renal function or aging. [7–10,33] Recently published international guidelines for amikacin dosing recommend doses up to 30 mg/kg/day. [8,33] Therefore, there is no consensus regarding the optimal dose of amikacin treatment. However, several studies has pointed out that individualized dosing strategies could improve clinical outcomes of this drug with no additional toxicity. [14,34,35]

The aims of the present study were (i) to evaluate the efficacy and safety of amikacin dosage recommended by the current international guidelines, (ii) to create an interactive amikacin dosage nomograms tool based on PKPD criteria and (iii) to evaluate the impact of intrinsic factors on amikacin dosing regimens with special focus on serum albumin.

Materials and methods

Pharmacokinetic model

A specific amikacin PK model previously developed was used. Amikacin PK was described by a one-compartment model with first order linear elimination. The population pharmacokinetic (PopPK) model was parameterized in terms of CL and V (equations 1-2, respectively). Serum albumin (ALB), total bodyweight (TBW), estimated glomerular filtration rate (eGFR) calculated with CKD-EPI equation and co-medication with vancomycin (VANCO) showed a significant impact on amikacin PK. [36] Additional details of the PopPK model are provided in Pérez-Blanco JS et al. [14]

$$CL\ (L/h) = (0.525 + 4.78\ \times\ CKD - EPI/98)\ \times\ 0.77^{VANCO}$$ Eq. 1

$$V\ (L) = 26.3\ \times\ (ALB/2.9)^{-0.51}\ \times [1 + 0.006\ \times\ (TBW - 70)]$$ Eq. 2

Where CL (L/h) is the total amikacin clearance, CKD-EPI is the estimated glomerular filtration rate by CKD-EPI equation (mL/min), VANCO represents co-medication of vancomycin (0 for absence of vancomycin co-administered; 1 for co-medication with vancomycin), V (L) is the amikacin volume of distribution, ALB is the serum albumin concentration (g/dL) and TBW is the total bodyweight (kg).

The maximum and minimum concentrations at the steady state and the %T>MIC expressed as percentage of the dosing interval are shown in equations 3-5, respectively.

$$C_{max}^{SS}\ (mg/L) = \frac{D/T \times \left(1 - e^{-\ CL/Vd \times\ T}\right)}{Vd \times CL/Vd \times (1 - e^{-\ CL/Vd\ \times \tau})}$$ Eq. 3

$$C_{min}^{SS}\ (mg/L) =\ C_{max}^{SS}\ \times\ e^{-\ CL/Vd\ \times (\tau - T)}$$ Eq. 4

$$T > MIC\ (\%) = (T - ln\ (MIC/C_{max}^{SS})/\ (CL/Vd \times\ \tau)) \times 100$$ Eq. 5

Where D (mg) is the total amikacin dose administered, T (h) is the duration of infusion, CL (L/h) is the clearance, Vd (L) is the volume of distribution and τ (h) is the dosing interval, MIC (mg/L) is the minimum inhibitory concentration and %T>MIC, time with concentrations exceeding the MIC (% of dosing interval, τ).

Amikacin dosage guidelines evaluation

Amikacin dosage recommendation guidelines selected in this work were: 1) European Committee on Antimicrobial Susceptibility Testing guidance 2020 (EUCAST), 2) Antimicrobial Therapeutic Guide Mensa 2020 (Mensa), 3) Aminoglycoside Dosing in Adults Guideline of State of Queensland 2018 (Queensland), 4) The Sanford Guide to Antimicrobial Therapy 2019 (Sanford) and 5) UpToDate® 2020 electronic clinical resource (UpToDate). Table 1 summarise amikacin dosing recommendations at different renal function for each of the guidelines evaluated.

Table 1. Amikacin dosing recommended by the international dosing guidelines

	Renal function (mL/min)						
Guideline	≤ 10	10 – 20	20 – 30	30 – 40	40 – 60	60 – 80	> 80
EUCAST	25-30 (24)	25-30 (24)	25-30 (24)	25-30 (24)	25-30 (24)	25-30 (24)	25-30 (24)
Mensa	7.5-10 (48)	-	12 (48)	-	12 (24)ǫ	15-20 (24)	15-20 (24)
Queensland	16Δ	16Δ	16Δ	16Δ	16-20 (36)	20 (24)♦	20 (24)♦
Sanford	3 (72)†	4 (48)	7.5 (48)	4 (24)	7.5 (24)	12 (24)	15 (24)
UpToDate	7.5 (48-72)¶	7.5 (24-72)¶	7.5 (24-72)¶	15 (48)	15 (36)	15 (24)	15 (24)&

Amikacin doses are expressed in mg/kg and interval dosing in hours between brackets.
EUCAST: Initial dose based on ideal bodyweight in seriously ill patients prior to therapeutic drug monitoring and dose adjustment. Renal function calculated by CKD-EPI equation.
Mensa: Amikacin dose based on adjusted bodyweight. Renal function calculated by Cockcroft-Gault equation.
Queensland: Amikacin dose based on ideal bodyweight or total bodyweight whichever is lower. Use ideal bodyweight for overweight patients (25.0-29.9 kg/m^2) and adjusted bodyweight for obese patients (≥ 30.0 kg/m^2). Renal function calculated by an easily available estimated glomerular filtration rate equation. Cockcroft-Gault equation is not recommended.
Sanford: Amikacin dose based on ideal bodyweight for non-obese patients (< 30.0 kg/m^2). Use adjusted bodyweight in obese patients (≥ 30.0 kg/m^2). Renal function calculated by Cockcroft-Gault equation using ideal bodyweight for non-obese patients and Salazar-Corcoran equation for obese patients.
Uptodate: Amikacin dose based on total bodyweight for underweight patients (< 18.5 kg/m^2); ideal bodyweight for patients with total bodyweight 1-1.25 folds ideal bodyweight and adjusted bodyweight for patients with total bodyweight > 1.25 folds ideal bodyweight. Renal function calculated by Cockcroft-Gault equation using lean bodyweight.
ǫ Amikacin dose only for creatinine clearance 40-50 mL/min.
Δ Single dose only. Further doses should be under therapeutic drug monitoring.
♦ For critically ill and febrile neutropenic patients, administer a single dose of 30 mg/kg and monitor concentrations.
† Amikacin postdialysis dose should be administered.
¶ Amikacin dose based on serum concentrations.
& Use traditional intermittent dosing for creatinine clearance > 120 mL/min.

Monte Carlo simulations were carried out using the PopPK model previously described to evaluate the efficacy (Cmax/MIC and %T>MIC) and safety (Cmin) of each scenario. The amikacin mean dose and the mean of CKD-EPI of the respective ranges proposed by the guidelines were selected for simulation purposes (120 mL/min for the > 80 mL/min classification). In severe renal dysfunction stages (CKD-EPI ≤ 30 mL/min), amikacin administration each 48 h and 36 h was selected for the UpToDate guideline at renal function values 10-20 mL/min and 20-30 mL/min, respectively. Total dose recommended was administered in one-hour infusion. Cmax/MIC of 10 and %T>MIC ≥ 60% were selected as the efficacy PKPD thresholds with a MIC of 4 mg/L. Probability of target attainment (PTA) was calculated for 1000 virtual subjects of 70 kg for a MIC of 4 mg/L taking into account the PK variability. Treatment response was defined as effective and/or toxic when the PTA ≥ 90% for efficacy criteria (Cmax/MIC and/or %T>MIC) and Cmin ≥ 4 mg/L at the steady state, respectively.

AMKnom: interactive amikacin nomograms

An interactive R-based application, AMKnom, was developed to perform interactive amikacin nomograms based on PKPD criteria and subject characteristics. AMKnom outputs are also helpful for better understanding of the quantitative impact of physiological factors on amikacin exposure and treatment success. AMKnom was developed in R through Shiny package for implementing interactive functions into the simulation environment. [37]

AMKnom was divided in two main sections:

A. Input menu (left panel): information was displayed in three tabs: i) Patient: TBW (kg), ALB (g/dL), CKD-EPI (mL/min) and co-medication with vancomycin (yes/no); ii) Treatment (time of infusion (h), dosing interval (h) and MIC (mg/L)) and PKPD thresholds (Cmax/MIC, %T>MIC and Cmin); iii) Graphical settings (resolution, grid, etc.). PK parameters and PKPD target values for the specific scenario defined (patient, treatment and PKPD thresholds) are summarized at the bottom of patient tab.
B. Graphical output (main panel): amikacin dose expressed in mg/kg (black solid lines) required to reach the Cmax/MIC threshold selected (Treatment & PKPD tab of input menu) at steady state was calculated for all possible combination of two of the following variables: TBW, ALB and CKD-EPI. For each combination, the remaining variable was fixed to the value introduced in the patient tab of the input menu. Three different tabs are defined based on the fixed variable (CKD-EPI, TBW and ALB). For each dosing scenario calculated to reach Cmax/MIC criterion, the %T>MIC and Cmin were calculated. A green area was drawn when %T>MIC complied with the threshold defined in Treatment & PKPD tab (input menu). A red area was drawn when Cmin was equal or higher than the toxicity threshold (Cmin) defined in Treatment & PKPD tab (input menu). Specific scenario defined in input menu is represented across the three graphical representations.

The range of continuous covariates were defined in accordance with the development population of the PopPK model: TBW: 40-150 kg, ALB: 1-6 g/dL and CKD-EPI: 30-200

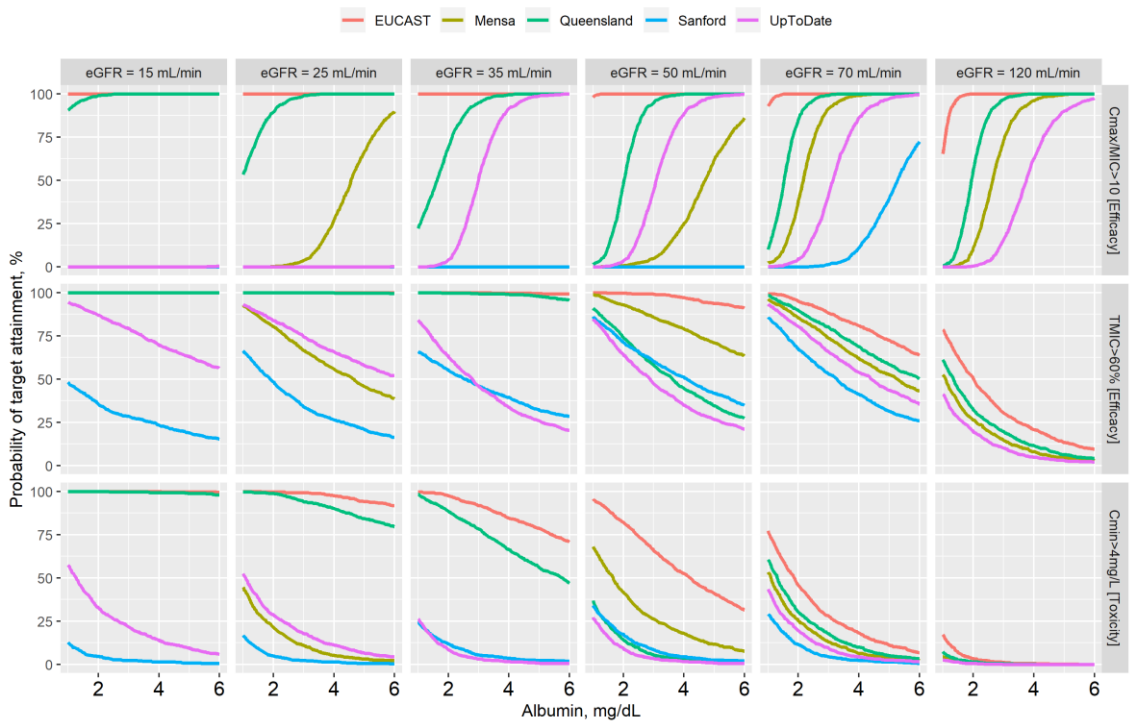
mL/min. The typical subject was defined as TBW of 70 kg, ALB of 4.0 g/dL, CKD-EPI of 120 mL/min and absence of vancomycin co-administration.

Results

Amikacin dosage guidelines evaluation

Large discrepancies were observed in amikacin dosage recommendations across the five dosing guidelines evaluated (Table 1). In addition, missing dosage recommendation (Mensa) or a wide range of interval administration, from 24 h up to 72 h (UpToDate), were found for specific renal function status. Moreover, initial dosage recommendations in seriously ill patients assuming the need of therapeutic drug monitoring (TDM) adjustment instead of recommending a specific dosing interval were observed (EUCAST).

Treatment efficacy (Cmax/MIC ≥ 10 and %T>MIC ≥ 60%) and toxicity (Cmin ≥ 4 mg/L) for the different dosing recommendations of each guideline through the ALB possible values defined by renal function stages are shown in Figure 1. These results show that, at the dosage recommended, mainly based on renal function status, the higher is the albumin: i) the higher will be the PTA for Cmax/MIC criterion, ii) the lower will be the PTA for %T>MIC efficacy criterion and iii) the lower will be the PTA for toxicity. Overall, EUCAST and Queensland showed an adequate amikacin treatment efficacy at the dosages recommended. In the other hand, these guidelines presented a high probability of toxicity being hypoalbuminemia and renal dysfunction subjects the worst scenario. Sanford and UpToDate guidelines showed the most safety profiles across the different scenarios evaluated. However, potential efficacy issues were observed due to the low doses recommended by these guidelines.



	15 mL/min	25 mL/min	35 mL/min	50 mL/min	70 mL/min	120 mL/min
EUCAST	27.5 mg/kg (q24h)	27.5 mg/kg (q24h)	27.5 mg/kg (q24h)	27.5 mg/kg (q24h)	27.5 mg/kg (q24h)	27.5 mg/kg (q24h)
Mensa	NA	12 mg/kg (q48h)	NA	12 mg/kg (q24h)	17.5 mg/kg (q24h)	17.5 mg/kg (q24h)
Queensland	16 mg (q24h)	16 mg/kg (q24h)	16 mg/kg (q24h)	18 mg/kg (q36h)	20 mg/kg (q24h)	20 mg/kg (q24h)
Sandford	4 mg/kg (q48h)	7.5 mg/kg (q48h)	4 mg/kg (q24h)	7.5 mg/kg (q24h)	12 mg/kg (q24h)	15 mg/kg (q24h)
UpToDate	7.5 mg/kg (q48h)	7.5 mg/kg (q36h)	15 mg/kg (q48h)	15 mg/kg (q36h)	15 mg/kg (q24h)	15 mg/kg (q24h)

Figure 1. Efficacy and toxicity probability (upper panel, graphical representations) of amikacin dosage recommended (bottom table) by EUCAST, Mensa, Queensland, Sanford and UpToDate guidelines stratified by estimated glomerular filtration rate (eGFR). Cmax, maximum concentration; MIC, minimum inhibitory concentration; %T>MIC, time with concentrations exceeding the MIC (% of dosing interval); Cmin, minimum concentration; 1000 virtual subjects simulated with total body weight of 70 kg, no vancomycin administration, infusion time of 1h and amikacin administered once-daily; MIC=4 mg/L. NA, non-applicable.

AMKnom: interactive amikacin nomograms

A user-friendly web application, AMKnom, has been developed and it is freely available at http://shiny.cumulo.usal.es/amknomogram/. AMKnom allows an easy evaluation of optimized amikacin dosage based on patient and treatment information together with PKPD selection criteria. An amikacin nomogram can be computed and downloaded from the application for the specific scenario defined. Dynamic simulations can be performed by activating the "play button" for each covariate taking into account in the simulations. This action allows to observe how amikacin dosage recommended changes with the increase/decrease of a determined

variable together with the impact on treatment efficacy (%T>MIC ≥ 60%) and safety (Cmin < 4 mg/L). An example of the AMKnom application is shown in Figure 2. Considering the interactive properties of the AMKnom application, we strongly encourage the reader to explore the online tool to better understand the features implemented.

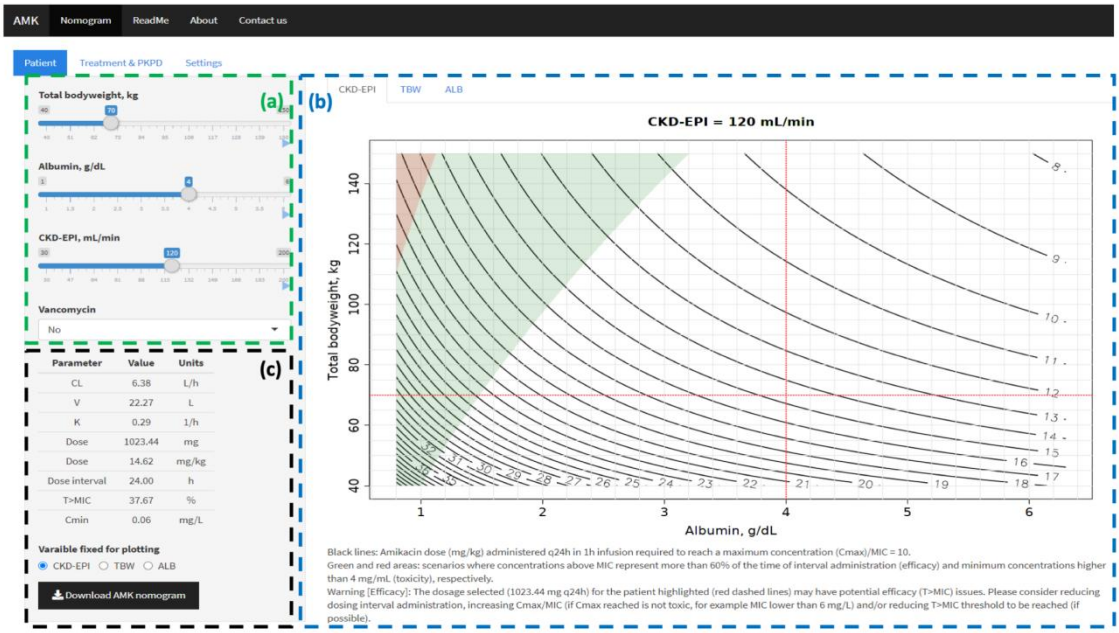


Figure 2. AMKnom application. (a) Input menu (3 tabs). (b) Graphical output: title indicates the value of a specific variable fixed when simulations are performed; red dashed lines, subject of 70 kg, 4 g/dL of albumin and 120 mL/min of renal function calculated with CKD-EPI equation; black solid lines, amikacin dose (mg/kg) required to achieve the Cmax/MIC threshold defined in Treatment & PKPD tab of (a); green area, efficacy scenarios where time above MIC is equal or higher than the threshold defined in Treatment & PKPD tab of (a); red area, toxic scenarios where Cmin is equal or higher than the threshold defined in Treatment & PKPD tab of (a). (c) PK and PKPD results for the scenario defined in the input menu together with a download button of the three possible nomograms performed.

Influence of TBW, ALB and CKD-EPI on amikacin dose (mg/kg) once-daily administered in absence of vancomycin concomitant administration to the typical subject (TBW: 70 kg, ALB: 4 g/dL, CKD-EPI: 120 mL/min) is shown in Figure 3. Additional %T>MIC efficacy and toxicity (Cmin) results are presented in green and red areas, respectively, where all the toxicity scenarios also achieve the %T>MIC efficacy.

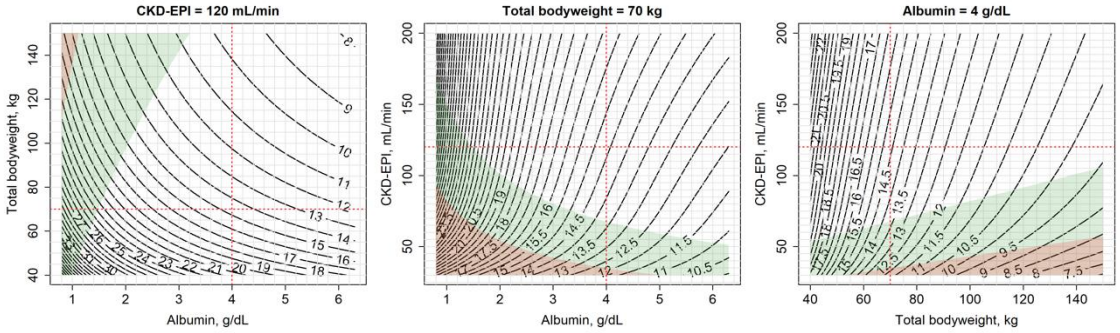


Figure 3. Amikacin dose (mg/kg) administered once-daily in 1h infusion required to reach a maximum concentration (Cmax)/MIC=10 across albumin, total body weight and estimated glomerular filtration rate (calculated with CKD-EPI equation) variations in the absence of vancomycin concomitant administration. Title of each plot, value of the variable fixed when simulations are carried out; red dashed lines, subject of 70 kg, 4 g/dL of albumin and 120 mL/min; MIC=4 mg/L; green and red areas, scenarios where concentrations above MIC represent more than 60% of the time of dosing interval (efficacy) and minimum concentrations higher than 4 mg/L (toxicity), respectively.

These results show a significant influence of ALB on amikacin dosing optimization with a larger impact on treatment efficacy than CKD-EPI which is currently the main driver of amikacin dosage selection. For instance, for reaching a Cmax/MIC ≥ 10 in the typical subject, a 36% dose must be increased if ALB changes from 4 g/dL to 2 g/dL while a 10% dose reduction would be needed if the renal function decreases from 120 mL/min to 50 mL/min. Moreover, a decrease of 1 mg/kg/day when TBW increases by 10 kg from 70 kg to 80 kg, within the same subject, would be necessary to achieve the defined efficacy Cmax/MIC ratio. This change in dosing selection based on TBW modifications has a higher impact at low TBW (15% dose decrease from 40 kg to 50 kg) than in heavier subjects (3% dose decrease from 140 kg to 150 kg).

Discussion

Despite continued progress toward “one-dose-fits-all” in antibiotic treatment strategies, amikacin dosage regimens should be further individualized supported on efficacy and safety PKPD criteria together with individual patient information and clinical evolution. Along this line, model-informed precision dosing is been shown in the last few years as a promising tool to

increase treatment success. [38] This methodology integrates PK information together with patient characteristics and exposure-response or PKPD relationships in an easy-to-use model-informed dose selection framework.

Antimicrobial therapy recommendations based on body and adjusted weight according to renal function or aging present a wide variability across the international guidelines evaluated in this work (Table 1). Our results showed that intrinsic factors such as TBW, ALB or CKD-EPI influence efficacy and safety of amikacin treatments. Considering these factors, amikacin 15-20 mg/kg/day once-daily regimen, lately adopted for most of antibiotics treatment, would cover a large majority of the treatments. However, this dosage could potentially involve under dosing in specific situations such us patients with hypoalbuminemia and increased of toxicity in severe renal dysfunction stages.

Renal elimination plays a key role in the PKPD of water-soluble drugs such as amikacin, primarily eliminated by the kidneys. [39] The majority of the antimicrobial therapy guidelines evaluated in this work recommend to adjust amikacin dose and frequency of administration based on renal function calculated with Cockcroft-Gault, CKD-EPI and Salazar-Corcoran equations. [7–10] However, recent studies have proposed CKD-EPI and revised Lund-Malmö as the better equations to characterise amikacin elimination in most of the physiopathological situations for drug dosing. [36,40] In the other hand, Aminoglycoside Queensland Health System and EUCAST guidelines recommends the same initial single dose (mg/kg) for critically ill/febrile neutropenic patients with or without chronic renal impairment followed by TDM adjustment. Our results showed a reduced amikacin dose decrease (10%) required when it is administered once-daily to reach treatment success in terms of efficacy comparing for subjects with normal renal function (eGFR=120 mL/min) versus a moderate renal impairment subject (eGFR=50 mL/min). These results are aligned with EUCAST and Queensland guidelines suggesting reduced amikacin dose adjustment must be required in a wide range of renal function. It is important to highlight that special populations such as paediatrics, obese or renal failure patients (eGFR < 15 mL/min) have not been considered in this work.

As other hydrophilic antimicrobials, amikacin exhibits a volume of distribution limited to the extracellular space, which is significantly affected by albumin concentrations decreased. [41] Increases in the volume of distribution are likely to decrease Cmax and total amikacin concentrations over time. In consequence, it is important to considerate serum albumin for optimizing amikacin dosage in order to achieve the efficacy and safety PKPD targets proposed, avoiding potential under dosing and sub-therapeutic concentrations. Several disease stages are associated with hypoalbuminemia, such as analbuminemia, starvation, liver or renal disease, cancer, stress response, burns, trauma, surgery or septic shock. [21,23,42–46] Although some of the antimicrobial therapy guidelines recommend special caution in situations with increased volume of distribution such as sepsis or septic shock, cystic fibrosis, severe burns or ascites among others, there are no special considerations based on albumin serum concentrations unlike dosing nomograms. [7,8,10] Our findings show a significant influence of albumin in amikacin dosage regimens and how patients with hipoalbuminemia should receive higher doses than normoalbuminemic ones for warrantying an adequate treatment efficacy.

Amikacin dosing has been based on weight (mg/kg) for decades. TBW, ideal bodyweight (IBW), lean bodyweight (LBW) and adjusted bodyweight (ABW) have been proposed for being used in dose calculations by many authors and specific scenarios without consensus (most of them for critically ill and obese patients). [2,6,15,47–53] Similarly, antibimicrobial guidelines also have no consensus on which of the previous weight measures best fit amikacin PK. Amikacin dosing recommendations are based on TBW, IBW and ABW depending on whether the patient is obese or not, but regardless body mass index (BMI) classification. Amikacin dosing recommendations based on TBW seems to be valid for normal-weight patients (18.5-24.9 kg/m^2) (Figure 4). However, in overweight and obese patients ($\geq$ 25 kg/m^2) or physiopathological stages such as sarcopenic patients with cancer, among others, drugs´ distribution can be largely modified. [54,55] IBW could not be an optimal measure, as patients with the same sex and height would receive the same dose regardless of body composition. On the other hand, LBW describes the weight devoid of almost all adipose tissue (total weight of organs, bones and muscles). [54,56]

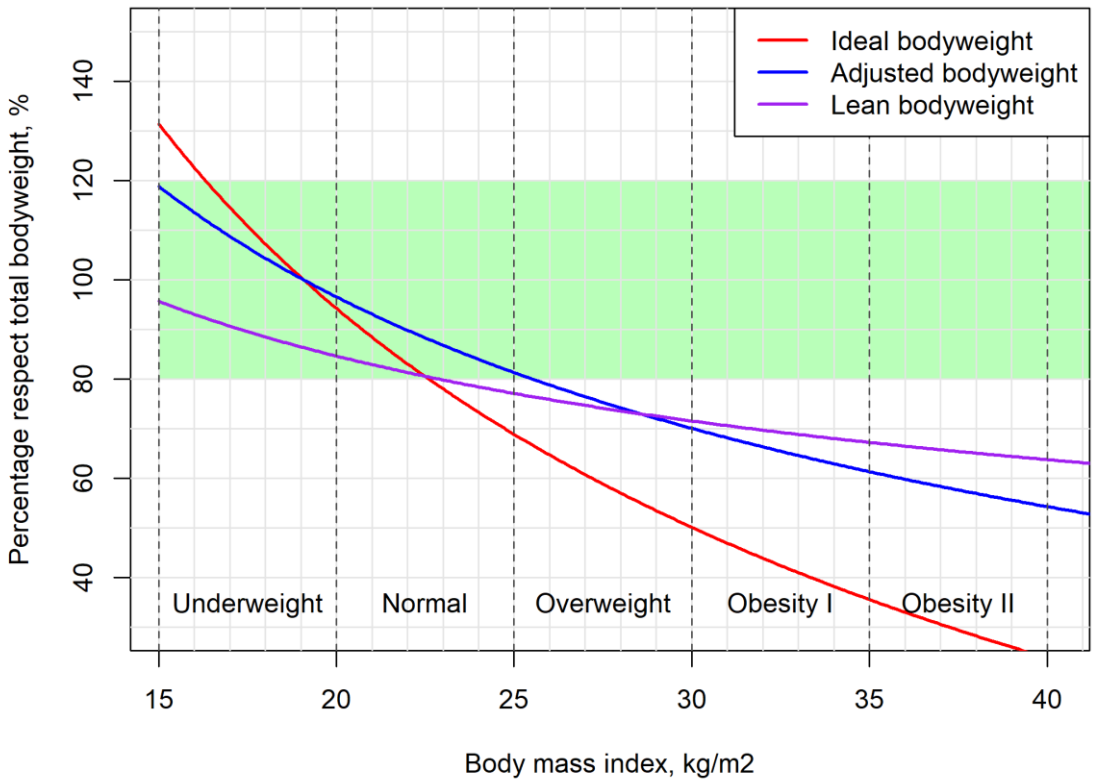


Figure 4. Comparison between different bodyweight measures and total bodyweight (TBW) classified according to body mass index (kg/m^2). Red, blue and purple solid lines, percentage of ideal bodyweight (IBW), adjusted bodyweight (ABW) and lean bodyweight (LBW) respect to TBW, respectively. Green area, situations where weights calculated with the different equations would be within ±20% of TBW.
IBW (kg) = 50 kg + [0.9 x (height (cm) – 152.4 cm)] [9]
ABW (kg) = IBW (kg) + 0.4 x [TBW (kg) – IBW (kg)] [9]
LBW (kg) = [1.1013 x TBW (kg)] – [0.01281 x BMI x TBW (kg)] [57]

In the amikacin PopPK model used in this work, TBW was the best body measurement metric to describe amikacin PK within the range of weights evaluated (43-190 kg) and therefore, TBW has been used in this work for dosage optimization together with the development of the simulations carried out. [14] However, several exceptions are recommended along the different guidelines (i.e. ABW above 30 mg/kg/m^2) in addition to new body size scalars proposed, such as skeletal muscle area, as better predictor of interpatient PK variability than TBW. [58] Therefore, results obtained in obese patients and its impact on dosage recommendation together with efficacy and toxicity associated with alternative body sizes proposed in each guideline must be considered carefully.

Amikacin is often used in combination with other drugs which can modify its PK and/or clinical outcome such as vasoactive drugs or other nephrotoxic agents as vancomycin, furosemide or amphotericin B, among others. Vasoactive drugs are commonly required to improve hemodynamic function in patients with sepsis or septic shock and can modify the extracellular fluid compartment and volume of distribution of water soluble antibiotics such as aminoglycosides. [59] In addition, total parenteral nutrition has been correlated with an expanded volume of distribution and lower peak concentrations of amikacin in parenterally-fed patients as well as with an increase in creatinine clearance. [60] These co-administrations, apart from vancomycin and parenteral nutrition were not taken into account in the present research. In consequence, additional consideration may be required in amikacin dose individualization under additional supportive care of these drugs.

Amikacin presents nephrotoxicity, usually transient, and ototoxicity, commonly irreversible, related with high concentrations at the end of the administration interval (Cmin > 4 mg/L). [61,62] Dosage recommended by the studied amikacin guidelines, except Sanford, presented toxicity issues in moderate to severe renal failure patients (eGFR < 60 mL/min) getting worse in hypoalbuminemia subjects. Our results also showed an increase of amikacin toxicity in patients with decreased renal elimination, low serum albumin or high TBW, if doses are not optimized adequately. Aminoglycosides nephrotoxicity can limit their use in clinical practice. Therefore, contributing factors to this toxicity such as concomitant nephrotoxic drugs administration, could promote kidney injury and drug clearance decrease which must be considered carefully. [63]

Monte Carlo simulations performed for the dosage recommended in the international amikacin guidelines evaluated in this work showed the high relevance of serum albumin on this antibiotic treatment efficacy and toxicity (Figure 1). Thus, a specific dosage recommended can vary from absence to fully achieved of efficacy and/or toxicity only due to the serum albumin value within a patient. In addition, impact of changes in serum albumin, from 4 g/dL to 2 g/dL, comparing with changes in renal function stage, from 120 mL/min to 50 mL/min, showed a significant higher impact of albumin than renal function on dose adjustment required to reach treatment efficacy (36% increase vs 10% reduction, respectively). These findings reveal the significant

role of serum albumin in amikacin dosage optimization based on PKPD criteria and support its potential inclusion in future updates of the principal international amikacin dosing guidelines.

Antimicrobial therapy guidelines establish general amikacin dosing recommendations of great utility for different population groups, whereas amikacin dosing model-based nomograms could be more precise in certain situations. Thus, an interactive amikacin dosing evaluation and nomogram builder, AMKnom, has been developed and is freely available at http://shiny.cumulo.usal.es/amknomogram/. AMKnom allows the researchers and clinicians to extend these preliminary insights to different dosing regimens (i.e. q12h, q36h), PKPD thresholds (Cmax/MIC, %T>MIC, Cmin) or MIC values, among others. However, specific populations where significant PK differences have been shown, such us paediatric, overweight and obese (BMI $\geq$ 25 kg/m^2), burns, amputees, patients with specific additional supportive care (i.e. vasoactive drugs, parenteral nutrition) or end-stage renal disease (eGFR < 15 mL/min) were not studied in this work and must be considered for amikacin dosage individualization. Therefore, additional studies including previously mentioned populations are suggested as potential improvements of the insights presented in this research.

Conclusions

The present study shows the efficacy and toxicity associated to the dosage recommended by the main international amikacin guidelines together with the impact of total bodyweight, renal function and serum albumin on amikacin model-informed precision dosing recommendation. EUCAST and Queensland dosing guidelines showed an adequate treatment efficacy also associated with potential toxicity issues in renal failure subjects getting worse in hypoalbuminemia patients. A significant impact of serum albumin has been shown suggesting further evaluations for potential inclusion in the following amikacin guidelines updates. AMKnom, a useful interactive amikacin nomogram builder based on PKPD criteria and patient characteristics has been developed and is freely available for amikacin dosing optimization.

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Appendix 1. Summary of amikacin population pharmacokinetic models developed in adults

Reference	Population				Treatment and sampling		Covariates in final model		Estimated parameters ¶ (IIV, CV %)				Software
	N (male)	Age (years)*	Albumin (g/dL)*	Patients	Amikacin dose	Samples	CL	Vd	CL (L/h)	V_1 (L)	Q (L/h)	V_2 (L)	
Pérez-Blanco [1]	215 (124)	61 [18-93]	2.9 [1.2-5.0]	General medicine and critically ill	250-2000 mg q24h	623	eGFR, vancomycin	Albumin, weight	4.78 (28.3)	26.3 (10.4)	-	-	NONMEM
Burdet [2]	60 (47)	61.5 [28-84]	1.9 [1.4-4.4]	Critically ill	11-28 mg/kg q24h	291	CL_{CR}	PaO_2/FiO_2, weight	4.3 (31)	15.9 (22)	12.1 (27)	21.4 (47)	Monolix
Matar [3]	56 (32)	57.4 [19-90][Δ]	-	Critically ill	500 mg q12h	331	CL_{CR}	-	5.08 (NA)[Ψ]	16.7 (38)	36.9 (NA)[Ψ]	25.8 (NA)[Ψ]	USC PACK
Jang [4]	197 (113)	61.0±17.5	-	General medicine and critically ill	125-1000 mg q24h	698	CL_{CR}, ward	Cholecystitis, weight	2.8 (30)	18.0 (NA)	-	-	NONMEM
Delattre [5]	88 (57)	65.0 [22-89]	1.8 [0.8-4.9]	Sepsis	25 mg/kg q24h	507	CL_{CR}	-	0.77 (59)	19.2 (39)	4.4 (17)	9.4 (44)	NONMEM
Lugo-Goytia [6]	42 (NA)	59±15	NA	Sepsis	7.5-30 mg/kg q8-q24h	NA	Catecholamines, CL_{CR}, PEEP	APACHE II	3.85 (41)	31.7 (29)	-	-	USC PACK
Joubert [7]	14 (NA)	52.7±20.2	-	Critically ill	600-1350 mg q24h	744	CL_{CR}	-	-	17.1 (22.2)	5.22 (104)	-	NONMEM
Romano [8]	134 (77)	53.0±16.4	-	Haematological	18.5±5.5 mg/kg q24h[♦]	3.2±1.9[♦]	AML diagnosis, CL_{CR}	Hypoalbuminemia, weight	No AML: 5.53 (29) AML: 6.63 (29)	Normoalbumin: 23.98 (26) Hypoalbumin: 31.17 (26)	-	-	NONMEM
Romano [9]	120 (73)	52.9±18.5	-	Critically ill	15.6±6.2 mg/kg q24h[♦]	4.2±2.7[♦]	CL_{CR}, trauma diagnosis	Sepsis diagnosis, weight	No trauma: 4.5 (28.2) Trauma: 5.5 (28.2)	No sepsis: 27.1 (23.2) Sepsis: 33.6 (23.2)	-	-	NONMEM
Tod [10]	57 (35)	51.0±16.0	NA	Haematological	7.5 mg/kg q12h or 20 mg/kg q24h	278	Age, creatinine, sex, weight	-	Male: 3.82 (21) Female: 3.40 (21)	8.92 (15)	4.43 (30)	11.4 (25)	NONMEM
Lugo [11]	73 (NA)	60.0±12.0[Ω] 57.8±8.0[†]	-	Sepsis	7.5-30 mg/kg q24h	NA	Cirrhosis	Cirrhosis	-	No cirrhosis: 31.0 (NA) Cirrhosis: 41.5 (NA)	-	-	USC PACK

Appendix 1. Summary of amikacin population pharmacokinetic models developed in adults (continued)

Reference	Population				Treatment and sampling		Covariates in final model		Estimated parameters ¶ (IIV, CV %)				Software
	N (male)	Age (years)*	Albumin (g/dL)*	Patients	Amikacin dose	Samples	CL	Vd	CL (L/h)	V_1 (L)	Q (L/h)	V_2 (L)	
Lugo [12]	30 (17)	50.0±15.0	2.4±0.6	Sepsis	7.5 mg/kg♦	NA	Catecholamines, CL_{CR}, PEEP	Albumin, oxygen extraction ratio, weight	3.6 (34)	32.0 (35)	-	-	PCNonlin
Debord [13]	40 (30)	51.8±18.2	-	Critically ill	2.2-31.4 mg/kg q24h	212	CL_{CR}	-	4.5 (69)	25.6 (28)	-	-	USC PACK
Maire [14]	50 (NA) 50 (NA)	62 (±NA) 80 (±NA)	- -	General medicine Geriatrics	NA NA	124 277	CL_{CR}	Weight	NONMEM: 2.74 (70) NPEM: 3.76 (46) NPML: 3.77 (57)	NONMEM: 19.6 (28) NPEM: 22.3 (33) NPML: 21.4 (36)	-	-	NONMEM USC PACK
Debord [15]	40 (NA)	51 [18-77]Δ	-	Critically ill	7.5 mg/kg q24h	7 (NA)✦	- -	- -	- -	0.4 L/kg (NA) 0.36 L/kg (NA)	- 0.013 (NA)Ψ L/kgh	- 1.08 (NA)Ψ L/kg	USC PACK USC PACK

AML, acute myeloblastic leukaemia; APACHE, Acute Physiology and Chronic Health Evaluation; CL, total clearance; CL_{CR}, creatinine clearance; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; IIV, inter-individual variability; NA, not available; $PaO_2/FiO2$, ratio between the partial pressure of arterial oxygen and the fraction inspired oxygen; PEEP, positive end-expiratory pressure; Q, intercompartmental clearance; Vd, volume of distribution; V_1 or V_2, volume of distribution of central and peripheral compartment, respectively; Weight, total bodyweight expressed in kilograms.

¶ Values expressed as mean.

* Values expressed as mean ± standard deviation or median [range].

Δ Values expressed as mean [range].

✦ Values expressed as mean ± standard deviation per patient.

Ω Patients without cirrhosis.

† Patients with cirrhosis.

♦ Dose interval adjusted according to pharmacokinetic dosing method.

Ψ Parameters calculated with the microconstant values provided in the population pharmacokinetic models: k_{12}, first-order transfer rate constant from the central compartment to the peripheral compartment; k_{21}, first-order transfer rate constant from the peripheral compartment to the central compartment; Kslope, renal component of the elimination rate constant. IIV of each microconstant available in the population pharmacokinetic models.

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IV. DISCUSIÓN

Los antibióticos aminoglucósidos continúan siendo ampliamente utilizados como opción de primera línea en el tratamiento de infecciones causadas por bacterias gram negativas multirresistentes. Amicacina, asociada a betalactámicos, sigue siendo una terapia antibiótica de gran utilidad en el tratamiento empírico de la sepsis en paciente crítico. En el tratamiento antibiótico, especialmente en sepsis, la rapidez con la que se alcanzan concentraciones adecuadas del antibiótico condiciona la respuesta clínica y microbiológica al tratamiento.

La sobredosificación, con los problemas de toxicidad asociados, y la infradosificación que puede conducir a fallo terapéutico y aparición de resistencias, aún están presentes en la terapéutica antibiótica. Realmente, el tratamiento médico definitivo de las enfermedades infecciosas es la administración del antimicrobiano más apropiado, entendiendo como tal no solo la selección del antibiótico sino también la dosificación adecuada desde la perspectiva farmacocinética y farmacodinámica (PKPD). No disponiendo de un parámetro clínico que asegure la idoneidad del tratamiento y la resolución de la infección, último objetivo del tratamiento, se utilizan parámetros PKPD subrogados de la eficacia terapéutica, como ya se comentó para amicacina.

La dosificación inicial de amicacina plantea un importante reto, pues una dosis no cumple las necesidades en todos los pacientes. Los aminoglucósidos, con un efecto concentración-dependiente y unos parámetros PKPD bien definidos, están sometidos a una elevada variabilidad farmacocinética inter e intra-individual que obliga a la adopción de estrategias personalizadas de dosificación. Como ejemplo cabe mencionar que la dosis requerida para alcanzar una concentración máxima de 60 mg/L puede variar entre 500 y 1500 mg, dependiendo de las características PK individuales del paciente. Ajustando los regímenes de dosificación de amicacina con el objetivo de alcanzar los parámetros PKPD definidos, es posible incrementar la probabilidad de alcanzar las concentraciones séricas y resultados terapéuticos deseados.

El carácter hidrofílico de los aminoglucósidos condiciona sus características PK, tales como la distribución y eliminación. Fundamentalmente se distribuyen en el líquido extracelular, presentan volúmenes de distribución relativamente pequeños y son excretados por vía renal, sujetos fundamentalmente a filtración glomerular. Esto se traduce en una importante

variabilidad farmacocinética interindividual, agravada por el hecho de que la propia situación clínica del paciente puede provocar cambios en el volumen de distribución (Vd) y en el aclaramiento (CL) renal del antibiótico. En determinados grupos de pacientes, ej. críticos o hematológicos, frecuentemente tratados con amicacina, se producen cambios fisiopatológicos asociados a importantes modificaciones en la farmacocinética del antibiótico que, desafortunadamente, no siempre son considerados en su dosificación. En sepsis se produce un incremento significativo del volumen de distribución de amicacina al que contribuyen distintos factores: fugas capilares, hipoalbuminemia, administración de grandes volúmenes de líquido por vía intravenosa o comorbilidades. Las modificaciones en la función renal del paciente que pueden incrementar o reducir el aclaramiento del antibiótico, junto con los cambios en el volumen de distribución, condicionan de forma significativa los requerimientos de dosificación de amicacina, tanto en la dosis como en el intervalo posológico. Especial importancia revisten los incrementos en el volumen de distribución con la consiguiente reducción de la concentración máxima. Con amicacina, cuyo efecto es concentración-dependiente, una reducción en la concentración máxima puede comprometer la eficacia de los tratamientos. Igual importancia revisten las modificaciones en la función renal del paciente, con repercusiones clínicas también significativas en su eficacia o toxicidad.

Las dosis empíricas o estandarizadas solamente son adecuadas en una proporción muy reducida de pacientes. El problema de la variabilidad farmacocinética únicamente puede abordarse desde las Estrategias de Dosificación de Precisión basadas en Modelos de predicción debidamente validados (EDPM). Para ello es necesario identificar todos los factores que condicionan la variabilidad y la magnitud del efecto, información que, plasmada en modelos poblacionales, nos permitirá individualizar la posología desde el inicio del tratamiento. Teniendo en cuenta que los cambios fisiopatológicos paralelos a la evolución de la enfermedad pueden dar lugar a modificaciones farmacocinéticas intra-individuales, solamente la monitorización sistemática de concentraciones séricas (TDM) del antibiótico durante el tratamiento podrá maximizar las probabilidades de éxito del mismo.

La cuantificación de la función renal del paciente es un pilar indispensable en la programación posológica de fármacos eliminados fundamentalmente por vía renal. Una estimación segura de la función renal del paciente resulta esencial para la óptima dosificación de medicamentos eliminados del organismo por esta vía. La sobreestimación de la función renal puede conducir a la administración de dosis elevadas y posiblemente tóxicas de estos fármacos, al contrario de la infraestimación que puede desembocar en una dosificación infraterapéutica y fallos del tratamiento.

Los aminoglucósidos, como amicacina, son completamente eliminados mediante filtración glomerular, es por ello que la tasa de filtración glomerular (TFG) del paciente controla su aclaramiento. Los ajustes posológicos adaptados a la función renal excretora resultan indispensables para estos medicamentos. Sin embargo, existe gran debate relacionado con la óptima metodología a utilizar en la dosificación de fármacos.

El gold-estandard para la valoración de la filtración glomerular se realiza mediante la cuantificación del aclaramiento plasmático de una sustancia exógena de referencia. Sin embargo, la complejidad, coste y dificultad para llevar a cabo este tipo de estudios, ha conducido al desarrollo de ecuaciones para la estimación del filtrado glomerular de forma rápida y segura en la práctica clínica. La más antigua y ampliamente utilizada durante décadas es la ecuación de Cockcroft-Gault (CG) generada en 1976, 20 años más tarde se desarrolló la ecuación denominada MDRD (Modification of Diet in Renal Disease). Ambas fueron obtenidas con datos de creatinina sérica cuantificada con una técnica no estandarizada, hecho que según algunos autores representa su principal limitación. En 2009 se desarrolló la ecuación CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) y en la última década se han publicado nuevas ecuaciones, como Lund-Malmö, que posteriormente fue revisada (rLM), BIS1 (Berlin Iniciative Study 1) y FAS (Full Age Spectrum). Todas ellas se desarrollaron en poblaciones específicas, siendo rLM y FAS las únicas que incluyeron pacientes de todas las edades (1).

La ecuación CG proporciona un estimado del aclaramiento de creatinina (eCLCr), subrogado de la TFG, y el resto de las ecuaciones proporcionan directamente la TFG. A efectos de comparación y clasificación de la insuficiencia renal, en la práctica clínica se utilizan

indistintamente ambos parámetros, siendo frecuente sustituir el eCLCr por la TFG. Numerosos estudios han comparado el comportamiento y resultados de estas ecuaciones en la valoración de la función renal del paciente, llegando todos ellos a resultados dispares entre las distintas fórmulas (1–3). Ello es atribuido en parte a las diferencias en los parámetros utilizados en el diseño de cada una de las fórmulas, incluida la técnica analítica para la determinación de la creatinina sérica.

A excepción de CG, todas las ecuaciones expresan la TFG normalizada para una superficie corporal (SC) de 1,73 m^2. En los estudios comparativos de fórmulas para la estimación de la TFG los resultados discrepantes se han atribuido en ocasiones al efecto de la normalización, especialmente si la población de estudio incluía pacientes con valores extremos de SC. Este es el motivo por el cual los resultados deberían expresarse adaptados a la SC real del paciente, lo que ha sido recomendado, entre otros, por la Agencia Europea del Medicamento (EMA) (4). La ecuación CG ha sido la utilizada tradicionalmente, sin embargo, con la aparición de las nuevas ecuaciones su uso está actualmente cuestionado (1,2). En el laboratorio clínico es frecuente que la concentración de creatinina sérica vaya automáticamente acompañada del valor de la TFG estimada (5,6). Aunque en años anteriores se indicaba la TFG estimada en función de la ecuación MDRD, en la actualidad se ha extendido la utilización de la fórmula CKD-EPI, informando del resultado normalizado para SC de 1,73 m^2 (6). La fórmula utilizada en el laboratorio para la estimación de la TFG no despierta gran interés en los destinatarios del resultado. Sin embargo, especialmente cuando esta información va a ser utilizada para la dosificación de fármacos, es necesario ser conscientes de la ecuación disponible y sus limitaciones para este uso.

De manera similar a la evaluación de la función renal, las ecuaciones de estimación de la TFG también han sido comparadas para su utilización en la dosificación de fármacos en distintos grupos de población (7–10). Más específicamente, disponemos de estudios de comparación de estas ecuaciones en la dosificación de antibióticos aminoglucósidos (11,12). Para este propósito, la ecuación de CG ha sido la más utilizada y es la recomendada por la FDA para los estudios farmacocinéticos en el desarrollo de fármacos, aunque también ha propuesto la ecuación MDRD

como alternativa (13). El argumento más frecuentemente utilizado en la recomendación de CG para la dosificación de fármacos es su seguridad, evitando la sobreestimación de la TFG a la que se encuentran sometidas las otras ecuaciones, con el riesgo de sobredosificación, especialmente en pacientes geriátricos y aquellos con insuficiencia renal (7,9). Sin embargo, estudios más recientes no recomiendan la utilización CG, siendo CKD-EPI la ecuación más aceptada (2).

En la individualización posológica de amicacina, excretada mediante filtración glomerular, la estimación segura de su aclaramiento resulta ser una herramienta de gestión terapéutica básica para la personalización de los tratamientos. Ante el debate existente en la literatura, hemos evaluado la utilidad y capacidad predictiva de las ecuaciones antes mencionadas para el aclaramiento de amicacina (14). Tratamos, por tanto, de conocer el mejor descriptor del aclaramiento de amicacina. Con un total de 566 datos de concentración obtenidos en la TDM habitual de amicacina en 198 pacientes, mediante la aplicación de un modelo poblacional no lineal de efectos mixtos, utilizando el programa NONMEM®, analizamos el efecto de las distintas ecuaciones en el aclaramiento de amicacina. La mayoría de los pacientes incluidos en el estudio presentaban hipoalbuminemia, siendo el 59% oncohematológicos y el 16% pacientes críticos con sepsis. La individualización posológica de amicacina habitualmente se realiza mediante la TDM y el control adaptado bayesiano utilizando modelos farmacocinéticos poblacionales (PopPK). Aunque disponemos de distintos modelos PopPK de amicacina, todos ellos están basados en la TFG (o CLCr) estimada mediante las ecuaciones más antiguas. Este estudio incorpora nuevas ecuaciones predictoras de la TFG para poder identificar aquella que mejor predice el aclaramiento de amicacina, siendo este el objetivo de este tipo de comparaciones en terapéutica. Mediante un análisis poblacional hemos identificado las ecuaciones CKD-EPI y Lund-Malmö revisada como aquellas que presentan mejor capacidad predictiva del aclaramiento de amicacina en la población general. Sin embargo, en pacientes con insuficiencia renal moderada o grave (ClCr < 60 mL/min) la ecuación CG con peso total es la que mayor precisión presenta, siendo la recomendada por nosotros en esta situación. Este resultado está de acuerdo con estudios previos que recomiendan la utilización de la ecuación CG en la dosificación de fármacos en pacientes geriátricos o pacientes con insuficiencia renal, para

evitar la sobredosificación a la que pueden conducir las otras ecuaciones disponibles (9,10). A su vez, otros estudios también habían advertido de la posible inferioridad de la ecuación CKD-EPI en el cálculo del aclaramiento de fármacos en pacientes con insuficiencia renal (2). Hasta donde conocemos, este es el primer estudio que evalúa diversas ecuaciones de estimación de la TFG para la predicción del aclaramiento de amicacina. Por otra parte, la ecuación Lund- Malmö revisada, que ha sido evaluada y recomendada para la estimación de la función renal, es analizada por primera vez desde el punto de vista de la dosificación terapéutica (15).

Recientemente, se han propuesto las EDPM para predecir la dosis óptima individualizada de un medicamento que alcanzaría objetivos predefinidos de exposición al fármaco (16). Para poner en práctica en nuestro entorno la estrategia EDPM, se ha planteado como segundo objetivo de la Tesis caracterizar la farmacocinética de amicacina en pacientes con hipoalbuminemia mediante una aproximación poblacional. El modelo se desarrolló con datos recogidos retrospectivamente de 215 pacientes adultos (mediana: 61 años; intervalo: 18–93 años) en tratamiento con este antibiótico en perfusión intravenosa (623 concentraciones plasmáticas de amicacina), administrado en el 70% de los casos a intervalos ≥ 24 horas. El 75% de los pacientes presentaban valores de albumina < 3,5 g/dL y función renal normal o insuficiencia renal moderada (mediana CKD-EPI: 98 mL/min; intervalo: 17–194 mL/min).

El modelo PopPK que mejor ha descrito la disposición de amicacina en nuestra población ha sido un modelo monocompartimental que considera en el aclaramiento la influencia de la función renal del paciente y el tratamiento concomitante con vancomicina y en el volumen de dsitribución la albuminemia y el peso del paciente (Ecuaciones 1 y 2). Tanto los parámetros de efectos fijos como aleatorios se estimaron con suficiente precisión y exactitud para permitir la simulación de distintos escenarios clínicos.

$$CL\ (L/h) = (0{,}525 + 4{,}78 \times CKD\text{-}EPI/98) \times 0{,}77^{vancomicina} \qquad \text{Ecuación 1}$$

$$Vd\ (L) = 26.3 \times (albúmina/2{,}9)^{-0.51} \times [1 + 0.006 \times (peso - 70)] \qquad \text{Ecuación 2}$$

Los parámetros medios estimados en nuestra población con el modelo propuesto, CL=5,3 L/h y V=26,3 L, son próximos a los descritos por otros autores en pacientes críticos (17). Valores de albumina por debajo del valor normal (3,5 g/dL) aumentarían el volumen de distribución, con la consecuente disminución de concentraciones plasmáticas de amicacina. Al ser amicacina un fármaco hidrofílico, el incremento del volumen de distribución está justificado por el incremento del agua extracelular, incluso con edemas generalizados, debido a la reducción de la presión oncótica secundaria a la hipoalbuminemia. La administración concomitante de vancomicina produce una disminución del 23% en el aclaramiento renal de amicacina según nuestro modelo. Esto concuerda con la elevación de la creatinina sérica y la nefrotoxidad asociada al tratamiento concomitante de vancomicina y aminoglucósidos.

Para la utilización clínica de un modelo de población es necesaria su previa validación. Por ello se planteó en el trabajo evaluar la capacidad descriptiva y predictiva del modelo poblacional desarrollado, mediante estrategias de validación interna y externa. La validación interna, mediante una técnica de replicación de muestra (1000 replicaciones), confirmó que el modelo es adecuado para describir la evolución temporal de las concentraciones plasmáticas de amicacina y su variabilidad en la población de estudio, estando todos los parámetros estimados dentro del intervalo de confianza del 95%. Para la validación externa se recogieron retrospectivamente datos de 79 pacientes adicionales (250 concentraciones plasmáticas de amicacina) que presentaron características demográficas y clínicas similares a la población de desarrollo del modelo. Similarmente a la validación interna, las concentraciones predichas con el modelo propuesto no presentaron diferencias estadísticamente significativas con las observadas en la población de validación.

En los últimos años ha aumentado el interés por la modelización con estrategias de regresión no lineal de efectos mixtos. La FDA considera que estos modelos, además de establecer recomendaciones para la individualización terapéutica, pueden guiar el desarrollo de fármacos, y facilitar la toma de decisiones por las agencias reguladoras (18). Pero como dice Hennig et al. (2020) en un trabajo recientemente publicado, hay pocos estudios que permitan la transferencia de estos conocimientos a la práctica clínica (19). La complejidad de este tipo de modelos hace

que sus resultados sean difíciles de interpretar, se necesite mucho tiempo y equipos multidisciplinares para su utilización e implantación en la práctica clínica.

En el caso de los tratamientos con amicacina, cuando el clínico se enfrenta a infecciones graves, es crucial asegurar una adecuada exposición al fármaco desde el inicio del tratamiento: máxima eficacia, con el menor riesgo de toxicidad y resistencia al antibiótico. Para ello, es necesario tener en cuenta los múltiples factores que influyen en la probabilidad de éxito del tratamiento. Hay que calcular la dosis necesaria para conseguir un balance adecuado de los índices de eficacia y toxicidad habitualmente utilizados para amicacina, considerando la susceptibilidad del patógeno: concentración máxima / concentración mínima inhibitoria (Cmax/CMI), tiempo que la concentración del antibiótico se mantiene superior a la CMI (%T>CMI), área bajo la curva de concentraciones-tiempo / CMI (ABC/CMI) y concentración mínima (Cmin). A su vez, ésta dosis dependerá de los parámetros clínicos y cinéticos del individuo y del régimen posológico que se vaya a utilizar. Las estrategias EDPM presentan la ventaja de combinar todos estos factores, permitiendo alcanzar los objetivos propuestos del tratamiento, pero debido a la dificultad para manejar toda esta información, es habitual que en la práctica clínica se adapten las recomendaciones generales de dosis sin una óptima individualización.

El siguiente objetivo planteado ha sido implementar el modelo desarrollado en una aplicación interactiva que facilite la toma de decisiones clínicas sobre individualización terapéutica de amicacina (AMKdose).

AMKdose permite identificar fácilmente y en tiempo reducido el régimen inicial de dosificación más adecuado para un paciente concreto. En primer lugar, introduciendo únicamente los datos de peso, albuminemia, comedicación con vancomicina y función renal del paciente, se obtiene una recomendación de la dosis mínima necesaria para alcanzar el valor objetivo de los índices de eficacia y seguridad. Los resultados se representan gráficamente de una forma muy intuitiva de manera que de un solo vistazo, es posible conocer las concentraciones esperadas (con su probabilidad de éxito asociada) y los valores de los tres índices de eficacia en condiciones de tratamiento estándar (1 hora de infusión e intervalo de dosificación de 24 horas). Posteriormente, es posible modificar el objetivo de los índices de eficacia del tratamiento y/o el

régimen posológico, para adecuarlo a la situación específica en la que se va a administrar el fármaco. Toda esta información, así como los parámetros cinéticos del paciente se pueden extraer en un informe editable, diseñado para su archivo en la historia clínica electrónica.

Igualmente, la aplicación permite al clínico evaluar la probabilidad de éxito del tratamiento para diferentes regímenes de dosificación, situaciones clínicas del paciente y susceptibilidad del patógeno (CMI). Para la dosis seleccionada, se puede simular la probabilidad de alcanzar el 90% del valor objetivo de los tres índices de eficacia evaluados considerando diferentes CMI. Esto permite comparar distintos escenarios en situaciones de incertidumbre del patógeno causante de la infección. Por último, se puede ver la evolución de los parámetros de eficacia y la probabilidad de alcanzarlos con una determinada dosis, cuando varían las principales covariables del modelo (peso y albúmina).

Partiendo de la capacidad de nuestro modelo de predecir adecuadamente la evolución de las concentraciones de amicacina en diferentes situaciones, se ha procedido a la comparación de las recomendaciones de dosificación de amicacina internacionales más utilizadas, elaboradas con un amplio consenso: European Committee on Antimicrobial Susceptibility Testing guidance 2020 (EUCAST), Guía terapéutica antimicrobiana Mensa 2020, Aminoglycoside dosing in adults guideline of State of Queensland 2018, The Sanford Guide to Antimicrobial Therapy 2019 y UpToDate® 2020.

Utilizando el modelo PopPK desarrollado y mediante simulaciones de Monte Carlo, se ha calculado la probabilidad de alcanzar en el estado de equilibrio los índices de eficacia (Cmax/CMI=10 y %T>CMI=60) y toxicidad (Cmin < 4 mg/L) de cada recomendación de dosificación de amicacina para 1000 sujetos de 70 kg con diferentes grados de función renal y valores de albúmina sérica. La mayoría de las recomendaciones de dosificación evaluadas adaptan sus recomendaciones a la función renal del paciente, pero ninguna consigue los objetivos de eficacia y seguridad en todas las situaciones clínicas estudiadas. La guía Sanford no consigue alcanzar los índices de eficacia definidos en este estudio en ningún caso, mientras que la recomendación de EUCAST, iniciando el tratamiento con la misma dosis en todos los pacientes y posteriormente realizando TDM, consigue eficacia, pero con una alta probabilidad

de toxicidad en pacientes con insuficiencia renal, aumentando el riesgo en situaciones de hipoalbuminemia. Un resultado parecido se obtiene con las recomendaciones de Queensland que reducen las dosis al disminuir la función renal, la principal diferencia se encuentra en pacientes con filtración glomerular de 40-60 mL/min que incrementa el intervalo de dosificación a 36 horas consiguiendo reducir la probabilidad de toxicidad a costa de no alcanzar el objetivo de %T>CMI=60. Una mayor reducción de dosis para pacientes con insuficiencia renal recomienda la guía Mensa, lo que compromete la eficacia en todas las situaciones. Las bajas dosis recomendadas por UpToDate en pacientes con insuficiencia renal grave no consiguen alcanzar el índice Cmax/CMI deseado; lo alcanzan para mayores tasas de filtración glomerular, pero solo cuando los pacientes no presentan hipoalbuminemia. En pacientes que presentan hipoalbuminemia, el aumento del volumen de distribución reduce aún más las probabilidades de alcanzar valores eficaces de concentración máxima con las recomendaciones de las guías clínicas. Queda claramente de manifiesto la escasa utilidad de los regímenes de dosificación estándar para amicacina y la necesidad de individualizar las recomendaciones según la situación clínica del paciente.

Evaluar la influencia que puede tener la concentración sérica de albúmina y otros factores como el peso y la función renal en los requerimientos de dosificación inicial de amicacina, se ha planteado como último objetivo del trabajo. Basados en el modelo poblacional propuesto, se ha desarrollado una herramienta de construcción de nomogramas interactivos, mediante la aplicación AMKnom, que muestra los cambios de dosificación necesarios para alcanzar el éxito del tratamiento (índices de eficacia y seguridad) según los distintos valores de TFG, peso y albúmina que puede presentar un paciente. Hasta ahora estaba claramente aceptado dosificar amicacina en función del peso del paciente (utilizando diferentes medidas) y del grado de función renal, expresado habitualmente como TFG. Modificando los valores de entrada en los nomogramas, se puede comprobar cómo las necesidades de dosificación inicial de amicacina son más dependientes de la albúmina sérica que de los otros dos factores mencionados. Realmente, el efecto de la hipoalbuminemia en los requerimientos de dosificación de amicacina constituye una de las mayores aportaciones de esta Tesis.

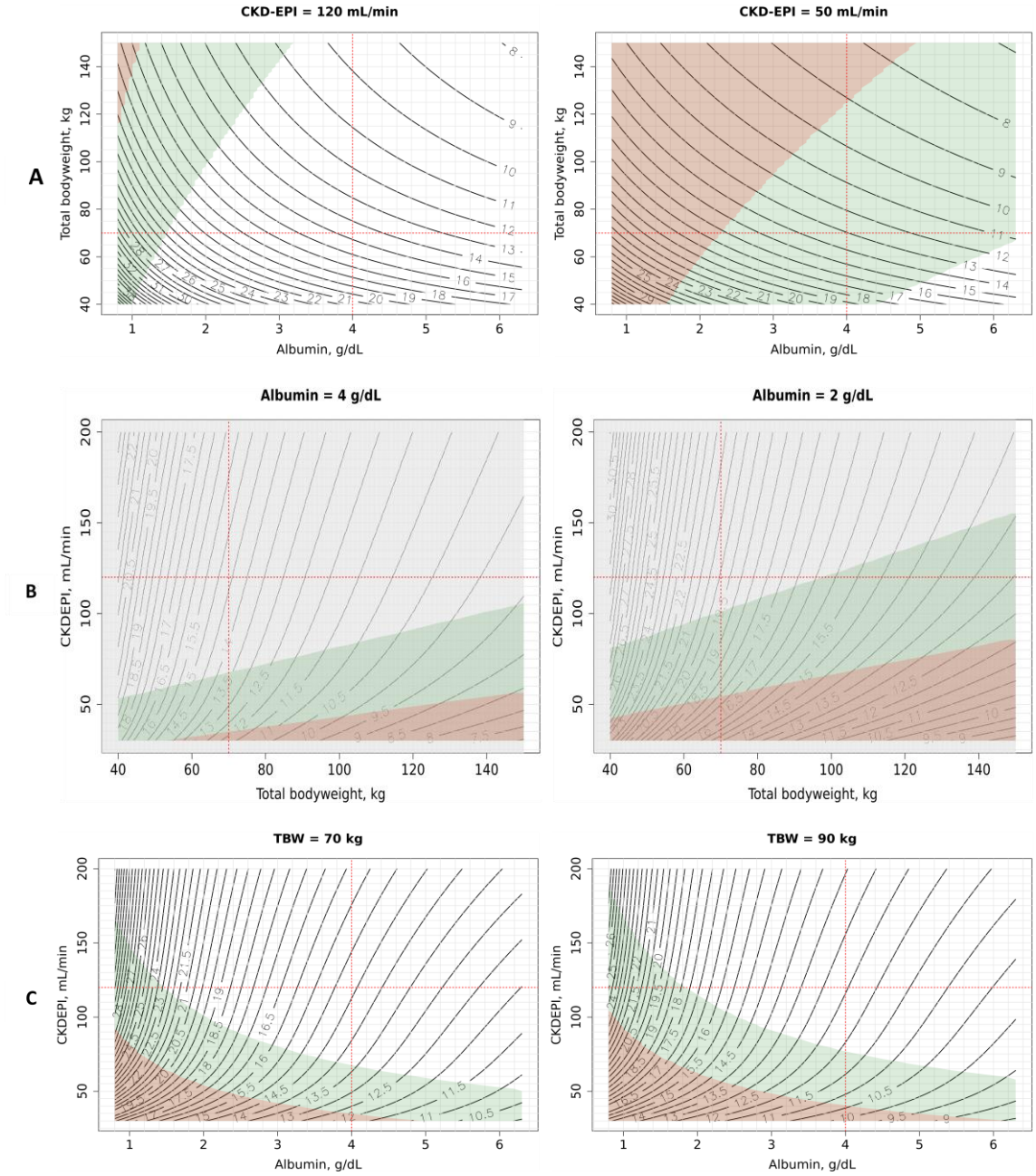

Figura 1. Dosis de amicacina (mg/kg) administrada cada 24 horas, en infusión de 1 hora y ausencia de tratamiento concomitante con vancomicina, necesaria para alcanzar un índice Cmax/CMI=10 en un paciente con diferente función renal (CKD-EPI) (A), albúmina sérica (B) y peso (C), calculada con AMKnom. Título de cada plot, valor de la variable fija en la simulación; líneas discontinuas rojas, valor de las variables no fijas en un paciente típico (70 kg de peso, albúmina de 4 g/dL, CKD-EPI=120 mL/min). Áreas verdes y rojas, escenarios donde las concentraciones por encima de la CMI representan más del 60% del intervalo de dosificación (eficacia) y las concentraciones mínimas son superiores a 4mg/L (toxicidad), respectivamente.

En un paciente normoalbuminémico, se puede recomendar una dosis que sea efectiva y segura con los datos del peso y la función renal, sin embargo, si mantenemos la dosis en este mismo paciente en situación de hipoalbuminemia no se alcanzarían los objetivos del tratamiento

deseados. El impacto de los cambios de albúmina sérica sobre las necesidades de dosificación es mucho mayor que el de los cambios en el peso o en la función renal.

En la Figura 1 se puede observar como la dosis necesaria para alcanzar determinados índices de eficacia en un paciente de 70 kg con función renal normal (CKD-EPI=120 mL/min) y albúmina sérica de 4 g/dL, debe reducirse únicamente un 10% (desde 14,5 mg/Kg a 13,0 mg/Kg) cuando su función renal se reduce aproximadamente a la mitad. En cambio, si la albúmina sérica se reduce a la mitad sería necesario aumentar la dosis de amicacina a 20 mg/kg (36%). Igualmente, aumentando 20 kg el peso del paciente habría que reducir la dosis un 14%.

A la vista de estos resultados, podemos afirmar que la hipoalbuminemia es el factor clínico con mayor peso en la farmacocinética de amicacina, por lo que consideramos que las guías clínicas deberían incluir la influencia de la albuminemia en las recomendaciones de dosificación.

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V. CONCLUSIONES

1. Mediante análisis fármaco-estadístico se ha demostrado que entre distintas ecuaciones de las utilizadas para la estimación de la función renal, las ecuaciones Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) y Lund-Malmö revisada (rLM) son las que poseen mayor capacidad predictiva del aclaramiento de amicacina en el conjunto de la población estudiada, justificando su uso en el ajuste de regímenes de dosificación de fármacos eliminados principalmente por vía renal.
2. En pacientes con insuficiencia renal grave la ecuación de Cockcroft-Gault con peso corporal total mostró una mayor precisión que el resto de ecuaciones comparadas, por lo que en esta situación clínica, podría ser el método de elección para la programación de regímenes posológicos de fármacos eliminados a través del riñón.
3. Se ha desarrollado y validado, interna y externamente, un modelo farmacocinético poblacional de amicacina utilizando una metodología de efectos mixtos no lineales con el programa NONMEM®, en el que la albúmina sérica, el peso corporal total, el filtrado glomerular estimado mediante la ecuación CKD-EPI y el tratamiento concomitante con vancomicina fueron los factores con un impacto significativo en su comportamiento farmacocinético.
4. La hipoalbuminemia produce un incremento significativo del volumen de distribución de amicacina, lo que en regímenes de dosificación con ampliación del intervalo ($\geq$ 24 horas) implica requerimientos de dosis superiores a los necesarios para alcanzar los objetivos PKPD terapéuticos en situaciones de normoalbuminemia.
5. Se ha desarrollado una aplicación interactiva (AMKdose), basada en el modelo farmacocinético poblacional elaborado, y disponible de manera gratuita *online*, para la dosificación inicial de amicacina. Esta aplicación puede resultar de gran utilidad en la individualización posológica inicial de amicacina favoreciendo el éxito del tratamiento sin necesidad de disponer de información farmacocinética individual.
6. Existen importantes diferencias entre las distintas recomendaciones internacionales de dosificación de amicacina. Aunque éstas resultan de gran utilidad en grupos de población

con características similares, la dosificación basada en nomogramas adaptados a las características individuales del paciente puede ofrecer mayor precisión.

7. Las recomendaciones posológicas del European Committee on Antimicrobial Susceptibility Testing (EUCAST) y Queensland Health System presentan una alta probabilidad de alcanzar los parámetros PKPD de eficacia de amicacina. Sin embargo, en pacientes con insuficiencia renal podrían estar asociadas a toxicidad, aumentando el riesgo en situación de hipoalbuminemia. Por el contrario, las dosis recomendadas en la Guía Sanford y UpToDate ofrecen en la mayoría de los pacientes escaso riesgo de toxicidad, pero también baja probabilidad de alcanzar la eficacia terapéutica deseada.
8. Se ha desarrollado una aplicación interactiva (AMKnom), disponible de manera gratuita online, basada en criterios PKPD y características del paciente, muy intuitiva y de gran utilidad para la elaboración de nomogramas y optimización de regímenes posológicos de amicacina individualizados.
9. La magnitud del efecto de la hipoalbuminemia en la farmacocinética de amicacina sugiere su consideración en las guías de dosificación inicial de este antibiótico y posiblemente de todos los aminoglucósidos.