UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE MEDICINA

TESIS DOCTORAL

Epidemiología y características clínicas de las infecciones por bacterias multirresistentes en pediatría

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

David Aguilera Alonso

Directores

Jesús Saavedra Lozano
Luis Escosa García

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Agradecimientos

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Listado de publicaciones

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Esta tesis doctoral se presenta como un compendio de las siguientes publicaciones:

I. Aguilera-Alonso D, Escosa-García L, Saavedra-Lozano J, Cercenado E, Baquero-Artigao F. Carbapenem-Resistant Gram-Negative Bacterial Infections in Children. Antimicrob Agents Chemother. 2020 Feb 21;64(3):e02183-19.

II. Aguilera-Alonso D, Kirchschläger Nieto S, Ara Montojo MF, et al. Staphylococcus aureus Community-acquired Pneumonia in Children After 13-Valent Pneumococcal Vaccination (2008-2018): Epidemiology, Clinical Characteristics and Outcomes. Pediatr Infect Dis J. 2022 May 1;41(5):e235-e242.

III. Aguilera-Alonso D, Epalza C, Sanz-Santaeufemia FJ, et al. Antibiotic Prescribing in Children Hospitalized With COVID-19 and Multisystem Inflammatory Syndrome in Spain: Prevalence, Trends, and Associated Factors. J Pediatric Infect Dis Soc. 2022 May 30;11(5):225-228.

IV. Aguilera-Alonso D, Escosa-García L, Epalza C, et al. Antibiotic resistance in bloodstream isolates from high-complexity paediatric units in Madrid, Spain: 2013-2021. J Hosp Infect. 2023 Jun 16;139:33-43.

V. Pseudomonas aeruginosa bloodstream infections in children and adolescents: risk factors associated with carbapenem resistance and mortality. En revision en Infection.

Otras publicaciones recientes del doctorando relacionadas con la materia:

i. Pintado V, Ruiz-Garbajosa P, Aguilera-Alonso D, et al. Executive summary of the consensus document of the Spanish Society of Infectious Diseases

and Clinical Microbiology (SEIMC) on the diagnosis and antimicrobial treatment of infections due to carbapenem-resistant Gram-negative bacteria. Enferm Infecc Microbiol Clin (Engl Ed). 2022 Dec 13:S2529-993X(22)00281-7.

ii. Goycochea-Valdivia WA, Melendo Pérez S, Aguilera-Alonso D, et al. Position statement of the Spanish Society of Paediatric Infectious Diseases on the introduction, implementation and assessment of antimicrobial stewardship programmes in paediatric hospitals. An Pediatr (Engl Ed). 2022 Nov;97(5):351.e1-351.e12.

iii. Aguilera-Alonso D, Cantón R, Giske CG, et al. Searching high and low: call for a joint ESPID-EUCAST survey on dosage of antibacterial agents in children-part one. Clin Microbiol Infect. 2022 Apr;28(4):625-627.

iv. Aguilera-Alonso D, Martínez Campos L, Fernández Llamazares CM, Calvo C, Baquero-Artigao F. New antibiotic susceptibility testing definitions: «I» no longer means intermediate susceptibility. An Pediatr (Engl Ed). 2022 Feb;96(2):157-158.

v. De La Villa S, Sánchez-Carrillo C, Sánchez-Martínez C, et al. Clinical impact of time to results from the microbiology laboratory in bloodstream infections caused by carbapenemase-producing Enterobacterales (TIME-CPE STUDY). J Antimicrob Chemother. 2023 Jun 16:dkad188.

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BGN	Bacilos gramnegativos
BLEE	β-lactamasas de espectro extendido
BMR	Bacterias multirresistentes
CLSI	Clinical Laboratory Standards Institute
CMI	Concentración mínima inhibitoria
DTR	Resistencia de difícil tratamiento (*difficult-to-treat resistance*).
EARS-Net	The European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EE.UU.	Estados Unidos
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	*Food and Drug Administration* de EE.UU.
IC	Intervalo de confianza
IDSA	Infectious Disease Society of America
IRT	Inhibitor-resistant TEM
ITU	Infecciones del tracto urinario
IPPB	Infecciones de piel y partes blandas
IMP	Active-on-imipenem
IOA	Infecciones osteoarticulares
KPC	*Klebsiella pneumoniae* carbapenemase
MBL	Metalo-β-lactamasas
MDR	Multirresistente
MIS-C	Síndrome inflamatorio multisistémico relacionado con el SARS-CoV-2
NAC	Neumonías adquiridas en la comunidad
NDM	New Delhi metallo-β-lactamase
OMS	Organización Mundial de la Salud
OR	Odds ratio
ORa	Odds ratio ajustado
PDR	Panrresistente
PRAN	Plan Nacional Resistencia Antibióticos
PROA	Programas de Optimización del uso de Antimicrobianos
RAN	Resistencia de alto nivel
RC	Resistente a carbapenemes

SARM	*Staphylococcus aureus* resistente a meticilina
SASM	*Staphylococcus aureus* sensible a meticilina
SEIMC	Sociedad Española de Infectología y Microbiología Clínica
SNC	Sistema nervioso central
UCIP	Unidad de cuidados intensivos pediátricos
VIM	Verona integron-mediated metallo-β-lactamase.
XDR	Extremadamente resistente

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Resumen

Introducción

La resistencia a antimicrobianos supone actualmente uno de los principales problemas de salud pública. La incidencia de infecciones por bacterias multirresistentes (BMR) se ha incrementado en las últimas décadas de forma significativa, habiendo sido recientemente incluidas por la Organización Mundial de la Salud (OMS) dentro de las diez amenazas para la salud global. Las infecciones por BMR presentan un peor pronóstico debido al retraso del inicio de la antibioterapia adecuada y la necesidad de antibióticos alternativos, menos efectivos y con peor perfil de toxicidad. Mientras que la epidemiología de estas infecciones en adultos ha sido ampliamente descrita, la evidencia científica en pediatría es menor.

Objetivos

Como objetivo principal se estableció conocer la epidemiología reciente de las infecciones por BMR en pediatría, su perfil clínico y microbiológico, así como los determinantes asociados con su desarrollo.

Material y métodos

Los trabajos que componen esta tesis presentan diferentes diseños con el propósito de dar respuesta al objetivo planteado. Se realizó, en primer lugar, una revisión sobre las infecciones por bacilos gramnegativos (BGN) resistentes a carbapenemes en niños, incluyendo una revisión de los artículos publicados hasta la fecha. El estudio sobre neumonías adquiridas en la comunidad (NAC) por *Staphylococcus aureus* incluyó niños menores de 17 años hospitalizados entre 2008 y 2018 por NAC bacteriana en 5 hospitales terciarios de España. Se realizó un análisis descriptivo y se compararon los casos producidos por *S. aureus* según la sensibilidad a meticilina y con una muestra de casos producidos por *S. pneumoniae*. El estudio sobre consumo de

antibióticos durante los primeros meses de la pandemia de COVID-19, como determinante de adquisición de resistencias a antibióticos, incluyó los pacientes < 18 años hospitalizados desde el 1 de marzo de 2020 hasta el 31 de marzo de 2021, con infección por SARS-CoV-2 confirmada o que cumplieron los criterios de la OMS de síndrome inflamatorio multisistémico relacionado con el SARS-CoV-2 (MIS-C) dentro de la cohorte nacional EPICO-AEP, que incluye 76 hospitales. El estudio sobre bacteriemias en unidades de alta complejidad incluyó los aislamientos en hemocultivo de pacientes <18 años ingresados en las unidades de cuidados intensivos pediátricos (UCIP), neonatología y oncología-hematología entre 2013 y 2021. Se compararon los datos demográficos, la susceptibilidad antibiótica y los mecanismos de resistencia entre dos períodos (2013-2017 y 2017-2021). El estudio sobre bacteriemias por *Pseudomonas aeruginosa* incluyó los pacientes <20 años con esta infección en cuatro hospitales terciarios de Madrid durante 2010-2020. Los factores de riesgo de presentar una bacteriemia por *P. aeruginosa* resistente a carbapenemes y la mortalidad a los 30 días se evaluaron mediante un modelo de regresión logística multivariado.

Resultados

En la revisión sobre infecciones por BGN resistentes a carbapenemes encontramos múltiples factores de riesgo de presentar una infección o colonización por estos microorganismos, como la exposición previa a antibióticos, el uso de dispositivos médicos, la estancia en UCIP, cirugía previa y la hospitalización prolongada. En el estudio sobre NAC por *S. aureus* se objetivó una prevalencia de resistencia a meticilina del 26,5%, manteniéndose estable durante el periodo del estudio. El 50% de los casos con NAC por *S. aureus* tuvieron alguna complicación pulmonar y el 62% requirieron ingreso en UCIP, sin objetivarse diferencias significativas de la gravedad clínica entre los casos producidos por *S. aureus* sensible a meticilina y los producidos por *S. aureus* resistente a meticilina (SARM), siendo más frecuente el antecedente de patología médica crónica en los casos producidos por SARM. En el estudio sobre prescripción de antibióticos en niños ingresados con infección por SARS-CoV-2 o MIS-C se evidenció un consumo muy elevado de antibióticos en nuestro estudio, recibiendo un 54,2% de los pacientes uno o más antibióticos sistémicos. Durante el periodo del estudio se objetivó una disminución

de la prescripción de antibióticos en los pacientes con COVID-19. En el estudio sobre bacteriemias en pacientes ingresados en unidades de alta complejidad se evidenció una mayor prevalencia de resistencias en los aislamientos de Enterobacterales procedentes de pacientes ingresados en UCIP. Se observó, además, un incremento en la prevalencia de resistencia a cefalosporinas de espectro extendido, fluoroquinolonas y carbapenemes en Enterobacterales durante el periodo del estudio. En el estudio sobre bacteriemias por *P. aeruginosa* se objetivó una prevalencia elevada (29,8%) pero estable a lo largo de los años de resistencia a carbapenemes. La resistencia a carbapenemes se asoció con el tratamiento con carbapenemes en el mes anterior y el trasplante de órgano sólido. La mortalidad a 30 días fue del 23,2%, asociándose ésta con la necesidad de ventilación mecánica, sepsis al diagnóstico, una terapia antibiótica empírica inadecuada, siendo el control de la fuente un factor protector.

Conclusiones

Las NAC por *S. aureus* en niños en la Comunidad de Madrid presentan una elevada prevalencia de resistencia a meticilina, con una tendencia estable a lo largo de los últimos años, sin objetivarse mayor gravedad en NAC producidas por SARM. Durante los primeros meses de la pandemia de SARS-CoV-2, en niños hospitalizados en España con COVID-19 o MIS-C se objetivó una elevada prescripción de antibióticos. En bacteriemias en pacientes pediátricos ingresados en unidades de alta complejidad se evidenció una elevada prevalencia de resistencia a antibióticos, siendo de particular preocupación la tendencia creciente en la prevalencia de resistencia en Enterobacterales. Se observó una prevalencia elevada de resistencia a carbapenemes en las bacteriemias por *P. aeruginosa* en niños, lo que conduce a una alta mortalidad, asociándose el tratamiento empírico inadecuado y la sepsis con la mortalidad.

Abstract

Introduction

Antimicrobial resistance is currently one of the major public health issues. The incidence of infections caused by multidrug-resistant bacteria (MDR) has significantly increased in recent decades, recently being included by the World Health Organization (WHO) as one of the top ten threats to global health. Infections caused by MDR bacteria have a worse prognosis due to the delayed onset of appropriate antibiotic therapy and the need for alternative, less effective, and more toxic antibiotics. While the epidemiology of these infections in adults has been extensively described, the scientific evidence in pediatrics is limited.

Aims

The main objective was to understand the recent epidemiology of MDR infections in pediatrics, their clinical and microbiological profile, as well as the determinants associated with their development.

Methods

The studies that make up this thesis have different designs with the purpose of addressing the stated objective. First, a review was conducted on infections by carbapenem-resistant gram-negative bacilli (GNB) in children, including a review of articles published to date. The study on community-acquired pneumonia (CAP) caused by *Staphylococcus aureus* included children under the age of 17 hospitalized for bacterial CAP in 5 tertiary hospitals in Spain between 2008 and 2018. A descriptive analysis was performed and the cases caused by S. aureus were compared according to sensitivity to methicillin and with a sample of cases caused by S. pneumoniae. The study on antibiotic consumption during the first months of the COVID-19 pandemic, as a determinant of the acquisition of antibiotic resistance, included patients under 18 years

of age hospitalized from March 1, 2020, to March 31, 2021, with confirmed SARS-CoV-2 infection or who met the WHO criteria for multisystem inflammatory syndrome related to SARS-CoV-2 (MIS-C) within the national cohort EPICO-AEP, which includes 76 hospitals. The study on bloodstream infections (BSIs) in high-complexity units included blood culture isolates from patients under 18 years of age admitted to pediatric intensive care units (PICU), neonatology, and oncology-hematology units between 2013 and 2021. Demographic data, antibiotic susceptibility, and resistance mechanisms were compared between two periods (2013-2017 and 2017-2021). The study on *Pseudomonas aeruginosa* BSIs included patients under 20 years with this infection in four tertiary hospitals in Madrid during 2010-2020. Risk factors for carbapenem-resistant *P. aeruginosa* BSI and 30-day mortality were evaluated using a multivariate logistic regression model.

Results

In the review of infections with carbapenem-resistant gram-negative bacteria BSI, we found multiple risk factors for developing an infection or colonization by these microorganisms, such as prior antibiotic exposure, the use of medical devices, stay in the PICU, prior surgery, and prolonged hospitalization. In the study on CAP caused by *S. aureus*, a methicillin resistance prevalence of 26.5% was observed, remaining stable during the study period. 50% of the cases with *S. aureus* CAP had some pulmonary complications, and 62% required admission to the PICU, with no significant differences in clinical severity between cases caused by methicillin-sensitive *S. aureus* and cases caused by methicillin-resistant *S. aureus* (MRSA). Chronic medical conditions were more frequent in cases caused by MRSA. In the study on antibiotic prescription in children admitted with SARS-CoV-2 infection or MIS-C, a very high antibiotic consumption was evident in our study, with 54.2% of patients receiving one or more systemic antibiotics. There was a decrease in antibiotic prescription during the study period for patients with COVID-19. In the study on BSIs in patients admitted to high-complexity units, a higher prevalence of resistance was observed in isolates of Enterobacterales from patients admitted to the PICU. Furthermore, there was an increase in the prevalence of resistance to extended-spectrum cephalosporins, fluoroquinolones, and carbapenems

in Enterobacterales during the study period. In the study on *P. aeruginosa* BSIs, a high but stable prevalence (29.8%) of carbapenem resistance was observed over the years. Carbapenem resistance was associated with prior carbapenem treatment and solid organ transplantation. The 30-day mortality rate was 23.2%, and it was associated with the need for mechanical ventilation, sepsis at diagnosis, inadequate empirical antibiotic therapy, with source control being a protective factor.

Conclusions

CAP caused by *S. aureus* in children in the Community of Madrid shows a high prevalence of methicillin resistance, with a stable trend over the past few years, and no significant increase in severity observed in CAP cases caused by MRSA. During the early months of the SARS-CoV-2 pandemic, a high rate of antibiotic prescription was observed in children hospitalized in Spain with COVID-19 or MIS-C. In BSIs in pediatric patients admitted to high-complexity units, a high prevalence of antibiotic resistance was evident, with particular concern about the increasing trend in resistance prevalence in Enterobacterales. A high prevalence of carbapenem resistance was observed in BSIs caused by *P. aeruginosa* in children, leading to high mortality, with inadequate empirical treatment and sepsis being associated with mortality.

Introducción

“Existe el peligro de que un hombre ignorante pueda fácilmente aplicarse una dosis insuficiente de antibiótico y, al exponer a los microbios a una cantidad no letal del medicamento, los haga resistentes”.

Alexander Fleming, discurso al recibir el Premio Nobel, 1945

1. Infecciones por bacterias multirresistentes

1.1. Magnitud sanitaria de las resistencias a antimicrobianos

La resistencia a antimicrobianos supone actualmente uno de los principales problemas de salud pública[1]. La aprobación de nuevos antibióticos ha estado asociada, conforme su uso se ha extendido, al incremento de resistencias frente a los mismos. Así, por ejemplo, la actividad de penicilina frente a *Staphylococcus aureus*, comercializada en 1942, disminuyó significativamente a los pocos años, dejando de ser el tratamiento de elección de este microorganismo en la actualidad[2].

La incidencia de infecciones por bacterias multirresistentes (BMR) se ha incrementado en las últimas décadas de forma significativa, habiendo sido recientemente incluidas por la Organización Mundial de la Salud (OMS) dentro de las diez amenazas para la salud global[3]. A nivel internacional, se estima que en 2019 ocurrieron alrededor de 5 millones de muertes asociadas a BMR[4]. En ese mismo año, se estimó que en Europa 541.000 muertes estuvieron asociadas a BMR, habiendo sido el mayor número de ellas relacionadas con bacteriemias (195.000 muertes)[5]. En este mismo estudio, por orden decreciente de mortalidad, los principales microorganismos implicados fueron *Escherichia coli*, *S. aureus*, *Klebsiella pneumoniae* y *Pseudomonas aeruginosa*. Otro estudio realizado en España estimó que unas 35.400 muertes causadas por BMR ocurrieron en 2018 [6].

Las infecciones por BMR son particularmente importantes en el entorno sanitario. Sin embargo, cada vez se observa con mayor frecuencia su circulación en la comunidad, como ocurre con los Enterobacterales productores de β-lactamasas de espectro extendido (BLEE)[7]. Existe una importante variabilidad epidemiológica según la región analizada, con distintas distribuciones de los diferentes microorganismos, así como de los mecanismos de resistencia[8–11]. Además, generalmente la epidemiología de las resistencias en adultos difiere significativamente de la observada en niños[12]. Sin embargo, la mayoría de los datos publicados hasta la fecha están centrados en adultos

o no diferencian por grupos de edad. Esto supone, en muchas ocasiones, importantes limitaciones a la hora de establecer recomendaciones en el paciente pediátrico.

La OMS estableció en el año 2017 un listado de bacterias prioritarias para guiar la investigación y desarrollo de nuevos antibióticos[3]. Clasifica los diferentes microorganismos y sus mecanismos de resistencia en tres grupos, según el grado de prioridad:

- Prioridad 1: prioridad crítica. Incluye:
  - *Acinetobacter baumannii* resistente a carbapenemes.
  - *P. aeruginosa* resistente a carbapenemes.
  - Enterobacterales resistentes a carbapenemes o resistentes a cefalosporinas de tercera generación.
- Prioridad 2: prioridad alta. Incluye:
  - *Enterococcus faecium* resistente a vancomicina.
  - *S. aureus* resistente a meticilina (SARM) o resistente a vancomicina.
  - *Helicobacter pylori* resistente a claritromicina.
  - *Campylobacter* spp. resistente a fluoroquinolonas.
  - *Neisseria gonorrhoeae* resistente a cefalosporinas de tercera generación o a fluoroquinolonas.
- Prioridad 3: prioridad media. Incluye:
  - *Streptococcus pneumoniae* no sensible a penicilina.
  - *Haemophilus influenzae* resistente a ampicilina.
  - *Shigella* spp. resistente a fluoroquinolonas.

1.2. Definiciones de multirresistencia a antibióticos

Con el objetivo de homogeneizar las definiciones, Magiorakos propuso la definición de BMR, considerando así a aquellos aislamientos que presentaban resistencia a al menos un antibiótico de tres o más clases de antibióticos[13]. Esta definición se ha seguido en multitud de estudios[14,15]. Sin embargo, la elevada variabilidad en la lista de antibióticos evaluados en cada estudio supone una gran

heterogeneidad en la propia definición utilizada[16]. Además, en muchas ocasiones, la resistencia a diferentes antibióticos considerados de segunda línea no supone un empeoramiento del pronóstico de la infección. Por todo esto, en 2018 se propuso la definición de resistencia de difícil tratamiento (DTR, por sus siglas en inglés *Difficult-to-treat resistance*) en los aislamientos de bacilos gramnegativos[17].

Otras definiciones propuestas para evaluar la epidemiología de estas infecciones son: bacterias extremadamente resistentes (XDR, por sus siglas en inglés), considerándose a aquéllas que son resistentes a al menos un antibiótico de todas las clases de antibióticos, con la excepción de dos o menos clases, y bacterias panresistentes (PDR, por sus siglas en inglés) a aquéllas que son resistentes a todos los antibióticos[13]. Se define como DTR a la resistencia a todos los antibióticos de elección frente a estos microorganismos (β-lactámicos, excluyendo los recientemente aprobados, y fluoroquinolonas). En la Figura 1 se pueden ver las diferentes definiciones propuestas representadas de forma gráfica.

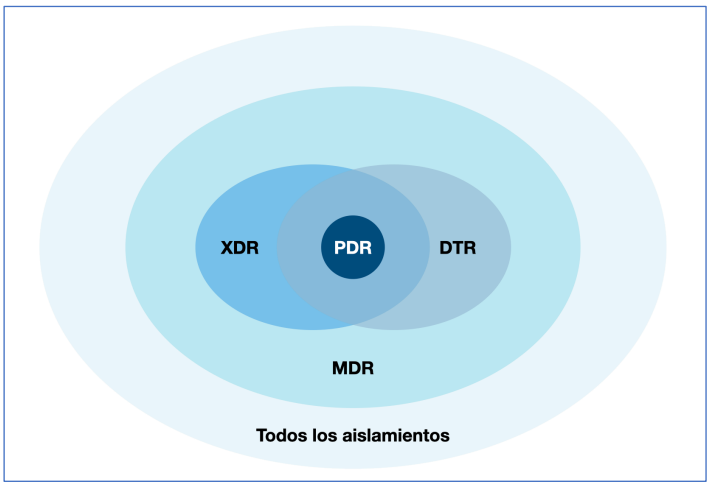

Figura 1. Representación gráfica de las diferentes definiciones de resistencia propuestas. Adaptada de Kadri S, 2018[17]. DTR, resistencia de difícil tratamiento; MDR, multirresistente; PDR, panrresistente; XDR, extremadamente resistente.

Otros elementos de variabilidad al analizar la diferente epidemiología entre países son los diferentes criterios utilizados para evaluar la sensibilidad de los aislamientos, siendo los más empleados en la actualidad los recomendados por EUCAST (European Committee on Antimicrobial Susceptibility Testing)[18], de mayor uso en

Europa, y por CLSI (Clinical Laboratory Standards Institute)[19], de uso extendido en el resto de los continentes. Además, la reciente definición de sensible con exposición incrementada, que incluiría muchos aislamientos previamente clasificados como de sensibilidad intermedia, e incluso como no sensibles a nivel de muchas clasificaciones, ha condicionado una mayor dificultad a la hora de establecer comparaciones[20].

1.3. Mortalidad asociada a las infecciones por bacterias multirresistentes

Las infecciones por BMR presentan un peor pronóstico debido al retraso del inicio de la antibioterapia adecuada y la necesidad de antibióticos alternativos, menos efectivos y con peor perfil de toxicidad[21,22]. El tratamiento de infecciones por BMR implica el uso de antibióticos con menor experiencia; algunos antiguos (p.ej., colistina o fosfomicina), y otros de más reciente aprobación (p.ej., ceftolozano-tazobactam o ceftazidima-avibactam), de los que apenas hay datos en población pediátrica[23,24]. La mayoría de la evidencia actual para el tratamiento de estas infecciones procede de estudios realizados en adultos y, muy frecuentemente, nos encontramos con la necesidad de recurrir al uso *off-label* en pediatría debido a los escasos antimicrobianos disponibles[25,26].

Las infecciones por Enterobacterales resistentes a carbapenemes en pediatría asocian una alta tasa de mortalidad, hasta 6-11 veces mayor que en infecciones por Enterobacterales sensibles a estos antibióticos, principalmente en bacteriemias[27–29]. En adultos, se han propuesto varios modelos predictivos de mortalidad en infecciones por Enterobacterales resistentes a carbapenemes[30]. Estos scores, a su vez, se han implementado en algoritmos terapéuticos que orientan la selección de la antibioterapia empírica según el riesgo de mortalidad[22].

Sin embargo, existe la duda de si la mayor mortalidad asociada a las infecciones por BMR es debido a una mayor virulencia del agente causal o a otros factores de confusión. Las discrepancias encontradas entre distintos estudios podrían explicarse por la existencia de otros factores implicados, como los relacionados con el huésped, la gravedad clínica o el retraso adecuado del tratamiento. En el estudio de Lodise et al que

evaluó el impacto en la mortalidad de diferentes variables entre pacientes con infección grave por Enterobacterales, encontró que la demora en la terapia adecuada era un factor determinante de mortalidad más importante en comparación con el estado de resistencia a los carbapenemes[31]. Estos autores llegan a la conclusión de que no es la resistencia a los antibióticos *per se* lo que afecta los resultados clínicos, sino que sería el retraso en la administración de una terapia antibiótica adecuada de manera temprana.

De forma similar, las infecciones por SARM han demostrado presentar mayor mortalidad que las ocurridas por *S. aureus* sensible a meticilina (SASM). Un estudio reciente que evaluó la mortalidad de los episodios de bacteriemia por *S. aureus* en pacientes adultos en EE.UU. demostró una mayor mortalidad en las producidas por SARM: del 16% en aquéllas producidas por SASM frente a un 25% de las producidaspor SARM[32]. De nuevo, surge el debate de si esta mayor mortalidad se debe a la mayor virulencia de las cepas de SARM. Hasta recientemente, vancomicina ha sido el tratamiento de elección de las bacteriemias por SARM[33]; sin embargo, este antibiótico presenta un considerable riesgo de nefrotoxicidad[34]. Además, en muchas ocasiones, hay dificultad para alcanzar concentraciones plasmáticas adecuadas[35]. Por ello, es probable que la mayor mortalidad en SARM se deba también al uso de vancomicina u otros antibióticos clásicos con peor perfil de seguridad y eficacia que los β-lactámicos. Así, un estudio que evaluó la mortalidad asociada a bacteriemias por SASM en adultos demostró que aquéllos que recibieron empíricamente β-lactámicos activos frente a *S. aureus* (nafcilina o cefazolina) presentaron una mortalidad del 3%, siendo inferior de la ocurrida en los casos que recibieron de forma empírica vancomicina, que fue del 20% [36].

1.4. Determinantes de la resistencia a antibióticos

La resistencia a antibióticos se configura como la consecuencia de un conjunto de factores que interaccionan entre sí y que afecta a toda la sociedad. La resistencia a antibióticos puede encontrarse en humanos, animales y en el medio ambiente. Por ello, los planes nacionales que tratan de hacer frente a este problema, como el PRAN (Plan Nacional Resistencia Antibióticos), incorpora a un grupo variado de profesionales, como farmacéuticos, veterinarios, médicos, epidemiólogos y enfermeras, lo cual consigue

estudiar el problema de una manera más global. Es lo que se conoce como estrategia *One Health*[37]. Para abordar adecuadamente la amenaza que representa la resistencia a antibióticos, es importante comprender los factores implicados en su desarrollo. Aunque la aparición natural de resistencias a los antibióticos es un fenómeno conocido y descrito en entornos que incluso no han estado en contacto con antimicrobianos[38], la actual crisis de resistencia a estos fármacos está mediada principalmente por causas externas.

1.4.1. Consumo de antibióticos en humanos

Entre las variables que afectan a la salud humana más estrechamente relacionadas con el desarrollo de resistencias está el consumo de antibióticos. La presión selectiva ejercida por el tratamiento antibiótico es capaz de seleccionar cepas resistentes[39]. Aunque el desarrollo de los antibióticos ha supuesto un avance muy importante en la medicina, su uso inapropiado e indiscriminado puede poner en riesgo sus potenciales beneficios.

Existen importantes diferencias en la tasa de consumo de antibióticos entre países, siendo España uno de los países con un consumo a nivel comunitario más elevado[40]. Varios estudios han demostrado una prevalencia mayor de resistencia en aquellos países con mayor consumo de antibióticos, como demostró el estudio clásico de Bronzwaer et al, al relacionar la resistencia a penicilina en aislamientos de *S. pneumoniae* con el mayor consumo de β-lactámicos y macrólidos [41]. En cuanto al consumo en pediatría, cabe destacar que los niños menores de 3 años son el grupo con mayor probabilidad acumulada de recibir un antibiótico a lo largo del tiempo, por encima de otras franjas etarias en adultos[42]. Además, dos estudios recientes realizados en Europa y EE.UU. demostraron que hasta un tercio de las prescripciones de antibióticos en niños en diferentes hospitales fueron considerados inapropiados[43,44].

Los programas de optimización de uso de antimicrobianos (PROA) son una de las estrategias más importantes para controlar y adecuar el consumo de antibióticos a nivel hospitalario y comunitario[45,46]. Los objetivos de estos programas son: 1) mejorar los

resultados clínicos; 2) reducir los efectos adversos relacionados con la utilización de antimicrobianos, incluyendo la resistencia antimicrobiana, y 3) garantizar una terapia coste-efectiva[47]. Un amplio número de estudios ha demostrado una reducción en el consumo de antibióticos tras la implementación de diferentes estrategias dentro de un PROA, incluyendo también la población pediátrica[48,49].

Con el objetivo de establecer unos criterios homogéneos de selección de antibióticos en la práctica clínica, la OMS estableció la clasificación AwaRe, que diferencia a los antibióticos en *Access* (espectro más estrecho, bajo riesgo de selección de resistencias; de elección en la mayoría de las infecciones), *Watch* (espectro más amplio y mayor riesgo de selección de resistencias) y *Reserve* (último recurso para infecciones por BMR críticas con escasas opciones terapéuticas)[50].

La pandemia por SARS-CoV-2 supuso un escenario ideal para evaluar el consumo de antibióticos, por la posibilidad de establecer cierta homogeneidad en el perfil de pacientes. Además, eran pacientes que en su mayoría no presentaban coinfecciones o sobreinfecciones bacterianas[51–53], por lo que, a priori, la prescripción de antibióticos era inadecuada en la mayoría de los casos. La profundización en el conocimiento de los patrones de prescripción de antibióticos en poblaciones específicas, como la población pediátrica con COVID-19, permite ayudar a detectar una posible intervención de tipo PROA dirigida a mejorar la prescripción de antibióticos.

1.4.2. Consumo de antibióticos en animales

En EE.UU., el uso de antibióticos en animales de granja destinados a la alimentación representa el 70% del consumo total de antibióticos[54]. En Europa, datos recientes, demuestran también un elevado consumo de antibióticos, aunque con una disminución en el total de antibióticos utilizados en animales en los últimos años[55].

Este elevado consumo condiciona la selección de cepas resistentes. Aunque el impacto en salud humana es difícil de cuantificar, cepas similares de bacterias resistentes se han encontrado en animales destinados al consumo humano y en los seres humanos, lo cual sugiere la transmisión bacteriana de los animales a las

personas[56]. Es evidente que la resistencia antibiótica puede transmitirse a los humanos desde los animales a través del medio ambiente, los productos alimentarios y/o por contacto directo[39,57].

1.4.3 Diseminación en centros sanitarios

Los centros sanitarios suponen una de las principales fuentes de selección de BMR por el elevado consumo de antibióticos, así como por el mayor riesgo de diseminación de microorganismos debido al estrecho contacto entre los pacientes ingresados y el personal sanitario, así como con otros enfermos hospitalizados.

El propio ingreso hospitalario supone un riesgo importante de adquisición de BMR, muchas de las cuales difieren de las cepas resistentes circulantes a nivel comunitario. En nuestro medio, algunos fenotipos como los Enterobacterales resistentes a carbapenemes son casi exclusivos de transmisión en entornos sanitarios o sociosanitarios[58].

Entre los riesgos ambientales directamente relacionados con el ingreso hospitalario se encuentran el ingreso en habitaciones previamente ocupadas por pacientes con una infección y/o colonización por BMR[59] o la transmisión de estas BMR a través de la colonización del personal sanitario[60,61]. Por ello, las políticas de control de la transmisión de infecciones, como la higiene de manos o la desinfección ambiental, son fundamentales para evitar la diseminación de estas bacterias.

1.4.4. Otros factores

Otros factores estudiados en salud humana han demostrado estar asociados con la adquisición de colonizaciones y/o infecciones por BMR. Entre éstos, destacan los procedimientos invasivos, las cirugías, o diferentes enfermedades crónicas[39]. Muchos de estos factores posiblemente tengan relación con la estancia más prolongada en centros sanitarios. Además, se considera que la colonización por estas cepas resistentes

antecede a la infección producida por las mismas. Por ello, varios investigadores han tratado de predecir el riesgo de infección por BMR en sujetos colonizados[62].

2. Resistencia antibiótica en bacilos gramnegativos

2.1. Mecanismos de resistencia en bacilos gramnegativos

Los bacilos gramnegativos presentan un entramado complejo de mecanismos de resistencia, que, en conjunto, confiere diferentes fenotipos[63]. Las β-lactamasas, enzimas capaces de hidrolizar distintos antibióticos β-lactámicos, producidas de forma constitutiva o inducible, suponen uno de los principales mecanismos de resistencia en este grupo de microorganismos. Para hacer frente a esta resistencia, se desarrollaron los inhibidores de las β-lactamasas, habiéndose diseñado y comercializado distintas combinaciones de β-lactámicos asociados a estos inhibidores de β-lactamasas[64].

Otros mecanismos de resistencia, de especial importancia en los bacilos gramnegativos no fermentadores (p.ej., *Pseudomonas* spp., *Acinetobacter* spp. o *Stenotrophomonas maltophilia*), incluyen la hiperproducción de bombas de expulsión, las mutaciones de porinas o la modificación en las dianas de acción de distintos antibióticos[65]. La Figura 2 ilustra los principales mecanismos de resistencia presentes en los bacilos gramnegativos.

Estos mecanismos de resistencia muchas veces coexisten en un mismo microorganismo a través de diferentes mutaciones o genes de resistencia presentes en distintos elementos genéticos, como plásmidos, integrones o cassettes génicos, dando lugar, en algunos casos, a clones de alto riesgo. Estos clones tienen un papel muy relevante en la diseminación de las resistencias a antibióticos[66].

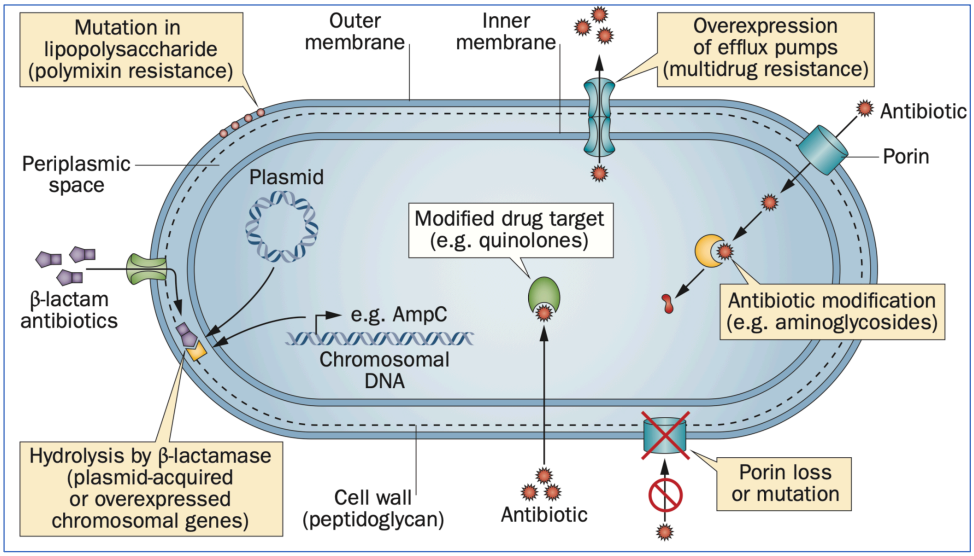

Figura 2. Principales mecanismos de resistencia presentes en los bacilos gramnegativos. Procedente de HM Zowawi, 2015 [63].

2.1.1. β-lactamasas

La producción de β-lactamasas, tanto de forma cromosómica como plasmídica, es uno de los principales mecanismos de resistencia a antibióticos. A lo largo de las décadas de 1960 y 1970 hubo un incremento progresivo de la resistencia a β-lactámicos en los bacilos gramnegativos como consecuencia de la selección de bacterias que producían β-lactamasas, principalmente de tipo TEM y SHV[67].

En los años 80 comenzaron a describirse β-lactamasas con un perfil de hidrólisis más amplio que las previas, conocidas como β-lactamasas de espectro extendido (BLEE), con capacidad para inactivar las oximino-cefalosporinas (como cefotaxima, ceftriaxona, ceftazidima) y aztreonam[68]. Fenotípicamente, se caracterizan por presentar resistencia a penicilinas, cefalosporinas de primera, segunda y tercera generación y aztreonam, pero no a cefamicinas o carbapenemes, y son inhibidas por los inhibidores clásicos de β-lactamasas (p.ej., clavulánico o tazobactam).

Las BLEE son de codificación principalmente plasmídica. Los plásmidos son fragmentos circulares de ADN que se consideran móviles por poder transmitirse entre bacterias, permitiendo la transferencia horizontal del gen[69]. Esto supone un riesgo de

diseminación entre diferentes bacterias del mismo o distinto género, o de diferentes especies. Además, los plásmidos a menudo portan múltiples genes de resistencia. A veces, estos genes adicionales se adquieren a través de elementos móviles denominados transposones. Los transposones son secuencias de ADN móviles que pueden integrarse en el cromosoma bacteriano o en un plásmido. Esta combinación en distintas bacterias de diferentes mecanismos de resistencia y/o de virulencia, da lugar a clones específicos, con una capacidad potencial de diseminación[70].

Debido al incremento en el uso de carbapenemes en relación con el aumento en la incidencia de infecciones por Enterobacterales productores de BLEE, se ha evidenciado en las últimas dos décadas un incremento en la prevalencia de resistencia a carbapenemes en Enterobacterales, principalmente debido a la producción de carbapenemasas. La primera carbapenemasa plasmídica (IMP-1) fue descrita en Japón en 1991. Posteriormente, se han ido describiendo en diferentes partes del mundo otras carbapenemasas pertenecientes a diferentes clases de β-lactamasas (entre las más destacadas epidemiológicamente: KPC-1 en EE.UU. en 1996, GES-1 en Francia en 1998, VIM-1 en Grecia en 2001, OXA-48 en Turquía en 2003 y NDM-1 en Suecia en 2008)[71]. Las carbapenemasas han presentado, a su vez, una distribución geográfica concreta. En España, por ejemplo, predomina las carbapenemasas de tipo OXA-48[72], frente a las KPC en EE.UU.[73].

Se han propuesto diferentes esquemas de clasificación de las β-lactamasas en función de su estructura molecular y de la función de la proteína. La clasificación de Ambler, fundamentada en las características moleculares, es una de las más extendidas por su mayor sencillez. Está basada en las secuencias de aminoácidos, y divide a las β-lactamasas en cuatro clases: las de clase A, C y D necesitan un aminoácido de serina para llevar a cabo su actividad hidrolítica, mientras que las enzimas de clase B, llamadas metalo-β-lactamasas (MBLs), requieren un ion de zinc divalente para ejercer su acción[74]. Cada una de las β-lactamasas descritas presentan un perfil de resistencia diferente, con una variada respuesta a la acción de los distintos inhibidores de las β-lactamasas. En la tabla 1 se incluye un resumen de las diferentes enzimas incluidas en cada una de las clases de Ambler, con su perfil de resistencia y actividad de los inhibidores de las β-lactamasas.

Clase	Enzimas representativas	Perfil de resistencia*	Actividad de inhibidores de β-lactamasas		
			Ác clavulá-nico	Tazobactam	Avibactam
A	Penicilinasas	Penicilinas	+	+	+
	IRT	+ Inhibidores clásicos de β-lactamasas	+/-	+/-	+
	BLEE (p.ej., TEM-10, SHV-2, CTX-M-15)	Penicilinas + Cefalosporinas (salvo cefamicinas) y monobactámicos	+/-	+/-	+
	Carbapenemasas (p.ej., KPC)	+ Carbapenemes	-	-	+
B	Carbapenemasas: metalo-β-lactamasas (VIM, IMP, NDM-1)	Todos los β-lactámicos, incluido carbapenemes, excepto los monobactámicos	-	-	-
C	Cefalosporinasas (AmpC)	Todos los β-lactámicos, excepto cefepima y carbapenemes	-	-	+
D	OXA-1	Similar a IRT	+/-	+/-	+
	Carbapenemasas (p.ej., OXA-48)	Resistencia a todos los β-lactámicos, incluido carbapenemes (variable a cefalosporinas de 3ª y 4ª generación)	-	-	+

Tabla 1. Clasificación molecular de las β-lactamasas, perfil de resistencias y actividad de diferentes β-lactamasas. "+" indica que es el inhibidor de β-lactamasas es activo frente a la β-lactamasa señalada y "-" que no lo es. *Antibióticos a los que presentan resistencia *in vitro*. En caso de coproducirse varios mecanismos de resistencia el perfil de resistencias se ve afectado. BLEE = β-lactamasas de espectro extendido; IRT = inhibitor-resistant TEM

Otra clasificación ampliamente utilizada es la clasificación funcional de Bush y Jacoby[75]. Esta clasificación tiene en cuenta los perfiles del sustrato y de la inhibición de la resistencia en un intento por agrupar las enzimas de manera que puedan correlacionarse con su fenotipo. Los principales grupos generalmente se correlacionan con la clasificación molecular previamente descrita. Esta clasificación incluye tres grupos:

- Grupo 1: presentan actividad cefalosporinasa y no son inhibidas por inhibidores de β-lactamasas como el ácido clavulánico.
- Grupo 2: incluye enzimas pertenecientes a las clases A y D de Ambler. Es un grupo amplio y variado de enzimas de amplio espectro de sustrato (penicilinas, cefalosporinas, oxacilina y carbapenemes), que son inhibidas por inhibidores clásicos de β-lactamasas (ácido clavulánico, tazobactam).
- Grupo 3: corresponde con la clase B de Ambler, que incluye las MBLs. A diferencia de otras carbapenemasas, no son inhibidas por el ácido clavulánico y no hidrolizan los monobactámicos.

2.1.2. Otros mecanismos de resistencia en bacilos gramnegativos

Como ya se ha comentado previamente, además de la inactivación de los antibióticos por la producción de β-lactamasas, otros mecanismos de resistencia están implicados en los bacilos gramnegativos. Éstos incluyen las mutaciones en el lugar de acción del antibiótico, la expulsión del antibiótico de la bacteria a través de bombas de expulsión o dificultando el acceso a la misma a través de mutaciones de las porinas[76].

En los Enterobacterales, los mecanismos distintos a la producción de β-lactamasas afectan principalmente a antibióticos no β-lactámicos. Aunque antibióticos como ertapenem también pueden verse afectados en este grupo de microorganismos a través de alteraciones o pérdidas de porinas, o de la hiperproducción de bombas de expulsión, en muchos casos en combinación con la producción de β-lactamasas de tipo AmpC o BLEEs[77]. Mientas que en los Enterobacterales la resistencia a carbapenemes es principalmente mediada por carbapenemasas, en los bacilos gramnegativos no

fermentadores, como *P. aeruginosa* o *A. baumannii*, otros mecanismos distintos adquieren importancia[11,78–80].

En el caso de la resistencia a fluoroquinolonas, generalmente se produce por una acumulación de mutaciones en los genes de las topoisomerasas tipo II (topoisomerasa II o ADN girasa) y topoisomerasa IV[81,82]. Éstas implican a los genes de la ADN-girasa (p.ej. *gyrA* y *gyrC*) y de la topoisomerasa IV (p.ej., *parC* y *par*E). Estas mutaciones se concentran en una región denominada QRDR (quinolone-resistance- determining-region), que codifican aminoácidos próximos al sitio activo de ambas enzimas.

Los dos mecanismos fundamentales de resistencia a aminoglucósidos en los bacilos gramnegativos son la modificación enzimática de estos compuestos o la modificación de su diana de acción[83]. Se han descrito tres tipos de enzimas inactivadoras: las acetiltransferasas, las fosfotransferasas y las nucleotidiltransferasas[82]. Cada enzima afecta a unos aminoglucósidos en concreto, lo cual se traduce en un fenotipo de resistencia específico. La modificación ribosómica como causa de resistencia a aminoglucósidos, que da lugar a un cambio en su diana de acción, puede deberse a alteraciones en las proteínas del ribosoma o a la modificación de sitios específicos el ARN ribosómicos 16S por metiltransferasas de codificación plasmídica[84]. Este mecanismo de resistencia suele ocasionar resistencia de alto nivel a todos los aminoglucósidos clásicos de utilidad en la práctica clínica. Otros mecanismos de resistencia a aminoglucósidos incluyen la alteración en la penetración en la bacteria o la eliminación activa por bombas de expulsión (AcrD)[76].

La resistencia adquirida a las polimixinas suele ocurrir por la modificación del lipopolisacárido debido a diversas mutaciones mediadas por distintos genes que da lugar a la adición de distintas moléculas[85]. Si bien, los genes necesarios para la mayoría de estas adiciones están codificados cromosómicamente, recientemente se han identificado genes de resistencia a polimixinas transmitidos por plásmidos (*mcr*), lo cual facilita su expansión[86].

2.2. Infecciones por Enterobacterales productores de β-lactamasas de espectro extendido en pediatría

Las BLEEs son enzimas que tienen capacidad de hidrolizar y causar resistencia o sensibilidad disminuida a penicilinas, oximino-cefalosporinas (cefotaxima, ceftriaxona, ceftazidima y cefepima) y monobactámicos (aztreonam), pero no a cefamicinas (cefoxitina) ni carbapenemes. Generalmente son inhibidas *in vitro* por varios inhibidores de las β-lactamasas (p.ej., ácido clavulánico, tazobactam o avibactam), lo cual ayuda a diferenciarlas fenotípicamente de las β-lactamasas de tipo AmpC, que solamente se inhiben por avibactam[25]. En algunos casos, estas cepas coproducen otras β-lactamasas como OXA-1, que induce resistencia a los inhibidores de las β-lactamasas tradicionales[87].

Actualmente, las más frecuentes en nuestro medio son las de tipo CTX-M[88]. Las cepas productoras de BLEEs habitualmente contienen otros genes que confieren resistencia a aminoglucósidos (principalmente a gentamicina, siendo más infrecuente a amikacina), cotrimoxazol o fluoroquinolonas, limitando aún más las posibilidades terapéuticas.

En las últimas décadas se ha evidenciado un incremento progresivo en la prevalencia de Enterobacterales productores de BLEEs, tanto a nivel hospitalario como comunitario. Una revisión sobre aislamientos de Enterobacterales productores de BLEEs en hemocultivos pediátricos a nivel mundial ha demostrado un incremento de su prevalencia del 3,5% al 8% desde 1996 a 2013[89]. También se ha objetivado una prevalencia de colonización rectal elevada en niños sanos en Europa (3-24%), demostrándose la transmisión entre niños preescolares y la transmisión intrafamiliar[90].

Datos más recientes demuestran una estabilización tras el incremento previo, con una disminución en Europa de la prevalencia en niños de bacteriemias por *E. coli* productor de BLEEs y un discreto aumento en el caso de *K. pneumoniae*[91]. Un aspecto relevante cada vez más conocido es la transmisión a sus recién nacidos de madres colonizadas por Enterobacterales productores de BLEEs[92]., lo que podría incrementar el riesgo de infecciones de transmisión vertical por las mismas.

La prevalencia de infecciones por Enterobacterales productores de BLEEs en niños en España muestra una tendencia similar a la observada a nivel mundial. Un estudio realizado en Guipúzcoa observó una prevalencia de colonización en heces de niños sanos de 8-16 meses de edad del 24%, siendo de las más altas descritas en Europa[93]. Otro estudio que evaluó la epidemiología de las infecciones del tracto urinario (ITU) comunitarias en niños <14 años en España en el año 2016 objetivó una prevalencia de Enterobacterales productores de BLEEs del 3,2%[94]. Otro estudio en menores de 2 años ingresados por ITU febril comunitaria entre 2005 y 2014 mostró una tasa similar del 3,5%[95], algo inferior que la descrita en otro estudio que analizó ITUs comunitarias por *E. coli* en niños menores de 14 años durante 2015 y 2016 (9,2%)[96].

En el caso de aislamientos en hemocultivo y líquido cefalorraquídeo en niños, según datos del ECDC (European Centre for Disease Prevention and Control), la prevalencia de aislamientos resistentes a cefalosporinas de tercera generación (principalmente mediada por BLEEs) fue del 3-8% en *E. coli* y del 20-30% en el caso de *K. pneumoniae*[97].

2.3. Infecciones por bacilos gramnegativos resistentes a carbapenemes en pediatría

La resistencia creciente entre los bacilos gramnegativos a las cefalosporinas de tercera generación a nivel global ha condicionado un incremento en el uso de carbapenemes a lo largo de las últimas décadas[98]. Esto ha contribuido de forma directa a la aparición de diferentes mecanismos de resistencia a los carbapenemes. El desarrollo de esta resistencia constituye uno de los escenarios más preocupantes dentro de las resistencias a antimicrobianos.

En el año 2019 se estimó que 243.000 muertes en el mundo fueron directamente atribuibles a cepas resistentes a carbapenemes[4]. Las enterobacterias *E. coli* y *K. pneumoniae*, así como *P. aeruginosa* y *A. baumannii*, son las bacterias que más frecuentemente presentan resistencia a los carbapenemes en la Unión Europea[99]. Actualmente, España es un país de baja prevalencia de Enterobacterales resistentes a

carbapenemes, suponiendo el 5,9% del total de aislamientos invasivos de *K. pneumoniae* en el año 2021, pero presenta una tendencia ascendente en los últimos años (Figuras 3 y 4)[97].

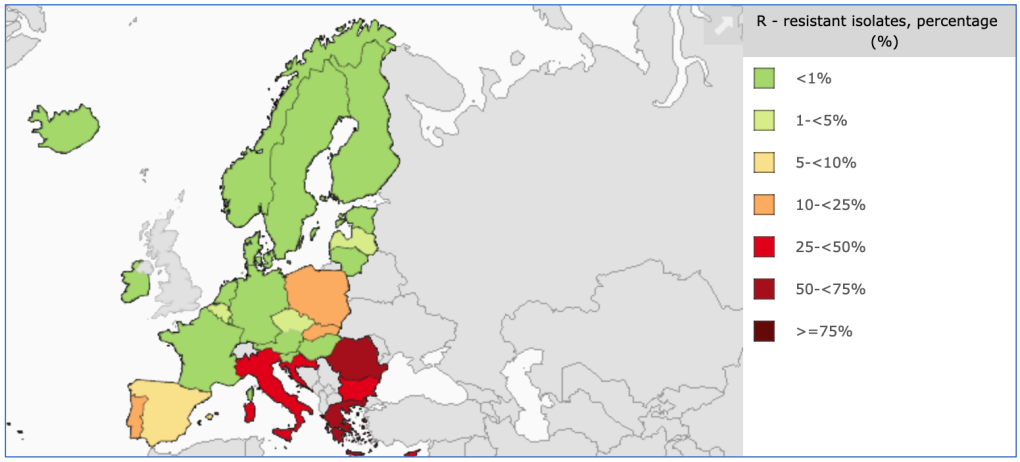

Figura 3. Porcentaje de aislamientos de *K. pneumoniae* resistentes a carbapenemes en muestras invasivas en Europa en el año 2021. Datos procedentes de EARS-Net (The European Antimicrobial Resistance Surveillance Network), accesible en: https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc

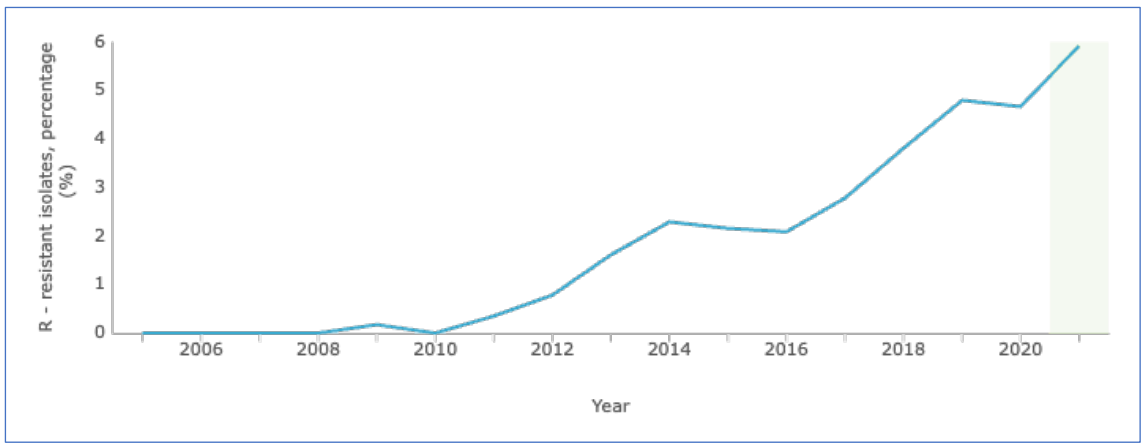

Figura 4. Evolución de la prevalencia de aislamientos de *K. pneumoniae* resistentes a carbapenemes en muestras invasivas en España durante los últimos años. Datos procedentes de EARS-Net (The European Antimicrobial Resistance Surveillance Network), accesible en: https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc

De forma paralela a lo descrito en población adulta, en niños se ha producido un aumento progresivo en la incidencia de infecciones por bacilos gramnegativos resistentes a carbapenemes. Varios estudios realizados en EE.UU. han mostrado un incremento en la prevalencia de resistencia a carbapenemes en niños: en aislamientos de Enterobacterales del 0% en 1999-2000 al 0,47% en 2010-2011[100]; en aislamientos de *P. aeruginosa* del 9,4% en 1999 al 20% en 2012[101], y en aislamientos de *A. baumannii* del 0,6% en 1999 al 6,1% en 2012[102]. Asimismo, un estudio realizado en Italia entre centros participantes en un registro de oncohematología pediátrica demostró un aumento de cuatro veces de los episodios de bacteriemias por Enterobacterales resistentes a carbapenemes de 2012 a 2013 (de 0,16 a 0,67/1000 días de estancia hospitalaria)[103]. Más recientemente, un estudio realizado en varios países de Europa evaluando los datos de aislamientos pediátricos procedentes del registro internacional ATLAS, mostró un incremento en la prevalencia de resistencia a carbapenemes en aislamientos de *K. pneumoniae* del 2,4% en 2004-2012 al 4,7% en 2013-2018[104].

La gran mayoría de las infecciones por Enterobacterales resistentes a carbapenemes suceden en población adulta, ocurriendo en niños ocasionalmente en la actualidad, principalmente en relación con brotes hospitalarios[97,105]. La carbapenemasa en Enterobacterales más frecuente en España actualmente es la OXA-48, seguida de las MBLs y KPC[106–108]. Su epidemiología no se conoce con exactitud, aunque se ha documentado un predominio de MBL tipo VIM, con un incremento reciente de OXA-48 en algunos centros[109, 110].

Los factores de riesgo asociados a estas infecciones son similares a los descritos para el resto de las infecciones por BMR, incluyendo la exposición previa a carbapenemes. Cabe destacar, que, en un estudio reciente realizado en España, el 13% (31/239) de los niños colonizados por enterobacterias resistentes a carbapenemes desarrolló una infección por la misma posteriormente[109]. El riesgo de presentar una infección en pacientes colonizados por bacilos gramnegativos resistentes a carbapenemes depende de múltiples factores, como el sitio de colonización, mecanismo de resistencia a carbapenemes, lugar de la infección o el grado de inmunosupresión[111,112].

2.4. Infecciones por *Pseudomonas aeruginosa* de difícil tratamiento

P. aeruginosa posee una cefalosporinasa tipo AmpC, cuya expresión constitutiva produce una resistencia intrínseca a las aminopenicilinas (incluida la asociación amoxicilina-clavulánico), cefalosporinas de primera y segunda generación, algunas cefalosporinas de tercera generación (cefotaxima, ceftriaxona) y ertapenem [76]. Esto condiciona que sea un microorganismo que, independientemente de que desarrolle mecanismos adquiridos de resistencia, presenta un fenotipo de más difícil tratamiento que los Enterobacterales. Las infecciones por *P. aeruginosa* son una causa importante de mortalidad, especialmente en pacientes críticos con comorbilidades[113] , siendo ésta del 15-52% en el caso de bacteriemias.[113–118]

Se ha descrito un aumento de aislamientos de *P. aeruginosa* con DTR en toda la población, lo cual se ha evidenciado también en la población pediátrica. En un estudio realizado en EE.UU. que incluyó pacientes pediátricos de diferentes estados, la proporción de aislamientos de *P. aeruginosa* resistentes a carbapenemes aumentó del 9,4% en 1999 al 20% en 2012[101]. En un estudio posterior realizado en China que incluyó a niños ingresados en unidades de cuidados intensivos con aislamientos de *P. aeruginosa* de 2016 a 2020, la prevalencia de *P. aeruginosa* resistente a carbapenemes fue del 18,4%, con una tendencia fluctuante que aumentó considerablemente en 2021 (24,2%)[119]. En Europa, las tasas de resistencia a carbapenemes en *P. aeruginosa* en niños también han aumentado, oscilando actualmente entre un 15-30% en muestras invasivas[97] .

En España, según los datos del ECDC, se ha evidenciado un discreto aumento en la prevalencia de resistencia a carbapenemes en aislamientos de *P. aeruginosa* (Figuras 5 y 6)[97]. Según un estudio multicéntrico de prevalencia realizado en población adulta en España, la tasa de aislamientos de *P. aeruginosa* resistente a carbapenemes fue del 15%[120]. En un estudio de colonización e infección por gramnegativos productores de carbapenemasas VIM en un hospital pediátrico en Madrid entre 2012 y 2015, *P. aeruginosa* representó el 11% de los aislamientos, con un pico de incidencia anual de 11,8 casos/1000 ingresos en 2014[121].

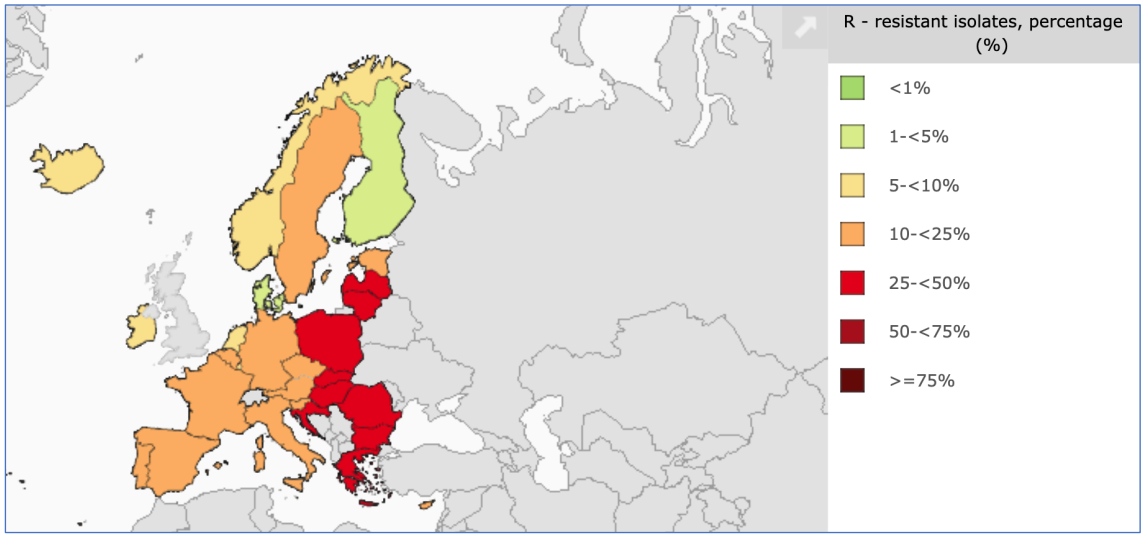

Figura 5. Porcentaje de aislamientos de *P. aeruginosa* resistentes a carbapenemes en muestras invasivas en Europa en el año 2021. Datos procedentes de EARS-Net (The European Antimicrobial Resistance Surveillance Network), accesible en: https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc

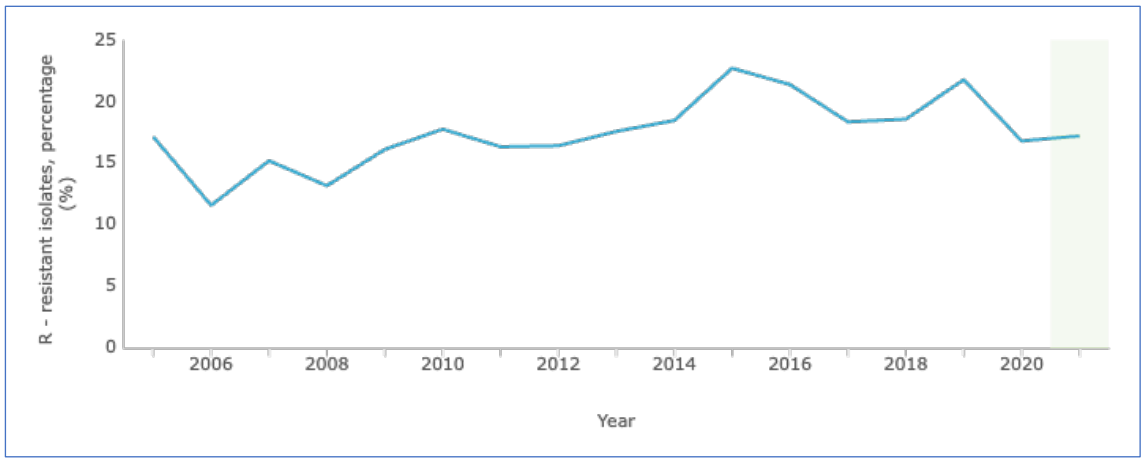

Figura 6. Evolución de la prevalencia de aislamientos de *P. aeruginosa* resistentes a carbapenemes en muestras invasivas en España durante los últimos años. Datos procedentes de EARS-Net (The European Antimicrobial Resistance Surveillance Network), accesible en: https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc

En el caso de *P. aeruginosa*, al contrario de lo descrito en Enterobacterales, hay estudios que han demostrado una prevalencia superior de resistencia a carbapenemes

en aislamientos pediátricos que en adultos. Un estudio europeo que comparó aislamientos pediátricos de la red ARPEC con aislamientos adultos de EARS-NET demostró que la resistencia a carbapenemes en aislamientos de *K. pneumoniae* fue mayor en adultos (13,5% frente a 6,5%), mientras que en el caso de *P. aeruginosa* fue más frecuente en niños (30,7% vs 23%) [12].

Varios estudios, en su mayoría en población adulta, han descrito la exposición previa a antibióticos activos frente a *P. aeruginosa*, el ingreso previo en una unidad de cuidados intensivos, la sepsis al diagnóstico, los procedimientos invasivos, la bacteriemia primaria, la inmunosupresión o la coexistencia de múltiples comorbilidades, como los factores de riesgo más frecuentes para el desarrollo de una infección por *P. aeruginosa* resistente a carbapenemes[114,122,123].

Varios estudios realizados en España han demostrado que la resistencia a carbapenemes en aislamientos de *P. aeruginosa* es principalmente por mecanismos distintos a la producción de carbapenemasas[120]., siendo la más frecuente, cuando se detecta, la de tipo VIM. Así, en un estudio español que incluyó una colección de 71 aislamientos de *P. aeruginosa* productores de carbapenemasas, el 87% de los aislamientos portaban una carbapenemasa tipo VIM [80].

2.5. Infecciones por bacilos gramnegativos multirresistentes en unidades de alta complejidad

En las últimas décadas, los avances en los tratamientos médicos y quirúrgicos, junto con el progreso tecnológico, han permitido una mayor supervivencia de niños con diversas enfermedades que representaban una amenaza para la vida durante la infancia[124]. Sin embargo, como resultado, el número de niños que padecen enfermedades crónicas o patología compleja ha aumentado[124].

Los pacientes ingresados en unidades de cuidados intensivos neonatales o pediátricos presentan, en la actualidad, una mayor supervivencia gracias, entre otros aspectos, al desarrollo de tecnología sanitaria más avanzada. Igualmente, la

supervivencia de algunas enfermedades, como el cáncer, también ha aumentado en muchas ocasiones a expensas de la exposición a tratamientos inmunosupresores que incrementan notablemente el riesgo de infecciones[125]. Esta mayor supervivencia también ha estado relacionada con la utilización frecuente de antimicrobianos en esta población, tanto para profilaxis como tratamiento.

Todo esto ha condicionado, no obstante, un aumento en la complejidad de los pacientes pediátricos atendidos en nuestros hospitales, así como un aumento en la cronicidad, en la dependencia de tecnología sanitaria y en la incidencia de complicaciones infecciosas. El elevado consumo de antibióticos en estos pacientes, muchas veces de amplio espectro, supone el desarrollo de infecciones por BMR de difícil tratamiento[126,127]. Esto se traslada, a su vez, en una desigual distribución de las infecciones por BMR entre unidades en los hospitales[15].

Este escenario sombrío presenta un enemigo adicional, como es la pérdida de la eficacia de las profilaxis antimicrobianas que hasta ahora habían demostrado su beneficio[128]. Por ello, la resistencia a antimicrobianos limita el tratamiento de estas infecciones, pero también aumenta el riesgo de que se desarrollen debido a la menor eficacia de la profilaxis antimicrobiana.

2.6. Tratamiento de las infecciones por enterobacterias productoras de β-lactamasas de espectro extendido

La elección del tratamiento antibiótico está basada en el foco, la gravedad de la infección, y el estado inmunológico del paciente. Tradicionalmente, los carbapenemes han sido los antibióticos de elección en infecciones con este perfil de resistencia[129]. Sin embargo, el incremento de la prevalencia de microorganismos resistentes a carbapenemes ha remarcado la necesidad de definir antibióticos «ahorradores» de carbapenemes que aseguren una efectividad similar sin favorecer la selección de cepas resistentes[130].

Aunque, frecuentemente, las bacterias productoras de BLEEs presentan sensibilidad *in vitro* a piperacilina-tazobactam, se han descrito fracasos terapéuticos, sobre todo en presencia de infecciones con un alto inóculo (p. ej., neumonía, abscesos no drenados, etc.). Estudios observacionales han demostrado la eficacia de piperacilina-tazobactam, principalmente en infecciones con bajo inóculo, infecciones no graves y mediante la administración en perfusión extendida[25,131].

El ensayo clínico MERINO, que evaluó en adultos la mortalidad a los 30 días del inicio de tratamiento de bacteriemias por *E. coli* y *K. pneumoniae* resistentes a cefalosporinas de tercera generación, no demostró la no inferioridad de piperacilina-tazobactam frente a meropenem[132]. Sin embargo, varias limitaciones del estudio (p. ej., mortalidad, principalmente debida a causas no infecciosas, administración de piperacilina-tazobactam mediante perfusión estándar, etc.) cuestionan la generalización de los resultados[133]. Un subanálisis posterior demostró una mortalidad similar en el caso de bacteriemias de foco urinario e infecciones no graves, coincidiendo con lo demostrado en estudios observacionales previos[134].

El uso de otros antibióticos (p. ej., aminoglucósidos, cotrimoxazol, amoxicilina-clavulánico, fosfomicina o fluoroquinolonas) pueden ser una opción en el caso de ITU no grave, y como paso secuencial de vía intravenosa a vía oral tras el control inicial del foco infeccioso[25]. En Enterobacterales productores de BLEE, ertapenem también es una buena alternativa a meropenem en algunos casos, permitiendo disminuir la presión antibiótica sobre *P. aeruginosa*, además de las ventajas que conlleva su administración más espaciada.

Fosfomicina oral es una alternativa recomendada en el tratamiento de la cistitis por *E. coli* BLEE, pero no para otros gramnegativos, ya que *K. pneumoniae* y otros gramnegativos son portadores del gen *fosA*, capaces de hidrolizar fosfomicina y producir fallo terapéutico[135].

En la tabla 2 se muestra el tratamiento de las infecciones por Enterobacterales productores de BLEEs.

Características de la infección	Antibióticos	
ITU no grave	Cotrimoxazol, nitrofurantoína, aminoglucósidos, amoxicilina-clavulánico, fosfomicina, fluoroquinolonas o piperacilina-tazobactam	
Infecciones no graves	Foco de inóculo bajo-intermedio	Piperacilina-tazobactam (dosis alta en perfusión extendida), ertapenem, fluoroquinolonas o cotrimoxazol
	Foco de inóculo alto o bacteriemia	Meropenem, imipenem o ertapenem
Infecciones graves (sepsis grave o shock séptico) o inmunosupresión grave	Meropenem o imipenem	

Tabla 2. Tratamiento de las infecciones por *Enterobacterales* productores de β-lactamasas de espectro extendido. Adaptada de Gutierrez-Gutiérrez B[25].

2.7. Tratamiento de las infecciones por enterobacterias productoras de AmpC

Cefepima es considerado inductor débil de AmpC y es relativamente estable en presencia de dicha enzima[136]. Se considera el tratamiento de elección en infecciones con una CMI de cefepima ≤ 2 mg/L. En caso de CMI de cefepima > 2 mg/L, se recomienda el tratamiento con carbapenemes, debido al riesgo de coproducción de BLEE y a los peores resultados clínicos demostrados en varios estudios[137]. En caso de utilizar carbapenemes, el tratamiento dirigido con ertapenem podría ayudar a reducir la presión antibiótica frente a *P. aeruginosa*.

Como alternativas a cefepima, pueden plantearse otros antibióticos no β-lactámicos, como fluoroquinolonas, aminoglucósidos o cotrimoxazol, según el foco y gravedad de la infección, tanto intravenoso como de forma secuencial a vía oral[136]. Piperacilina-tazobactam es una alternativa razonable en infecciones leves y con bajo inóculo, siempre que la CMI sea ≤ 8 mg/L.

En la tabla 3 se puede ver el tratamiento de infecciones por microorganismos con producción inducible de alto riesgo (*Enterobacter cloacae*, *Citrobacter freundii* y *Klebsiella aerogenes*) o adquirida de AmpC.

Características de la infección	**Antibióticos**	
ITU no grave	Cotrimoxazol, nitrofurantoína, aminoglucósidos, fosfomicina, fluoroquinolonas o piperacilina-tazobactam	
Infecciones no graves	Foco de inóculo intermedio-bajo	Cefepima, fluoroquinolonas, cotrimoxazol o piperacilina-tazobactam
	Foco de inóculo alto	Meropenem, imipenem, ertapenem, cefepima, fluoroquinolonas o cotrimoxazol
Infecciones graves	Meropenem o imipenem	

Tabla 3. Tratamiento de infecciones por microorganismos con alto riesgo de hiperproducción inducible (*Enterobacter cloacae, Citrobacter freundii* y *Klebsiella aerogenes*) o adquirida de AmpC.

2.8. Tratamiento de las infecciones por bacilos gramnegativos resistentes a carbapenemes

En los últimos años se han desarrollado nuevos antibióticos activos frente a bacilos gramnegativos resistentes[138], aunque aún se dispone de poca información en población pediátrica y muy frecuentemente nos encontramos con la necesidad de recurrir a su uso *off-label* o compasivo[139].

Las nuevas combinaciones de β-lactámicos con inhibidores de las β-lactamasas (ceftazidima-avibactam, meropenem-vaborbactam, imipenem-relebactam y ceftolozano-tazobactam), son actualmente los tratamientos de elección de las infecciones graves por bacilos gramnegativos resistentes a carbapenemes en adultos [135,140,141], al haber demostrado mejores resultados clínicos [142]. Su uso en pediatría está condicionado al estado de aprobación, gravedad de la infección y el perfil de resistencias del microorganismo aislado. Por ello, el tratamiento debe ser individualizado en función

de la gravedad del cuadro clínico, el foco de la infección y el perfil de sensibilidad de la bacteria aislada. Además del tratamiento antibiótico, es necesario priorizar el control del foco de infección (retirada de dispositivos invasivos, cirugía, etc.).

2.8.1. Tratamiento de Enterobacterales resistentes a carbapenemes

Las nuevas combinaciones de β-lactámicos con inhibidores de las β-lactamasas (ceftazidima-avibactam, meropenem-vaborbactam e imipenem-relebactam), son actualmente los tratamientos de elección de las infecciones graves por Enterobacterales resistentes a carbapenemes en adultos. En la Figura 7 se muestra la actividad de cada uno de estos antibióticos frente a los diferentes mecanismos de resistencia en bacilos gramnegativos. En la Tabla 4 se compara las recomendaciones de tratamiento de las infecciones por Enterobacterales resistentes a carbapenemes emitidas por las guías de SEIMC (Sociedad Española de Infectología y Microbiología Clínica), ESCMID (European Society of Clinical Microbiology and Infectious Diseases) e IDSA (The Infectious Diseases Society of America).

Antibiótico	KPC	OXA-48	MBL	*Pseudomonas* RC
Ceftazidima-avibactam				
Ceftolozano-tazobactam				
Meropenem-vaborbactam				
Aztreonam-avibactam				
Imipenem-relebactam				
Cediderocol				

Figura 7. Nuevos antibióticos y sensibilidad de bacterias gramnegativas resistentes a carbapenemes en nuestro medio. Adaptado de: PD Tamma, et al, 2019[139]. Porcentaje de aislamientos sensibles: verde >90%, naranja 30-90%, rojo <30%.
MBL, metallo-β-lactamasas (VIM, NDM, IMP); RC, resistentes a carbapenemes.

Tradicionalmente, en niños, el uso de pautas optimizadas de meropenem (a doble dosis en perfusión extendida) en combinación con un segundo antibiótico ha

posibilitado alcanzar los objetivos farmacocinéticos/farmacodinámicos en el caso de aislamientos con una concentración mínima inhibitoria (CMI) de meropenem ≤8 mg/L[143, 144], y ha demostrado una eficacia adecuada en estudios observacionales[145]. Así, la recomendación en pediatría antes de la aprobación de los nuevos antibióticos era una terapia combinada con, al menos, dos fármacos activos *in vitro*, principalmente en infecciones graves[146,147]. Sin embargo, datos recientes de ensayos clínicos y estudios observacionales en adultos han demostrado la no inferioridad o incluso superioridad de la monoterapia con los nuevos agentes descritos comparado con fármacos clásicos (meropenem, aminoglucósidos, fluoroquinolonas, etc.)[148]. Por tanto, actualmente se considera ceftazidima-avibactam (y, probablemente en un futuro próximo, otros nuevos β-lactámicos conforme adquieran la aprobación pediátrica) el antibiótico de elección en infecciones graves causadas por Enterobacterales resistentes a carbapenemes sensibles al mismo, reservando el uso de los esquemas tradicionales para infecciones no graves, microorganismos resistentes a los nuevos β-lactámicos, situaciones donde la identificación de carbapenemasas no sea posible o en niños menores de 3 meses de edad (hasta mayor evidencia con los nuevos antibióticos).

Ceftazidima-avibactam ha sido evaluada en ensayos de fase I y II en niños, demostrando perfiles de seguridad y eficacia similares a los observados en población adulta[149,150], y está aprobado en mayores de 3 meses de edad para el tratamiento de infección intraabdominal complicada (combinado con un antibiótico anaerobicida), ITU complicada, neumonía adquirida en el hospital (incluida la asociada a la ventilación mecánica) y en otras infecciones por bacilos gramnegativos con opciones terapéuticas limitadas[151]. Además, está actualmente siendo evaluado en un ensayo de fase II en niños menores de 3 meses[152]. Ceftazidima-avibactam presenta actividad frente a cepas productoras de carbapenemasas tipo OXA-48 y KPC, pero no frente a MBL[23, 153].

Las enterobacterias productoras de MBL que no asocian otro mecanismo de resistencia suelen conservar sensibilidad a aztreonam. La combinación de aztreonam con avibactam (actualmente con ceftazidima-avibactam, al no estar comercializada la combinación), ha demostrado su eficacia en cepas productoras de MBL resistentes a aztreonam (por coproducción de otras β-lactamasas)[154]. Por ello, podría ser una alternativa frente a este tipo de carbapenemasas[155], así como también podría serlo el

tratamiento con cefiderocol (no aprobado actualmente en pediatría). Cefiderocol es una nueva cefalosporina siderófora activa frente a la mayoría de carbapenemasas[156] y se encuentra actualmente en fase II de ensayo clínico en niños de más de 3 meses [157]. Actualmente hay experiencia clínica publicada en casos pediátricos aislados sin otras opciones terapéuticas[158].

Meropenem-vaborbactam presenta actividad frente a las carbapenemasas tipo KPC, pero no frente a OXA-48 o las MBL[159]. Es de interés en las infecciones por enterobacterias productoras de KPC resistentes a ceftazidima-avibactam. Se encuentra aprobado para población adulta y en ensayo en fase I en niños[160]. Por último, imipenem-relebactam, que presenta actividad principalmente frente a KPC, y discreta frente a OXA-48[161], se encuentra actualmente en fase II/III en población pediátrica[162,163].

Debido a los buenos resultados demostrados en adultos, habría que valorar el uso *off-label* o de forma compasiva en población pediátrica de estos otros β-lactámicos (meropenem-vaborbactam, imipenem-relebactam, cefiderocol…) en infecciones graves, especialmente en aquéllas con CMI frente a meropenem ≥4 mg/L o con fracaso terapéutico previo a meropenem y que sean resistentes a ceftazidima-avibactam. Los fármacos no β-lactámicos (p.ej., fluoroquinolonas, aminoglucósidos, colistina…) pueden utilizarse como alternativa en el caso de infecciones no graves, o en combinación en las infecciones graves[78,141].

Guía	KPC	OXA-48	MBL
IDSA 2022[135]	Ceftazidima-avibactam Meropenem-vaborbactam Imipenem-relebactam	Ceftazidima-avibactam	Ceftazidima-avibactam + aztreonam Cefiderocol
	ITU: Ciprofloxacino, levofloxacino, cotrimoxazol, aminoglucósidos		
ESCMID 2022[141]	Ceftazidima-avibactam Meropenem-vaborbactam	Ceftazidima-avibactam	Ceftazidima-avibactam + aztreonam Cefiderocol
	Infecciones leves: antibióticos clásicos activos contra el aislamiento		
SEIMC 2022[140]	Ceftazidima-avibactam Meropenem-vaborbactam Imip-rele (alternativa)	Ceftazidima-avibactam	Ceftazidima-avibactam + aztreonam Cefiderocol
	Alternativa: tratamiento combinado (meropenem, colistina, tigeciclina, aminoglucósidos…)		

Tabla 4. Recomendaciones de tratamiento de las infecciones por Enterobacterales resistentes a carbapenemes de IDSA, ESCMID y SEIMC.

2.8.2 Tratamiento de *Pseudomonas aeruginosa* resistentes a carbapenemes

La resistencia a carbapenemes en *Pseudomonas* spp. muchas veces es debida a mutaciones en las porinas, lo cual confiere resistencia a los carbapenemes, pero manteniendo sensibilidad a otros β-lactámicos (p.ej., ceftazidima, cefepima o aztreonam). En estos casos, el uso de estos antibióticos resulta adecuada, lo que es importante para reservar la utilización de los nuevos β-lactámicos para bacterias más resistentes[135].

En cuanto a los nuevos antibióticos, ceftolozano-tazobactam, aprobado desde el nacimiento para el tratamiento de ITUs e infecciones abdominales complicadas, es inactivo frente a todos los tipos de carbapenemasas, pero activo frente a *P. aeruginosa* con resistencia a carbapenemes no mediada por carbapenemasas[164,165]. Ceftazidima-avibactam e imipenem-relebactam pueden resultar de utilidad también en *P. aeruginosa* con resistencias de difícil tratamiento[11]. Cefiderocol, actualmente no

aprobado en pediatría, se considera una alternativa, si bien se tiende a reservar como fármaco de segunda línea en el tratamiento de neumonías o bacteriemias por resultados algo más desfavorables en ensayos clínicos en adultos[135,140,141].

Al igual que en infecciones por Enterobacterales resistentes a carbapenemes, los regímenes tradicionales pueden ser una opción en los mismos supuestos explicados previamente. En la Tabla 5 se compara las recomendaciones de tratamiento de las infecciones por *P. aeruginosa* resistente a carbapenemes emitidas por las guías de SEIMC, ESCMID e IDSA, según la gravedad de la infección.

Tipo de infección	**Recomendaciones**
Bajo riesgo, no grave	**IDSA:** ceftolozano-tazobactam, imipenem-relebactam, ceftazidima-avibactam, aminoglucósidos **ESCMID:** antibióticos clásicos activos contra el aislamiento **SEIMC:** ceftolozano-tazobactam; alternativa: ceftazidima-avibactam, imipenem-relebactam, colistina, cefiderocol (ITU)
Grave	**IDSA:** ceftolozano-tazobactam, imipenem-relebactam, ceftazidima-avibactam, cefiderocol (ITUc) **ESCMID:** ceftolozano-tazobactam **SEIMC:** ceftolozano-tazobactam; alternativa: ceftazidima-avibactam, imipenem-relebactam, colistina, cefiderocol (ITU)

Tabla 5. Recomendaciones de tratamiento de las infecciones por *P. aeruginosa* resistentes a carbapenemes de IDSA, ESCMID y SEIMC, según la gravedad de la infección.

3. *Staphylococcus aureus* resistente a meticilina

La resistencia a meticilina en *S. aureus* se describió por primera vez en Inglaterra en 1961, poco después de que se introdujera la meticilina en la práctica clínica[166]. A nivel global, se estima que en 2019 se produjeron más de 100.000 muertes atribuidas a infecciones por SARM[4]. En el laboratorio de microbiología esta resistencia se identifica mediante la evaluación de la sensibilidad a cefoxitina u oxacilina (u otras penicilinas antiestafilocócicas)[8]. La resistencia a estos antibióticos es un indicador de resistencia al resto de β-lactámicos, incluidas las cefalosporinas (con excepción de ceftarolina y ceftobiprol) y los carbapenemes. Además, los aislamientos de SARM frecuentemente presentan resistencia a otros antibióticos (p.ej., clindamicina, fluoroquinolonas, etc.)[167].

Tradicionalmente se han establecido diferencias entre los clones comunitarios y los hospitalarios, con diferente perfil de sensibilidad y virulencia, presentando los comunitarios, habitualmente, una mayor sensibilidad a clindamicina y producción más frecuente de la toxina leucocidina de Panton-Valentine. Sin embargo, en los últimos años sus diferencias genotípicas han ido homogeneizándose[24].

3.1. Mecanismos de resistencia

El principal mecanismo de resistencia es la adquisición de una nueva proteína de unión a la penicilina, denominada PBP2a, que está codificada principalmente por el gen *mecA*, incluido dentro de un casete cromosómico (SCC*mec*). Esta nueva proteína, la PBP2a, presenta baja afinidad por la mayoría de los β-lactámicos, produciendo resistencia a los mismos. El SCC*mec* contiene, además del complejo del gen *mecA*, un conjunto de genes que son responsables de su movilidad (ccrA y ccrB). Más del 90% de los genomas de *S. aureus* conocidos se pueden clasificar en solo cuatro complejos clonales predominantes (CC5, CC8, CC398 y CC30)[168]. La Figura 8 ilustra, como ejemplo, los principales elementos genómicos del clon de SARM USA300, uno de los clones de *S. aureus* más ampliamente descritos

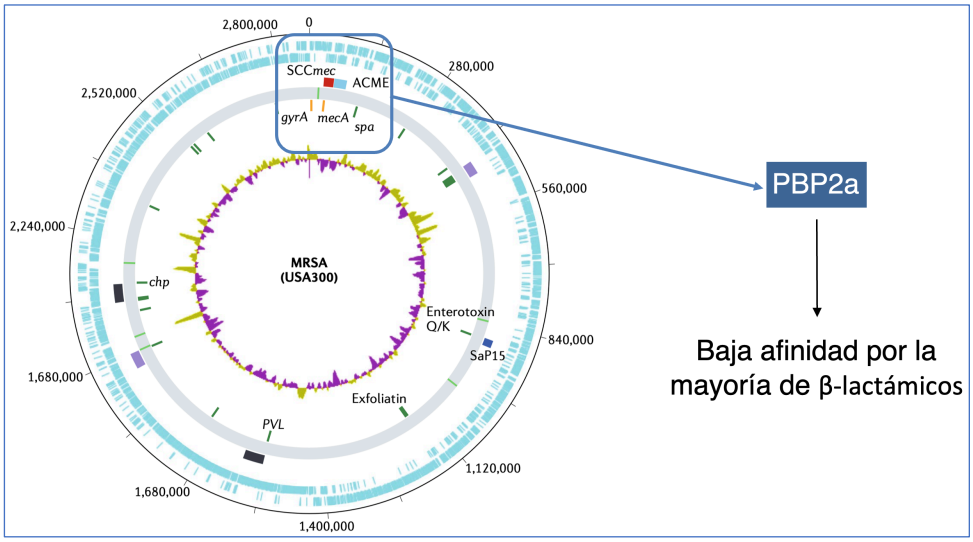

Figura 8. Principales elementos genómicos de *Staphylococcus aureus* resistente a la meticilina. Adaptado de Turner NA, Nat Rev Microbiol, 2019

En 2011 se identificó un nuevo homólogo del gen *mecA*, el *mecC*, en aislamientos procedentes de ganado vacuno y de humanos[169]. Estudios posteriores han descrito una distribución de estos clones en diferentes ganados, con potencial transmisión a humanos[170].

3.2. Epidemiología de *Staphylococcus aureus* resistente a meticilina

Aunque en otros países europeos vecinos la prevalencia de SARM ha disminuido progresivamente en los últimos años, en España se mantiene estable (Figura 9), situándose en torno al 10-20% de los aislamientos en hemocultivo en niños durante los últimos años, según los datos del ECDC[97]. La Figura 10 incluye la prevalencia a nivel global de resistencia a meticilina en aislamientos de *S. aureus.*

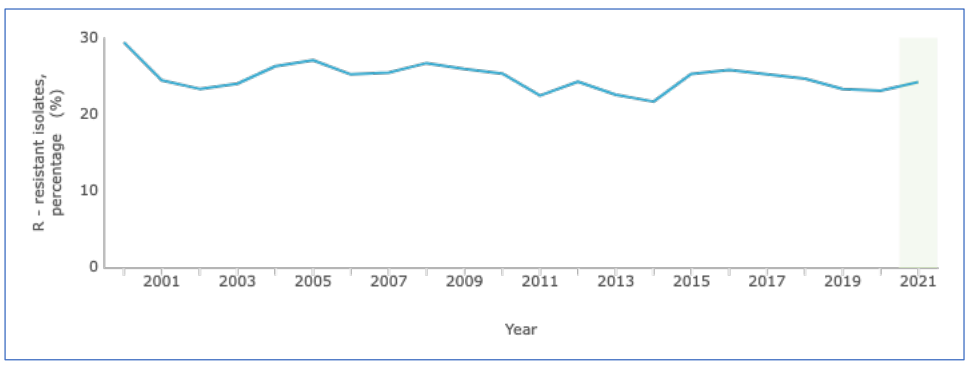

Figura 9. Prevalencia de resistencia a meticilina de aislamientos de *S. aureus* en muestras invasivas en España. Datos procedentes de EARS-Net (The European Antimicrobial Resistance Surveillance Network), accesible en: https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc

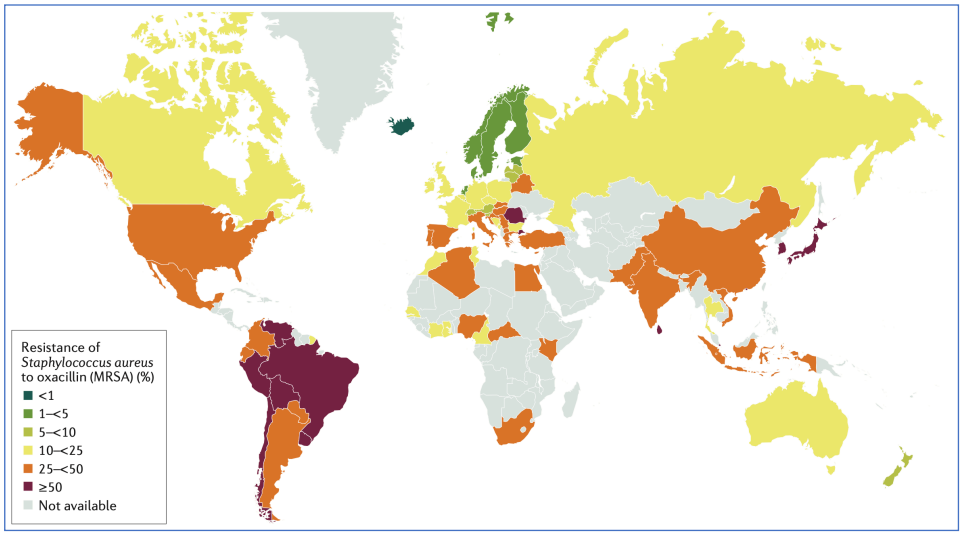

Figura 10. Prevalencia a nivel global de resistencia a meticilina de aislamientos de *S. aureus*. Procedente de Lee AS, Nat Rev Dis Primers, 2018[8].

La resistencia a meticilina en *S. aureus* adquirido en la comunidad en niños empezó a describirse en España en el año 2006 [171]. Varios estudios recientes han descrito la prevalencia de SARM en distintas infecciones en niños en España, situándose entre 4,4% y 26,5% (Tabla 6).

Tipo de infección	% SARM
Colonización nasal	4,4%[172]
Infección en cualquier localización	8,8%[173], 16,2%[174]
Neumonía	25%[175]
Bacteriemia	7,8%[176]
Infecciones de piel y partes blandas	12-13,2%[177]
Infecciones osteoarticulares	10,3%[178]

Tabla 6. Prevalencia de resistente a meticilina del total de aislamientos de *S. aureus* en niños en España, según varios estudios. SARM, *S. aureus* resistente a meticilina

El estudio COSACO ha evidenciado una prevalencia de colonización nasal por SARM en niños en España del 1,4%, presentando resistencia a meticilina el 4,4% de los aislamientos de *S. aureus*[172]. De forma destacable, en este estudio, el 17% de los aislamientos de *S. aureus* presentó resistencia a clindamicina, aumentando al 26% en el caso de SARM. En el caso de neumonía adquirida en la comunidad, se encontró resistencia a clindamicina en el 22% de las cepas de SARM, frente a un 8.7% en de las cepas sensibles a meticilina[175].

3.3. Neumonía adquirida en la comunidad por *Staphylococcus aureus* resistente a meticilina en pediatría

Las neumonías son una causa importante de morbimortalidad en la población pediátrica, y SARM se encuentra entre los microorganismos que producen neumonías adquiridas en la comunidad (NAC) de mayor gravedad clínica. En las últimas dos décadas, en relación con la vacunación sistemática frente a *Haemophilus influenzae* serotipo b y neumococo, se ha observado un aumento discreto en la prevalencia de *S. aureus* como agente causal.

Actualmente, en niños hospitalizados con NAC, es el agente etiológico del 1% de los casos con aislamiento microbiológico y en torno al 15% de las NAC típicas de etiología bacteriana. Varios estudios han descrito las características de las NAC por *S. aureus* en pediatría, mostrando un amplio rango en la prevalencia de resistencia a meticilina en los aislamientos de *S. aureus*, desde el 13% al 75,6%, según el periodo y región evaluada[179–184]. Estos aislamientos se caracterizan por tener una alta virulencia, al producir con más frecuencia leucocidina de Panton-Valentine[173,177]. Así, las NAC por SARM se han asociado a mayor morbilidad y riesgo de complicaciones[185], aunque con resultados contradictorios [184,186,187]. Además, varios estudios han descrito mayor

frecuencia de neumonías por SARM en niños de menor edad, especialmente en lactantes[183,184,188,189].

3.4. Tratamiento de las infecciones por *Staphylococcus aureus* resistente a meticilina en pediatría

El adecuado control del foco debe considerarse el primer escalón y una prioridad absoluta para un tratamiento eficaz en infecciones por este microorganismo[45]. Ello implica, por ejemplo, en el caso de bacteriemias relacionadas con un catéter vascular, su retirada, o en el caso de abscesos, su drenaje. En caso de bacteriemias persistentes a pesar de un tratamiento correcto y de un buen control del foco, deberá realizarse una búsqueda activa de focos a distancia, al tratarse de una posible causa de dicho fracaso[24].

Los glucopéptidos (vancomicina o teicoplanina) se han posicionado hasta la fecha como los antibióticos de elección para el tratamiento de las infecciones graves por SARM, incluido las bacteriemias[33,190]. Han aparecido nuevas alternativas, pero no ha habido ningún ensayo que demuestre la superioridad de estos nuevos antibióticos frente a vancomicina[191]. Entre las limitaciones de vancomicina, destaca su alta unión a proteínas plasmáticas, lo cual limita su difusión a tejidos. Por ello, es fundamental la monitorización de las concentraciones plasmáticas, garantizando unas concentraciones plasmáticas adecuadas[35].

En las últimas décadas, algunos centros han evidenciado un progresivo aumento de la CMI de estos antibióticos frente a los aislamientos de *S. aureus*[192] . Además, existen dudas sobre el mayor riesgo de fracaso terapéutico en el caso de cepas con CMI de vancomicina ≥1,5 mg/L[193], por lo que se recomienda no utilizar vancomicina si la CMI es ≥2 mg/L; y para CMI de 1,5 mg/L (E-test), valorar alternativas[194].

Entre las opciones disponibles, clindamicina y linezolid inhiben la síntesis de toxinas, por lo que su uso en monoterapia o combinado con otros antibióticos puede ser útil en el caso de infecciones por cepas productoras de toxinas, lo que es frecuente en estas infecciones[195,196]. Linezolid presenta muy buena difusión a tejidos y permite

realizar terapia secuencial de vía intravenosa a oral, aunque puede presentar toxicidad hematológica y neurológica en tratamientos prolongados (principalmente a partir de la tercera semana de tratamiento)[197,198]. En la actualidad, linezolid no está aprobado por la Agencia Europea del Medicamento (EMA) en menores de 18 años, pero sí por la FDA (*Food and Drug Administration* de EE.UU.).

Rifampicina presenta una excelente actividad frente al biofilm, siendo recomendable asociarlo al tratamiento antibiótico de elección en el caso de algunas infecciones por *S. aureus* relacionadas con material protésico[78,199]. Cotrimoxazol mantiene, en la actualidad, actividad frente a la mayoría de los aislamientos de SARM[8,24]. Además, está comercializado en España en solución oral, siendo una buena opción en infecciones leves o moderadas, o como paso secuencial a vía oral.

En bacteriemia o endocarditis por SARM con CMI de vancomicina ≥1,5 mg/L, una buena opción es daptomicina[200]. Este antibiótico es bactericida, está aprobado en niños mayores de un año y se administra en una sola dosis diaria[201]. Como aspectos negativos, destaca su inactivación por el surfactante pulmonar, por lo que no es apropiado en el caso de neumonías[202].

Ceftarolina es una cefalosporina de quinta generación aprobada desde el nacimiento para el tratamiento de infecciones de piel y partes blandas (IPPB) y NAC, con excelente perfil de seguridad y buena actividad frente a SARM, aunque la experiencia en niños es aún limitada[203,204]. Ceftobiprol, una cefalosporina activa frente a SARM similar a ceftarolina, ha sido aprobada recientemente en la edad pediátrica[205].

Dalbavancina y oritavancina son dos nuevos lipoglucopéptidos que han sido aprobados recientemente en adultos para el tratamiento de IPPB por SARM y otros microorganismos grampositivos[206,207]. Tedizolid es un nuevo fármaco con una estructura similar a linezolid, con menor toxicidad hematológica, aprobado a partir de 12 años para el tratamiento de las IPPB[208]. Dalvabancina ha sido aprobado en 2022 para las IPPB a partir de los tres meses de edad[209]. Tedizolid se encuentra en ensayo de fase III en menores de 12 años[210].

Diferentes combinaciones han demostrado actividad sinérgica in vitro (p.ej., daptomicina + ceftarolina, daptomicina + fosfomicina), pero con resultados clínicos discordantes en adultos[211]. Su uso parece razonable en el caso de bacteriemias persistentes a pesar de buen control del foco [210,212]. En la tabla 7 se incluye una propuesta de tratamiento según el tipo de infección elaborada por la Sociedad Española de Infectología Pediátrica (SEIP) [24].

Infección	**Tratamiento de elección**	**Alternativa**
IPPB	Clindamicina o cotrimoxazol	Linezolid, vancomicina, teicoplanina, ceftarolina o daptomicina
Neumonía	Clindamicina, vancomicina o linezolid	Ceftarolina, teicoplanina o cotrimoxazol
Bacteriemia y endocarditis	Vancomicina o daptomicina	Teicoplanina, linezolid o ceftarolina
Infecciones osteoarticulares	Clindamicina o cotrimoxazol	Vancomicina, linezolid o levofloxacino
SNC	Vancomicina	Linezolid

Tabla 7. Tratamiento de las infecciones producidas por *S. aureus* resistente a meticilina. IPPB, infecciones de piel y partes blandas; IOA, infección osteoarticular; SNC, sistema nervioso central.

4. Resistencia en *Enterococcus* spp.

El género *Enterococcus* consiste en cocos grampositivos anaerobios facultativos, que se distribuyen como diplococos o en cadenas cortas, que han sido aislados en una amplia variedad de animales, plantas y fuentes ambientales[213]. Aunque hasta la fecha se han descrito 58 especies, *Enterococcus faecalis*, seguido de *E. faecium,* son responsables de la mayoría de las infecciones en la edad pediátrica[214].

Estos microorganismos se encuentran frecuentemente formando parte de la microbiota del tracto gastrointestinal, aunque pueden convertirse en patógenos oportunistas, especialmente en neonatos, pacientes críticos o inmunocomprometidos[215]. Las infecciones por este grupo de microorganismos en niños sanos son infrecuentes fuera de la edad neonatal. La mayoría de las infecciones por este género ocurren en individuos con solución de continuidad de las barreras físicas superficiales, como el tracto gastrointestinal o el tracto urinario[216]. Otros factores asociados con las infecciones por *Enterococcus* spp. en los niños son la hospitalización prolongada, el tratamiento con antibióticos y las alteraciones del sistema inmunológico. Están asociados a distintas infecciones, incluidas las ITUs, especialmente en neonatos y niños con uropatías complejas, infecciones de distintos dispositivos, bacteriemias y endocarditis infecciosa y, más raramente, en las IPPB [213,215].

Un estudio que evaluó la epidemiología de las infecciones relacionadas con la asistencia sanitaria en EE.UU. posicionó a *Enterococcus* spp. como el tercer aislamiento más frecuente, siendo la principal causa de bacteriemias asociadas a la vía central en pacientes ingresados en unidades de cuidados intensivos y la segunda en unidades de oncología[217]. Además, a nivel global, se estima que en 2019 se produjeron más de 80.000 muertes atribuidas a infecciones por microorganismos resistentes del género *Enterococcus*[4].

4.1. Mecanismos de resistencia

Los microorganismos de este género se caracterizan por presentar un fenotipo resistente esperado (comúnmente denominado como resistencia intrínseca) a múltiples antimicrobianos, incluyendo casi todas las cefalosporinas (con la excepción de ceftarolina en el caso de *E. faecalis*), debido a la presencia de proteínas de unión a la penicilina (PBPs) con baja afinidad por las mismas, así como a cotrimoxazol, clindamicina y macrólidos, lo que conlleva dificultades en su tratamiento[218]. Aunque también presentan resistencia intrínseca a aminoglucósidos por la impermeabilidad de su pared celular frente a éstos, la combinación con un inhibidor de la pared celular (p.ej., ampicilina), permite la entrada del aminoglucósido, lo que conlleva a una actividad bactericida de esta asociación, por lo que se recomienda en infecciones graves[24,219]. Asimismo, también se obtiene sinergismo bactericida con la asociación de ampicilina y ceftriaxona, pero solamente frente a *E. faecalis*.

E. faecalis es casi uniformemente sensible a aminopenicilinas, siendo ampicilina, penicilina o amoxicilina los tratamientos de elección[24,218]. En casos raros, las cepas de *E. faecalis* pueden producir una β-lactamasa codificada por un plásmido similar a la β-lactamasa que se encuentra en los estafilococos[216]. Estos aislados son completamente resistentes a las penicilinas, por lo que se necesitan antibióticos alternativos o la combinación de una penicilina junto a un inhibidor de la β-lactamasa.

Las diferentes especies de *Enterococcus* pueden adquirir distintas resistencias (p.ej., a ampicilina, vancomicina, resistencia de alto nivel a aminoglucósidos, etc.), disminuyendo todavía más las opciones terapéuticas. La resistencia a vancomicina en *Enterococcus* spp. emergió en los años 80, distribuyéndose ampliamente durante las décadas siguientes[213]. La exposición previa a glucopéptidos ha demostrado ser un factor de riesgo de resistencia a vancomicina, y la disminución en su consumo podría ser un factor relacionado con una menor incidencia de aislamientos resistentes frente a este antibiótico[220].

E. faecium suele ser resistente a ampicilina, mediado por la hiperproducción de la PBP5, que tiene una baja afinidad natural por las penicilinas, pero sensible a

vancomicina. *Enterococcus gallinarum* y *Enterococcus casseliflavus*, mucho más infrecuentes, son intrínsecamente resistentes a vancomicina (aunque no a teicoplanina), pero habitualmente sensibles a aminopenicilinas.

E. faecalis y *E. faecium* pueden adquirir resistencia a vancomicina y a teicoplanina mediada por el gen *vanA*, o bien mediada por el gen *vanB*, que confiere resistencia *in vitro* a vancomicina, pero no a teicoplanina[218]. Sin embargo, se ha descrito la emergencia de resistencia a teicoplanina durante el tratamiento con este antimicrobiano, por lo que no se aconseja utilizarlo en estos casos. La resistencia a vancomicina de *E. gallinarum*, *E. casseliflavus* y *Enterococcus flavescens* es intrínseca y está mediada por el gen *vanC*, aunque solo confiere resistencia a vancomicina, pero no a teicoplanina, por lo que podría utilizarse para el tratamiento de infecciones por estos microorganismos[221].

La resistencia de *Enterococcus* spp. frente a linezolid y daptomicina, actualmente es muy infrecuente, y está principalmente relacionada con brotes en instituciones sanitarias o con la exposición previa a los mismos[222]. Sin embargo, existe una evidencia creciente sobre la resistencia *de n*ovo a daptomicina durante el tratamiento[223]. Además, la dosis estándar de daptomicina ha demostrado mayor mortalidad en bacteriemias por *E. faecium*, por lo que se recomienda una dosis alta en estos casos[223].

4.2. Epidemiología de las resistencias en *Enterococcus* spp.

Según los datos reportados por el ECDC, en los últimos años la resistencia a vancomicina en España en muestras invasivas procedentes de todos los grupos etarios ha sido del 0,1-0,3% para *E. faecalis* y del 1,8-2,5% para *E. faecium*, presentando una tendencia estable[97]. En comparación con otros países europeos, la tasa de resistencia a vancomicina en *E. faecium* es baja, situándose la tasa de resistencia más alta en los países del sur y este de Europa (Figura 11). La prevalencia de esta resistencia en España se mantiene estable durante los últimos años (Figura 12). Además, comparando la resistencia a vancomicina en *E. faecium,* en España. según los distintos grupos etarios, vemos que la mayor prevalencia se sitúa en los adultos (Figura 13).

Un estudio que evaluó la prevalencia de resistencias en aislamientos procedentes de hemocultivos en pacientes menores de 18 años en el 2011-2012 en 12 países europeos, mostró una prevalencia de resistencia a vancomicina del 8,3% en aislamientos *E. faecium* [12]. Otro estudio realizado en EE.UU. que evaluó los aislamientos pediátricos de *Enterococcus* spp. entre los años 2013 y 2018 objetivó una prevalencia de resistencia a vancomicina en *E. faecium* del 18%[214], muy superior a la registrada en la actualidad en España.

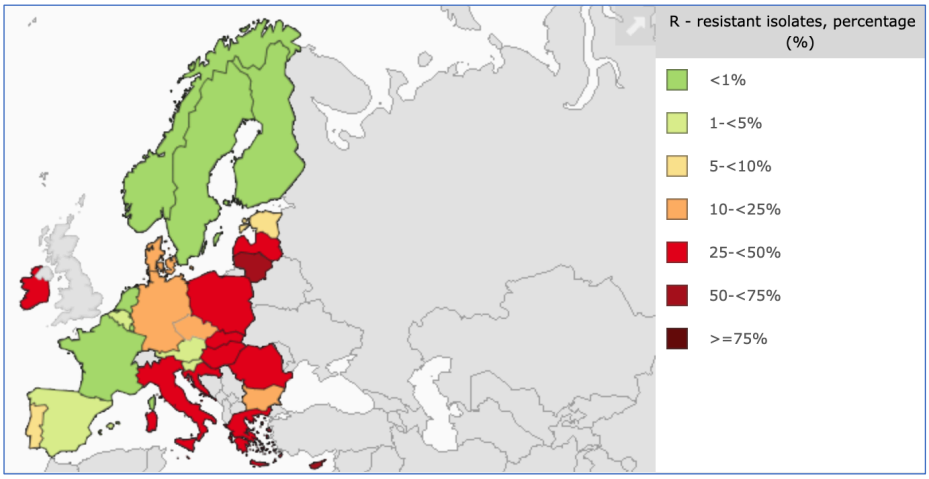

Figura 11. Porcentaje de aislamientos de *E. faecium* resistentes a vancomicina de muestras invasivas en Europa en el año 2021. Datos procedentes de EARS-Net (The European Antimicrobial Resistance Surveillance Network), accesible en: https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc

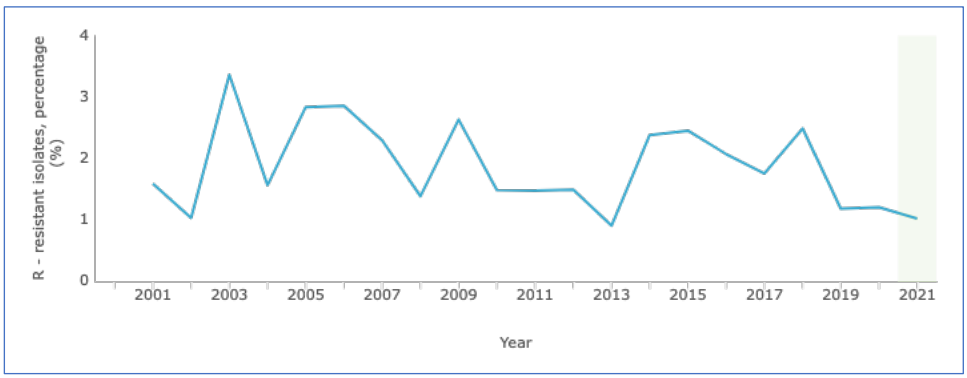

Figura 12. Evolución de la prevalencia de aislamientos de *E. faecium* resistentes a vancomicina de muestras invasivas en España durante los últimos años.

Datos procedentes de EARS-Net (The European Antimicrobial Resistance Surveillance Network), accesible en: https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc

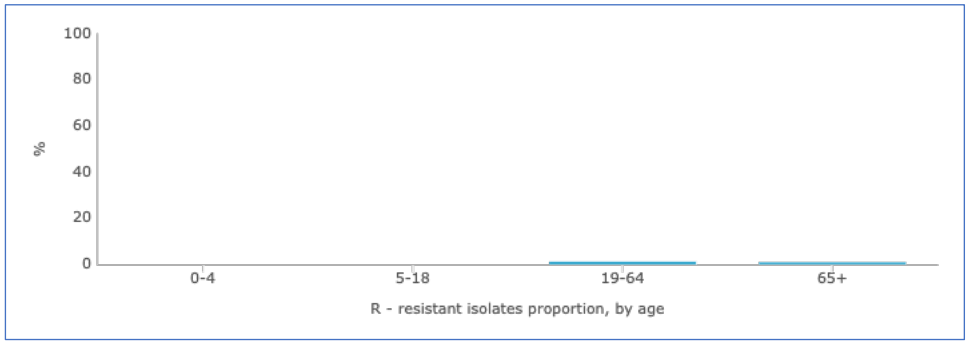

Figura 13. Comparación de la prevalencia de resistencia a vancomicina en aislamientos de *E. faecium* en España en el año 2021 según los diferentes grupos etarios. Datos procedentes de EARS-Net (The European Antimicrobial Resistance Surveillance Network), accesible en: https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc

4.3. Tratamiento de las infecciones por *Enterococcus* spp.

Siempre que el aislamiento sea sensible a ampicilina, este antibiótico será el tratamiento de elección (Tabla 8). La alternativa cuando exista resistencia a ampicilina serían los glucopéptidos (vancomicina o teicoplanina). En el caso de infecciones graves, como endocarditis, meningitis o bacteriemia complicada, generalmente se recomienda la combinación de dos antibióticos con el objetivo de alcanzar una sinergia bactericida[24,222,224]. Cuando se administran combinaciones con aminoglucósidos, hay que evaluar previamente si existe resistencia de alto nivel *in vitro* mediante la determinación de la CMI. En el caso de resistencia de alto nivel (p.ej., CMI de gentamicina ≥500 mg/L), habría que utilizar alternativas como ampicilina con ceftriaxona en el caso de *E. faecalis.* Cuando la cepa es resistente a ampicilina y glucopéptidos, daptomicina o linezolid pueden ser una alternativa[222]. En el caso de utilizar daptomicina para el tratamiento de bacteriemias, se recomienda el uso de dosis

altas. En la Tabla 8 se incluye una propuesta de tratamiento, según el perfil de resistencia y el tipo de infección elaborada por la SEIP[24].

Antibiótico principal	De elección	Ampicilina		
	Si R a ampicilina	Vancomicina o teicoplanina		
	Si R a ampicilina y glucopéptidos	Daptomicina o linezolid		
Combinación	Infecciones leves	No precisa		
	Infecciones graves (endocarditis, meningitis y bacteriemia complicada)	Ausencia de RAN a aminoglucósidos	Gentamicina (junto a ampicilina o vancomicina)	
		RAN a aminoglucósidos	Si S a ampicilina:	Ampicilina + ceftriaxona (sólo para a *E. faecalis*)
			Si R a ampicilina:	Daptomicina + (ceftarolina, ampicilina o fosfomicina), vancomicina + rifampicina o linezolid ± (fosfomicina o fluoroquinolonas)

Tabla 8. Tratamiento antimicrobiano de infecciones por *Enterococcus* spp. R, resistente; S, sensible; RAN, resistencia de alto nivel (CMI ≥500 mg/L de gentamicina).

II. Hipótesis y objetivos

1. Hipótesis

I. Las infecciones por bacilos gramnegativos resistentes a carbapenemes en pediatría son más frecuentes en pacientes complejos con factores de riesgo asociados, presentando estas infecciones, a su vez, mayor mortalidad que las producidas por bacilos gramnegativos sensibles a carbapenemes.

II. Se ha producido un incremento en la incidencia de NAC por SARM en niños en la Comunidad de Madrid, presentando peor pronóstico que otras etiologías bacterianas.

III. Durante los últimos años se ha evidenciado un incremento en la prevalencia de BMR en aislamientos bacterianos en hemocultivos de pacientes pediátricos ingresados en unidades de alta complejidad.

IV. Los pacientes pediátricos ingresados por infección por SARS-CoV-2 durante los primeros meses de la pandemia presentaron un elevado consumo de antibióticos, lo cual podría asociarse a mayor resistencia a los mismos.

V. La prevalencia de resistencia a carbapenemes en aislamientos pediátricos en sangre de *P. aeruginosa* ha aumentado en los últimos años, y se asocia, a su vez, con mayor mortalidad.

2. Objetivos

2.1. Objetivo primario

Conocer la epidemiología reciente de las infecciones por BMR en pediatría, su perfil clínico y microbiológico, así como los determinantes asociados con su desarrollo.

2.2. Objetivos secundarios

- Evaluar la epidemiología, características clínicas y perfil microbiológico de las infecciones por bacilos gramnegativos resistentes a carbapenemes en pediatría.
- Describir las características clínicas y epidemiológicas, tratamiento y evolución de las neumonías comunitarias por SARM en niños en la Comunidad de Madrid.
- Analizar la prevalencia de prescripción de antibióticos, los factores de riesgo relacionados con su prescripción y las tendencias de consumo en niños hospitalizados con COVID-19 o síndrome inflamatorio multisistémico relacionado con el SARS-CoV-2 (MIS-C) en España.
- Describir la prevalencia de BMR y sus cambios epidemiológicos durante los últimos años en aislamientos de hemocultivos de pacientes pediátricos hospitalizados en unidades de alta complejidad.
- Conocer las características clínicas y microbiológicas de las bacteriemias por *P. aeruginosa* en pediatría los últimos años e investigar la mortalidad a los 30 días y los factores de riesgo asociados con la resistencia a los carbapenemes.

III. Material, métodos y resultados

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MINIREVIEW

Carbapenem-Resistant Gram-Negative Bacterial Infections in Children

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ABSTRACT Carbapenem-resistant organisms (CRO) are a major global public health threat. *Enterobacterales* hydrolyze almost all β-lactams through carbapenemase production. Infections caused by CRO are challenging to treat due to the limited number of antimicrobial options. This leads to significant morbidity and mortality. Over the last few years, several new antibiotics effective against CRO have been approved. Some of them (e.g., plazomicin or imipenem-cilastatin-relebactam) are currently approved for use only by adults; others (e.g., ceftazidime-avibactam) have recently been approved for use by children. Recommendations for antibiotic therapy of CRO infections in pediatric patients are based on evidence mainly from adult studies. The availability of pediatric pharmacokinetic and safety data is the cornerstone to broaden the use of proposed agents in adults to the pediatric population. This article provides a comprehensive review of the current knowledge regarding infections caused by CRO with a focus on children, which includes epidemiology, risk factors, outcomes, and antimicrobial therapy management, with particular attention being given to new antibiotics.

KEYWORDS carbapenem-resistant *Enterobacterales*, antimicrobial resistance, antibacterial agents, children, epidemiology, carbapenems, multidrug resistance, pediatric drug therapy

Carbapenem-resistant organisms (CRO) are a major global public health threat. Specific pediatric reviews and recommendations have been established for the diagnosis and treatment of infections caused by CRO in children (1, 2). However, the most relevant information regarding this topic has been generated from observational studies conducted predominantly in adults (3). Furthermore, new knowledge about the epidemiology and therapy of these infections, including new drug combinations (e.g., ceftazidime-avibactam or meropenem-vaborbactam), has emerged over the past few years, making it necessary to update this topic in the pediatric field.

MICROBIOLOGY

Among the *Enterobacterales* (previously known as the family *Enterobacteriaceae*), at present, the most frequent mechanism of resistance to carbapenems is the production of carbapenemases. Carbapenemases are β-lactamases that hydrolyze penicillins, in most cases cephalosporins, and to various degrees carbapenems and monobactams. These enzymes are usually acquired, are encoded by genes on transposable elements located on plasmids, and are readily transferable. Furthermore, carbapenemase-producing strains frequently possess mechanisms of resistance to a wide range of antimicrobial agents, including aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole. Carbapenemases are classified into three main groups (Table 1) (4).

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TABLE 1 Molecular classification of carbapenemase enzymes

Ambler class	Common enzymes	Microorganisms	Hydrolyzing mechanism	Carbapenem resistance	Aztreonam	Novel active β-lactams	Novel active non-β-lactams
A	KPC, NMC, GES, SME, IMI	*K. pneumoniae*, *E. coli*, *Serratia marcescens*, *Enterobacter cloacae*, *P. aeruginosa*, *A. baumannii*	Serine based	High	Resistant	Ceftazidime-avibactam, aztreonam-avibactam,[a] imipenem-relebactam, meropenem-vaborbactam, cefiderocol	Eravacycline, plazomicin
B	VIM, IMP, NDM	*K. pneumoniae*, *E. coli*, *S. marcescens*, *E. cloacae*, *Citrobacter* spp., *Proteus* spp., *Morganella* spp., *Providencia* spp., *P. aeruginosa*	Zinc based	Variable	Susceptible[b]	Aztreonam-avibactam,[a] cefiderocol	Eravacycline, plazomicin[c]
D	OXA (most common, OXA-48-like)	*K. pneumoniae*, *E. coli*, *Citrobacter* spp., *Proteus* spp.	Serine based	Medium	Susceptible[b]	Ceftazidime-avibactam, aztreonam-avibactam,[a] cefiderocol	Eravacycline, plazomicin

[a]Currently not approved by FDA/EMA.
[b]Several strains coproduce other β-lactamases (ESBLs, AmpCs, etc.), making them nonsusceptible to aztreonam.
[c]Not active against many NDM-producing strains due to the frequent coproduction of 16S rRNA methyltransferase.

Decreased susceptibility to carbapenems may also be caused by the production of extended-spectrum β-lactamases (ESBLs) or AmpC enzymes combined with decreased permeability due to the modification or downregulation of porins. Carbapenemases differ in their activity against specific β-lactams.

Although the most frequent mechanisms of resistance of *Pseudomonas aeruginosa* to carbapenems, including porin production (the loss or reduced copy numbers of OprD), are nontransferable, the overproduction of active efflux pumps, the AmpC β-lactamase, and ESBLs have been reported to be the main contributors to multidrug resistance phenotypes in *P. aeruginosa* isolates. In addition, over the last decade, an increasing prevalence of carbapenemases, mainly the Verona integron-encoded metallo-β-lactamase (VIM) and the New Delhi metallo-β-lactamase (NDM), among *P. aeruginosa* strains has been reported. Resistance to carbapenems among *Acinetobacter baumannii* strains is very frequent and, in general, is chromosomally encoded and nontransferable. However, this species can also carry plasmid-mediated carbapenemases (5).

EPIDEMIOLOGY

In parallel to what has been observed in adult populations, a progressive increase in the incidence of infections due to multidrug-resistant (MDR) microorganisms has occurred in children. Published studies during the last decade have reported that the frequency of carbapenem resistance (CR) in children in the United States increased from 0% in 1999 and 2000 to 0.47% in 2010 and 2011 among *Enterobacterales* isolates (6), from 9.4% in 1999 to 20% in 2012 among *P. aeruginosa* isolates (7), and from 0.6% in 1999 to 6.1% in 2012 among *A. baumannii* isolates (8). An Italian nationwide survey among centers participating in a pediatric hematology-oncology cooperative study group reported a 2-fold increase in the carbapenem-resistant *Enterobacterales* (CRE) colonization rate and a 4-fold increase in the incidence of CRE bloodstream infections (BSIs) from 2012 to 2013 (9).

In most settings, colonization and infection by CRO mainly occur in the adult population. An active surveillance system involving 7 U.S. states detected a total of 599 isolates of CRE occurring in 481 patients during 2012 and 2013 (10). However, only 3 of those cases (0.6%) were under 18 years of age. In fact, with the exception of some countries where CRE are highly endemic (e.g., India or Turkey) and where these microorganisms are frequently isolated in pediatric units, CRE are mainly found in adult intensive care units (ICUs) and oncology wards (11–14). Thus, pediatric data reported worldwide (including in countries such as the United Kingdom, the United States, Spain, or Italy) have mostly been consistent with the sporadic spread and sporadic outbreaks of CRE infections (15–18).

Comparative surveillance data from routine bloodstream isolates in Europe demon-

strated a different antimicrobial resistance pattern between isolates from children and those from adults. The prevalence of CR among *Klebsiella pneumoniae* strains was higher in adults (13.5% versus 6.5% in children), whereas CR in *P. aeruginosa* was more frequent in children (30.7% versus 23% in adults) (19). A literature review of bacteremia in oncology patients also described a difference in the prevalence of CR among age groups (20). In two additional studies, the median rate of CR among Gram-negative isolates in adults was 20% (range, 11 to 72%), whereas in children it was 9 to 10% (21, 22). Several centers in different countries have described pediatric epidemiological peculiarities, with the bacterial clones in pediatric units being different from those in adult units within the same center or with the regional epidemiology being different among children and adults (21, 22).

Infections due to CRO in children are primarily health care associated (17). A recent Greek report on active surveillance of central line-associated BSIs (CLABSIs) in children conducted from 2016 to 2017, including in neonatal ICUs (NICUs), pediatric ICUs (PICUs), and oncology wards, described the impressively high prevalence of CRO: 45% CR among *Klebsiella* spp., 36% among *Enterobacter* spp., and 38% among *P. aeruginosa* strains (23). A study from Lake et al. assessed the pathogen distribution and antimicrobial resistance among pediatric health care-associated infections reported to the U.S. National Health Care Safety Network (24). It highlighted the notable difference in the prevalence of CRO isolates among different sources and locations. In the case of pathogens from CLABSIs, the prevalence of CR *K. pneumoniae* was higher in oncology wards (3.3%), whereas the prevalence of CR *P. aeruginosa* was higher in the general ward (22.2%).

A considerable number of studies have described the high prevalence and the large number of outbreaks of CRO infections in NICUs (11, 13, 25–28). The NICU population deserves special consideration because of the high risk of complications and mortality. Indeed, the highest burden of attributable deaths and disability-adjusted life years caused by infections with antibiotic-resistant bacteria in Europe has been described in infants (age $<$1 year), with CR or colistin-resistant *Escherichia coli*, *K. pneumoniae*, *Acinetobacter* spp., and *P. aeruginosa* strains as a group being the third most significant cause of attributable deaths and disability-adjusted life years within this age group (29). Several studies have highlighted the importance of MDR Gram-negative microorganisms as a cause of sepsis in NICUs in developing countries (13, 25). The high prevalence of CR in NICUs in these countries nowadays is quite remarkable, given that in reviews evaluating antimicrobial resistance among neonatal pathogens in developing countries published just 10 years ago, this type of resistance was not even mentioned (30). A cohort study characterizing the antimicrobial resistance profile of pathogens causing sepsis in neonates admitted to three NICUs in India showed alarming CR rates of 78% (174/222) among *Acinetobacter* spp., 31% (21/68) among *Pseudomonas* spp., 35% (59/169) among *Klebsiella* spp., 20% (9/44) among *Enterobacter* spp., and 15% (21/137) among *E. coli* strains (13). This high prevalence of CR isolates in neonatal sepsis has notable implications, since the empirical treatment proposed by WHO would not be adequate in these settings. Suboptimal infection control programs have been one of the most important factors proposed in relation to the high burden of CRE found in NICUs and PICUs in some hospitals compared to the prevalence found in adult units from the same hospital (14).

MORTALITY

CRO infections in the pediatric population have been shown to increase the risk of mortality 6- to 11-fold compared to that in children with non-CRO infections (31, 32); on the other hand, a number of studies were unable to document worse outcomes in pediatric patients with CRO infections (33). Mortality rates in children with CRO infections range from 8% to 52% (100% in a small case series) (9, 18, 31, 32, 34–39) (Table 2), depending on the source of infection, the underlying diseases, and age. One study that evaluated 50 health care-acquired CRE BSIs in children from a tertiary hospital in India, mostly caused by NDM-producing *K. pneumoniae*, found several significant risk

TABLE 2 Case series that describe treatment of pediatric infections caused by carbapenem-resistant Gram-negative microorganisms[a]

Reference	Yr	Country	No. of cases or episodes (description)	Age	Source(s)	Isolates	Resistance mechanism	% of patients receiving combined treatment[b] (no. of patients treated/total no.)	% mortality[c] (no. of patients who died/ total no.)
40	1999–2010	USA	6	3.5–18 yr	5 BSIs, 1 UTIs	*S. marcescens*, *E. coli*, *K. pneumoniae*	KPC, IMP, and other noncarbapenemases	83 (5/6)	17 (1/6)
51	2002–2010	Several countries (review)	64 (treatment data were available for 24)	0–17 yr	30% BSIs, 25% UTIs, 19% gastrointestinal, 17% respiratory, 9% others	*Enterobacterales*	KPC, NDM, VIM, and other noncarbapenemases	21 (5/24)	10 (5/52)
53	2010	USA	5 (3 infected)	3–11 yr	2 BSIs, 2 respiratory, 1 peritoneal	*K. pneumoniae*	KPC	66.7 (2/3)	0[d]
17	2011–2012	UK	24 (treatment data were available for 9)	0–12 yr (infected cases)	5 urine, 2 BSIs, 2 skin	*Enterobacterales*	KPC, NDM, and other noncarbapenemases	20 (1/5)	11 (1/9)
52	2012–2013	Italy	15 (treatment data were available for 6)	Mean, 10.6 yr (SD, 1.8 yr)	47% urine, 27% BSIs, 26% others	11 *K. pneumoniae* isolates, 4 *E. coli* isolates	KPC in 12, OXA-48 in 2, MBL in 1	66 (4/6)	33 (2/6)
38	2008–2013	Colombia	43 episodes (34 infected)	<15 yr	35% UTIs, 23% IAIs, 18% BSIs, 14% pneumonia, 10% others	*K. pneumoniae*	KPC	51.2 (22/43)	38 (11/34)
36	2002–2014	USA	15 episodes (treatment data were available for 12)	4 mo–11 yr	4 urine, 4 BSIs, 3 respiratory, 1 peritoneal	*K. pneumoniae*, *E. coli*, and *E. cloacae*	VIM, NDM, and IMP	41.7 (5/12)	16.7 (2/12)
18	2011–2014	Italy	74 isolates (69 cases; 34 infections)	0–18 yr	35% BSIs and CLC tip, 38% respiratory, 6% CSF, 21% others	*Enterobacterales*	KPC (61.4%), OXA-48 (13.6%), MBL	61.8 (21/34)	23.5 (8/34)
68	2011–2014	China	138 (54 infected)	<18 yr	BSIs	*K. pneumoniae*	NDM, IMP, KPC, and others	38.9 (21/54) and 63 (34/54)[e]	18.5 (10/54)
34	2011–2014	China	52	0–16 yr	BSIs	*K. pneumoniae*	NDM, IMP, KPC, and other noncarbapenemases	38.5 (20/52)[f]	11.5 (6/52)
35	2014–2015	India	50	<17 yr	BSIs	*K. pneumoniae* (66%), *E. coli* (34%)	Mostly NDM and also OXA and noncarbapenemases	68 (34/68)[g]	52 (26/50)
39	2015	Morocco	6	1–13 days	5 BSIs, 1 urine	*K. pneumoniae*	OXA-48	100 (6/6)[g]	100 (6/6)
32	2011–2016	USA	103 (31 infections)	<21 yr	39% urine, 35% respiratory, 13% wound, 11% BSIs, 3% peritoneal	*Enterobacterales*	Mostly KPC and also NDM, OXA, and noncarbapenemases	32.2 (10/31)	6.5 (2/31)
26	2015–2016	China	88 (39 infections)	Neonates	50% pneumonia, 43% UTIs, 7% others	*K. pneumoniae*	NDM (87.2%)	94.9 (37/39)	2.7 (1/37)
78	2017–2018	Greece	9 episodes (8 cases)	13 days–4.5 yr	6 BSIs (2 also CSF), 2 rectal, 1 urine	*K. pneumoniae*	CR *K. pneumoniae* in 7 episodes (mechanism not described)	100 (8/8)[h]	0 (0/8)

[a]BSIs, bloodstream infections; CLC, central line catheter; CSF, cerebrospinal fluid; KPC, *Klebsiella pneumoniae* carbapenemases; MBL, metallo-β-lactamase, NDM, New Delhi metallo-β-lactamase; OXA-48, oxacillinase 48; IAIs, intra-abdominal infections; IMP, imipenemase, UTIs, urinary tract infections; VIM, Verona integron-encoded metallo-β-lactamase.

[b]Combination treatment was described in different ways (i.e., empirically/targeted) and was not always specified.

[c]Mortality among infected patients.

[d]No deaths were related to infection.

[e]Twenty-one patients received empirical treatment, and 34 received targeted treatment

[f]The 20 patients received combination treatment. In 13 patients receiving monotherapy, the therapy was changed to combined therapy after the isolation of bacteria.

[g]The patients were treated empirically.

[h]All patients received ceftazidime-avibactam.

factors for mortality, including pediatric PICU admission, intubation, inotropic support, respiratory source, and failure to clear bacteremia (35). A meropenem MIC of >8 mg/liter for the isolate considerably increased the risk of mortality (odds ratio, 13.9 [95% confidence interval, 1.5 to 125.6]; $P = 0.008$) in that study. Regarding the difference in mortality between children and adults, a multicenter national study based in Greece showed higher mortality among adults with infections caused by CRO than among children with such infections (34.9% versus 21.1%) (37).

RISK FACTORS FOR INFECTION OR COLONIZATION

The risk factors for infection or colonization by CRO in children mirror those described for adults. In most cases, patients suffer from underlying comorbid conditions or were admitted to a PICU or NICU (16, 37, 40). Specific risk factors for colonization or infection with CRO in children include previous antibiotic exposure (mainly to broad-spectrum antibiotics and for an extended duration), the use of medical devices (mostly mechanical ventilation), an ICU stay, prior surgery, and prolonged hospitalization (18, 25, 31, 33, 41–45) (Table 3).

Regarding previous antimicrobial exposure, in a recent comparative study performed in children, only carbapenem exposure was significantly associated with CRO infections in the multivariate analysis (41). Other studies in the pediatric population have also observed that prior use of carbapenems was a risk factor for CRO infection (25, 31, 33, 43–45). However, the relation to the use of noncarbapenem antibiotics was less clear (33, 42, 43).

Patients from countries where CRO are endemic (e.g., India, Turkey, or Egypt) (11–14, 25) may introduce CRO into pediatric institutions in countries where they are not endemic, suggesting the need for specific interventions, such as screening for colonization and specific empirical antimicrobial treatment in patients from these countries newly admitted with infectious diseases (36, 40, 42).

Although being born to a mother colonized with an extended-spectrum-β-lactamase-producing *Enterobacterales* strain increases the risk of colonization in the newborn (46, 47), current data do not support significant mother-to-newborn transmission of CRE (48, 49), with only one case (50) being reported so far. Therefore, there must be other risk factors related to colonization in these newborns.

TREATMENT

Introduction. Specific recommendations for antibiotic therapy for infections due to CRO in pediatric patients are based on studies including only adults (3) (Table 4). The availability of pediatric pharmacokinetic (PK) and safety data is the cornerstone to broaden the use of proposed agents in adults to the pediatric population. Only scarce observational studies, case series, and single reports have described the efficacy of these treatments in infected children (17, 18, 26, 32, 34–36, 38, 40, 51–53) (Table 2). Furthermore, the regulatory approval status of antibiotics in patients under 18 years old makes the treatment of infections caused by CRO more complicated in children. Antimicrobial treatment must be individualized according to the severity and the source of infection (Table 5) and the susceptibility profile of the isolated bacteria. In addition to antimicrobial treatment, other strategies, like source control, when possible, and supportive therapy, if needed, are mandatory. In children, when a CRO is isolated, expert consultation is always warranted (1). Furthermore, the emergence of resistance to new antibiotics further highlights the need for a rationalized antimicrobial treatment approach in children (54). The proposed dosing of antibiotics for infections due to CRO is shown in Table 6.

Combination therapy. Several studies conducted in adults have evaluated the combination of classic antibiotics with different mechanisms of action (e.g., polymyxins, aminoglycosides, fosfomycin, carbapenems, etc.) for the treatment of infections caused by CRO. Although combination therapies have better outcomes in some groups of adults with CRE infections (55, 56), this has not been thoroughly evaluated in children. Additionally, some data from adult studies suggest that combination treatment may

TABLE 3 Studies that have evaluated risk factors for carbapenem-resistant infection or colonization in children[a]

Reference	Yr	Country	Population	Cases (no.)	Controls (no.)	Evaluation	Risk factors	
							Univariate analysis	Multivariate analysis
44	1991–2010	Thailand	NICU	CR *A. baumannii* (14)	CS *A. baumannii*/no isolation (38/44)	Infection (BSIs)	Lower birth weight, lower duration of CVC, antibiotic use[b] (use of cefoperazone-sulbactam or imipenem)	Not reported
149	2009–2011	USA	Pediatric	CRE (13)	Not isolated CRE (52)	Infection or colonization	Previous colonization/infection with vancomycin-resistant *Enterococcus* species or ESBL-producing *Enterobacteriaceae*, antibiotic use[b] (penicillin, third-generation cephalosporin, a carbapenem, fluoroquinolone, or trimethoprim-sulfamethoxazole)	Not reported
45	2012	Turkey	Pediatric	CR *K. pneumoniae* (83)	Non-CR *K. pneumoniae* (198)	Colonization	Transfer from another institution, antibiotic use[b] (a carbapenem)	Transfer from another institution, antibiotic use[b] (a carbapenem)
41	2014	Turkey	<18 yr	CR GNB (27)	CS GN (28)	Infection	Length of hospital stay before onset of infection of >21 days, prior hospitalization, presence of a Foley catheter, antibiotic use[b] (a carbapenem or glycopeptide)	Presence of a Foley catheter, prior prolonged hospitalization, antibiotic use[b] (a carbapenem or glycopeptide)
33	2008–2015	USA	<23 yr	KPC-producing CRE (18)	CSE/no isolation (18/54)	Infection	Pulmonary and neurologic comorbidities, GI and pulmonary devices, antibiotic use[b] (a carbapenem or an aminoglycoside)	Not reported
25	2014–2016	Egypt	NICU patients (late-onset sepsis)	CR GNB LOS (100)	CS GN LOS (58)	Infection (LOS)	Feeding (longer time to start enteral feeds, exclusive breast milk, formula feeds), previous corticosteroid use, antibiotic use[b] (a cephalosporin or carbapenem and previous longer antibiotic duration), duration of total parenteral nutrition, CVC and longer duration of CVC, gastrointestinal congenital anomalies	Duration of total parenteral nutrition, antibiotic use[b] (a carbapenem)
15	2010–2014	Turkey	NICU and PICU	CR *K. pneumoniae* infected (24)	CR *K. pneumoniae* colonized (61)	Infection	Diseases (neurological or metabolic disease), neutropenia, devices (urinary catheter or tracheostomy tube), surgery, antibiotic use[b] (a carbapenem)	Metabolic disease, neutropenia, surgery, antibiotic use[b] (a carbapenem)
18	2011–2014	Italia	Pediatric	CRE infected (34)	CRE colonized (35)	Infection and colonization	Admission in a PICU or NICU and length of hospital stay	Not reported
68	2011–2014	China	<18 yr	CR *K. pneumoniae* (54)	CS *K. pneumoniae*	Infection	Older age, underlying disease, hematologic malignancies, CVC, previous immunosuppressive therapy, previous neutropenia, antibiotic use[b] (a cephalosporin, antifungal agents, or a glycopeptide)	Hematologic malignancies, antibiotic use[b] (cephalosporins)
42	2011–2015	USA	Pediatric	CRE (63)	CSE (126)	Infection and colonization	Male sex, prior surgery, ICU admission, longer length of stay before collection of a sample for culture, prematurity, devices (CVC, endotracheal tube, or Foley catheter), antibiotic use[b] (a carbapenem or antipseudomonal)	Antibiotic use[b] (an antipseudomonal), prior surgery, mechanical ventilation
43	2014–2015	Turkey	1 mo–18 yr	CR GNB bacteremia (31)	CS GNB bacteremia (66)	Infection (BSIs)	Longer hospital stay, antibiotic use[b] (a carbapenem, fluoroquinolones, or glycopeptide)	Not reported
31	2012–2016	Brazil	PICU	CR GNB HA BSIs (19)	CS GNB HA BSIs (43)	Infection (HA BSIs)	Surgery, antibiotic use[b] (a carbapenem)	Not reported
150	Not reported	India	NICU	Colonized with CRE (36)	Not colonized with CRE (274)	Colonization	Longer duration of hospital stay, feeding (lower rate of breast-feeding), devices (NG tube or ventilation), antibiotic administration	Formula feeding, antibiotic administration

[a]BSI, bloodstream infections; CR, carbapenem resistant; CRE, carbapenem-resistant *Enterobacterales*; CS, carbapenem sensitive; CSE, carbapenem-sensitive *Enterobacterales*; CVC, central vascular catheter; ESBL, extended-spectrum β-lactamase; GI, gastrointestinal; GNB, Gram-negative bacteria; HA, hospital acquired; LOS, late-onset neonatal sepsis, NG, nasogastric; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit.
[b]Antibiotic use refers to previous exposure, with variable time criteria existing among studies.

TABLE 4 Proposed treatment for carbapenem-resistant Gram-negative bacterial infections in children[a]

Characteristic	Backbone recommended	Backbone alternative	Accompanying drug[b]
Susceptible to a β-lactam			Aminoglycoside, polymyxin,[c] fosfomycin, tigecycline, or a fluoroquinolone
Meropenem MIC $\leq$ 8 mg/liter	Meropenem in extended and high-dose infusion	Ceftazidime-avibactam, meropenem-vaborbactam, ceftolozane-tazobactam, aztreonam, ceftazidime, ampicillin-sulbactam, or imipenem-cilastatin-relebactam[e]	
Meropenem MIC $>$ 8 mg/liter[d]	Ceftazidime-avibactam, meropenem-vaborbactam, ceftolozane-tazobactam, aztreonam, ceftazidime, ampicillin-sulbactam, or imipenem-cilastatin-relebactam[d]		
Resistant to all β-lactams, susceptible to at least 2 drugs			Aminoglycoside, polymyxin,[c] fosfomycin, tigecycline, or a fluoroquinolone
Susceptible to polymyxins[b]	Polymyxin[c]	Aminoglycoside, tigecycline, or a fluoroquinolone	
Resistant to polymyxins[b]	Aminoglycoside, tigecycline, or a fluoroquinolone		
Pandrug-resistant or susceptible to only one drug	Combination of $\geq$2 drugs with *in vitro* activity, including experimental drugs[f]; consider *in vitro* testing of combinations for synergy, e.g., aztreonam plus ceftazidime-avibactam[g] (131), meropenem-ertapenem (151), meropenem-fosfomycin (121), ceftazidime-avibactam-fosfomycin (152), meropenem-colistin (142)		

[a]Adapted with permission from Rodríguez-Baño et al. (3).

[b]Consider the source of infection for the backbone and accompanying drug (Table 5).

[c]Colistin (polymyxin E) or polymyxin B.

[d]The backbone alternative should especially be considered when the meropenem MIC is 4 to 8 mg/liter. Currently, the off-label use of meropenem-vaborbactam or ceftolozane-tazobactam, and ceftazidime-avibactam in some countries, in children should be limited to those with severe infections if other β-lactams have no *in vitro* activity or to those with infections caused by isolates with meropenem MICs of $\geq$4 mg/liter. Although imipenem-cilastatin-relebactam is approved for use in some countries (e.g., the United States) in adults, evidence on its pharmacokinetics, safety, and efficacy in children is scarce, so its use should be avoided until more evidence is available. Data from adults suggest that combination therapy is not needed if a new β-lactam–β-lactamase inhibitor is used as the backbone. For the treatment of nonsevere infections and according to the source of the infection, monotherapy may be an option, but monotherapy with potentially suboptimal drugs (e.g., tigecycline or colistin) should be avoided.

[e]Ceftazidime-avibactam may be used for non-MBL carbapenemase producers. Meropenem-vaborbactam may be used for KPC carbapenemase producers. Ceftolozane-tazobactam may be used for noncarbapenemase-producing *P. aeruginosa* strains. Aztreonam may be used for MBL (VIM, NDM, and IMP) or OXA-48 producers if no coproduction of ESBLs or AmpC is detected. If coproduction is detected and synergistic *in vitro* activity with avibactam is detected, combination treatment with aztreonam plus ceftazidime-avibactam may be an alternative. Ceftazidime may be used for OXA-48 producers if no coproduction of ESBLs or AmpC is detected. Ampicillin-sulbactam may be used for susceptible *Acinetobacter* spp. Imipenem-cilastatin-relebactam may be used for KPC producers or MDR *P. aeruginosa*.

[f]For these isolations, cefiderocol may be an option.

[g]Currently, aztreonam-avibactam is not available. Alternatively, it may be used with the combination of aztreonam and ceftazidime-avibactam.

not be beneficial in all settings (57). Notably, the lack of enough knowledge regarding the optimal dose of several antibiotics prescribed for the treatment of CRO infections in children raises concern about suboptimal treatment if only one antibiotic for which documented experience is limited is prescribed. Furthermore, inappropriate empirical treatment has been associated with higher mortality among pediatric patients with CRE BSIs (58). Therefore, the implementation of better methods to rapidly identify CRE may improve outcomes (59).

Over the past few years, the use of combined treatment for CRO infections has increased in children (38). An observational study in India assessing risk factors for mortality in children with CRE BSIs found that mortality rates were significantly lower in the univariate analysis when ≥2 effective drugs were used in combination (35). However, given the small number of patients included in the study and the lack of details regarding the monotherapy regimens provided, it is difficult to draw any conclusions.

An Italian multicenter study that included 34 children with CRE infections and that evaluated the influence of combined treatment on the survival rate did not find any difference between patients treated with monotherapy and patients treated with combination therapy (18). Nevertheless, the heterogeneity of the sample could not exclude the possibility that patients with more severe infections may have benefited from combination therapy. Indeed, studies in adults have proven that only high-risk patients can benefit from combined treatment (55, 60). Unlike adult patients, mortality risk indexes (e.g., the Pitt or Charlson score in adults) are not broadly used in children, making this approach more difficult to apply.

Data from clinical trials and observational studies conducted in adults have demonstrated the noninferiority of monotherapy with newer agents, such as ceftazidime-avibactam, compared to combination therapy (61). The general consensus for the treatment of CRO infections in adults is that infections caused by susceptible strains can be treated in most cases with monotherapy with new agents (i.e., ceftazidime-avibactam, meropenem-vaborbactam, or ceftolozane-tazobactam), but nothing is known with certainty in children.

Taking into account this knowledge regarding the treatment of nonsevere infections, according to the source of the infection, monotherapy may be an option in certain circumstances, while monotherapy with potentially suboptimal drugs (e.g., tigecycline or colistin) should be avoided. However, due to the limitations of most of the published pediatric studies, such as small sample sizes or selection bias, further studies in pediatric patients are needed.

Carbapenems. Several studies have evaluated the safety and pharmacokinetics of meropenem in pediatric patients (62, 63). Due to the higher probability of reaching the pharmacodynamic target for isolates with MICs of ≤8 mg/liter when meropenem is administered at a higher dose by extended infusion in adults (64), this approach has been extrapolated to pediatric patients with CRO infections (2). In a Monte Carlo simulation of a pediatric population (from preterm neonates to adolescents), strategies that included an extended infusion and a higher dose (40 mg/kg of body weight/8 h) have proven to increase the likelihood of obtaining bactericidal targets for meropenem (65, 66).

Similar to clinical data from adults (67), infections with isolates with meropenem MICs of >8 mg/liter were associated with increased mortality in two pediatric studies (35, 68), and all children infected with isolates with meropenem MICs of ≥32 mg/liter died (35). In that study, the rate of mortality among children who received meropenem for an infection caused by an isolate with an MIC of >8 mg/liter was higher than that among children who received meropenem for an infection caused by an isolate with an MIC of ≤8 mg/liter (100% versus 45.5%, $P = 0.014$). Additionally, some concerns have arisen regarding a lower probability of reaching the target for Gram-negative organisms with MICs of 4 to 8 mg/liter in critically ill pediatric patients (66).

TABLE 5 Recommended drugs according to infection source for carbapenem-resistant Gram-negative bacterial infections in children[a]

Source	Backbone	Accompanying drug	Alternative accompanying drug	Other alternative[b]
Respiratory	β-Lactam	Fluoroquinolone	Polymyxin[c,d] or an aminoglycoside[c]	Fosfomycin or tigecycline[c]
UTIs	Aminoglycoside[e]	β-Lactam	Fosfomycin or a fluoroquinolone	Polymyxin[c,d] or tigecycline[c]
CLABSIs/BSIs	β-Lactam	Polymyxin[d]	Fosfomycin or an aminoglycoside	A fluoroquinolone or tigecycline[c]
IAIs[f]	β-Lactam	Tigecycline	Polymyxin[d] or a fluoroquinolone	An aminoglycoside or fosfomycin

[a]BSIs, bloodstream infections; CLABSIs, central line-associated bloodstream infections; IAIs, intra-abdominal infections; UTIs, urinary tract infections.
[b]Consider using if other alternatives are not available.
[c]For the treatment of these sources, consider optimizing the dosage (Table 6).
[d]Colistin (polymyxin E) or polymyxin B.
[e]For the treatment of nonsevere UTIs (without sepsis, septic shock, or other complications), consider using monotherapy treatment.
[f]For intra-abdominal infections, a drug with activity against anaerobic organisms (e.g., metronidazole) should be included, unless either meropenem or tigecycline is prescribed.

Considering the lack of indications for the use of many of the new drugs in the pediatric population due to the scarce experience with most of them in pediatric patients, along with the good clinical outcomes seen in studies with adults infected with isolates with meropenem MICs of ≤8 mg/liter, we consider that meropenem at a high dose by extended infusion is still the recommended treatment backbone until more evidence on new antibiotics is attained for the pediatric population. Backbone alternatives may be considered, especially in critically ill patients, when the meropenem MIC is 4 to 8 mg/liter.

Ceftazidime-avibactam. Avibactam, a β-lactamase inhibitor, inhibits class A β-lactamases (e.g., *Klebsiella pneumoniae* carbapenemase [KPC]), class C β-lactamases (e.g., AmpC), and certain class D β-lactamases (e.g., oxacillinase 48 [OXA-48]), but it does not restore activity against metallo-β-lactamases (MBLs) (69, 70). Data from adults consider ceftazidime-avibactam to be the new cornerstone in the treatment of severe infections caused by KPC- and OXA-48-producing *Enterobacterales* (3). Furthermore, combination therapy for the treatment of a susceptible isolate, according to adult data, may be unnecessary (61). Ceftazidime-avibactam retains adequate *in vitro* activity against CRE and CR *P. aeruginosa* strains, except for MBL-producing Gram-negative bacilli. A surveillance of Gram-negative isolates collected from pediatric patients hospitalized in U.S. medical centers reported the high *in vitro* activity of this antibiotic against *Enterobacterales* and *P. aeruginosa*, with >99.9% and 99.1% of strains, respectively, being susceptible (71).

The safety profile in one phase I trial and two phase II trials including children from 3 months to 18 years of age was similar to that observed in the adult population (72–74). Based on the results from these trials, the Food and Drug Administration (FDA) has recently approved its use in pediatric patients >3 months of age with complicated intra-abdominal infections (cIAIs), in conjunction with an agent active against anaerobic organisms, and also those with urinary tract infections (UTIs). Currently, clinical data on the treatment of CRE infections with ceftazidime-avibactam in the pediatric population are limited to a few case reports (32, 75–78).

Of concern is the emergence of resistant isolates during ceftazidime-avibactam treatment, which occurs in as many as 10% of cases (54). This emerging resistance most commonly occurs in KPC-producing organisms, especially in KPC-3 producers (79), but not in OXA-48-producing *Enterobacterales* (80). This resistance is mainly due to a mutation in the bla_{KPC} gene (81).

Ceftolozane-tazobactam. Ceftolozane-tazobactam has broad-spectrum activity against Gram-negative pathogens, including many strains of MDR *P. aeruginosa* (82–84). Ceftolozane is stable against common resistance mechanisms in *P. aeruginosa* (e.g., AmpC or alterations of the porin OprD). Tazobactam, a classic β-lactamase inhibitor, inhibits noncarbapenemase β-lactamases (e.g., ESBLs), enhancing the activity of the combination. Therefore, this agent lacks activity against carbapenemase-producing Gram-negative bacilli (69, 70).

Ceftolozane-tazobactam has been shown to have *in vitro* activity greater than that of currently available alternatives against *P. aeruginosa* isolates in some countries

TABLE 6 Proposed dosing for the drugs most frequently used against carbapenem-resistant Gram-negative bacterial infections in children[a]

Drug	Dose	Age group with regulatory approval	Comments
Meropenem	40 mg/kg/dose i.v. over 3 h q8h (max, 2 g/dose); for neonates with <32 wk gestation and <2 wk old, the same dose q12h	EMA, children >3 mo old; FDA, all ages (age <3 mo only for IAI)	
Ertapenem	For children ≥13 yr old and adults, 1 g q24h; for children <13 yr old, 30 mg/kg/day q12h (max, 1 g/day)	EMA and FDA, >3 mo	Combined ertapenem-meropenem regimen for extensive drug-resistant isolates (consider a higher dose [max, 2 g/day])
Gentamicin	5–7.5 mg/kg q24h; for neonates, dose by gestational and postnatal age (153)	FDA and EMA, all ages (use caution in premature infants)	Desired serum levels are a peak of 6–12 μg/ml and a trough of <2 μg/ml; consider higher doses (7.5–10 mg/kg/day) for patients with shock, lung infections, and cystic fibrosis
Amikacin	15–20 mg/kg q24h; for neonates, dose by gestational and postnatal age (153)	FDA and EMA, all ages (use caution in premature infants)	Desired serum levels are a peak of 20–35 μg/ml and a trough of <5 μg/ml; higher doses (25–30 mg/kg/day) might be considered in patients with shock, lung infections, and cystic fibrosis
Colistin (colistimethate sodium)	Maintenance dose of 75,000–150,000 IU/kg/day q8h to q12h; a loading dose of 75,000–150,000 IU/kg is recommended in critically ill patients (max daily dose, 10,800,000 IU)	FDA and EMA, all ages for the treatment of serious infections due to Gram-negative pathogens in patients with limited treatment options	Higher maintenance doses (150,000–250,000 IU/kg/day) should be considered in patients with shock, lung infections, and cystic fibrosis
Polymyxin B	Maintenance dose of 15,000–25,000 IU/kg/day q12h for those ≥2 yr old and 25,000–40,000 IU/kg/day q12h for those <2 yr old; consider a loading dose of 25,000/kg in critically ill patients (max daily dose, 2,000,000 IU)	FDA, all ages for the treatment of serious infections due to Gram-negative pathogens in patients with limited treatment options; EMA, not available in Europe	
Tigecycline	A 100-mg loading dose and then 50 mg q12h for those ≥12 yr old; a 2-mg/kg loading dose and then 1.2 mg/kg/dose q12h (max, 50 mg/dose) for those 8 to 11 yr old	EMA, restricted to children >8 yr of age with infections without alternative antibacterial therapy available; FDA, not recommended unless alternative treatment is not suitable	Consider a higher dose for patients with lung infections, cUTIs, BSIs, or shock: for those 8 to 11 yr of age, a 3-mg/kg loading dose (max, 200 mg) and then a 2-mg/kg/dose (max, 100 mg) q12h; for those ≥12 yr of age, a 200-mg loading dose and then 100 mg q12h
Fosfomycin	12–24 g/day i.v. q6h to q8h for those >12 yr old (wt, >40 kg); 200–400 mg/kg/day q6h to q8h for those 1–12 yr old (wt, 10–40 kg); 200–300 mg/kg/day q8h for those 1–12 mo old (wt, ≤10 kg); 200 mg/kg/day q8h for neonates (postnatal age, 40–44 wk); 100 mg/kg/day q12h for premature neonates (postnatal age, <40 wk)	EMA, all ages; FDA, not available in USA (i.v. formulation)	Consider a higher dose (400 mg/kg/day q6h to q8h in patients >12 mo old [max, 8 g q8h]) for severe infections, in particular when caused by organisms with moderate susceptibility; serum electrolyte levels and water balance must be monitored during therapy
Aztreonam	120–150 mg/kg/day q8h (max, 8 g/day); for neonates, dose by gestational and postnatal age (153)	FDA and EMA, all ages	The highest dose might be considered in severe infections
Ceftazidime-avibactam	A 2-h i.v. infusion q8h; for those 6 mo to <18 yr old, 50-mg/kg ceftazidime (max, 2 g/dose) and 12.5-mg/kg avibactam (max, 0.5 g/dose); for those 3 to <6 mo old, 40-mg/kg ceftazidime and 10-mg/kg avibactam	FDA, >3 mo; EMA, not approved for use in those <18 yr old	Consider a 3-h infusion for severe infections
Ceftolozane-tazobactam	A 1-h i.v. infusion q8h of ceftolozane at 20 mg/kg/dose (max, 1 g/dose) and tazobactam at 10 mg/kg/dose (max, 0.5 g/dose)	FDA and EMA, not approved for use in those <18 yr old	For severe lung infections, consider ceftolozane at 40 mg/kg/dose and tazobactam at 20 mg/kg/dose (max, ceftolozane at 2 g/dose and tazobactam at 1 g/dose) q8h; the pediatric dose is from a phase I clinical trial (87) and two phase II clinical trials (88)
Meropenem-vaborbactam	A 3-h i.v. infusion q8h of meropenem at 40 mg/kg/dose (max, 2 g/dose) and vaborbactam at 40 mg/kg/dose (max, 2 g/dose)	FDA and EMA, not approved for use in those <18 yr old	Dose from an ongoing phase I clinical trial in children <18 yr of age (https://clinicaltrials.gov/ct2/show/NCT02687906)
Imipenem-cilastatin-relebactam	For those 1 mo to <18 years old, imipenem at 15 mg/kg/dose (max, 500 mg/dose) with cilastatin at 15 mg/kg/dose (max, 500 mg/dose) and relebactam at 7.5 mg/kg/dose i.v. q6h	FDA and EMA, not approved for use in those <18 yr old	Dose from a phase I clinical trial in children <18 yr of age (128)
Ampicillin-sulbactam	Ampicillin at 400 mg/kg/day q6h (max, ampicillin 8 g/day).	FDA and EMA, >12 mo	

[a]BSI, bloodstream infection; cUTI, complicated urinary tract infection; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; q6h, every 6 h; q8h, every 8 h; q12h, every 12 h; q24h, every 24 h; i.v., intravenous; max, maximum. Colistin may be labeled as international units (IU) of colistimethate sodium (CMS), milligrams of CMS, or milligrams of colistin base activity (CBA). The conversion is as follows: 1,000,000 IU of CMS = 80 mg of CMS = 30 mg of CBA. Polymyxin B may be labeled as international units or milligrams. The conversion is as follows: 10,000 IU = 1 mg. Children with cystic fibrosis, in general, require higher dosages to achieve therapeutic serum concentrations equivalent to those in children without cystic fibrosis due to enhanced clearance (154).

(85). An observational cohort study suggested the preferential use of ceftolozane-tazobactam over polymyxin- or aminoglycoside-based regimens for the treatment of drug-resistant *P. aeruginosa* infections (86).

A single-dose phase I trial evaluated the administration of ceftolozane-tazobactam in children from birth (postnatal age, 7 days) to <18 years of age, including 6 preterm infants (≤32 weeks of gestational age) (87). The doses evaluated yielded exposure levels generally comparable to those previously observed in adults. This dosage was included in two phase II clinical trials in a pediatric population, demonstrating the safety and efficacy of ceftolozane-tazobactam for the treatment of complicated UTIs (cUTIs) and cIAIs (88). Furthermore, a new clinical trial, awaiting the start of recruitment, will evaluate the pharmacokinetics and safety of ceftolozane-tazobactam in neonates and infants (https://clinicaltrials.gov/ct2/show/NCT04126031). Current clinical experience in children is scarce and is limited to case reports of MDR *P. aeruginosa* infections (90–92).

Similar to the development of resistance to ceftazidime-avibactam, acquired resistance to ceftolozane-tazobactam also remains a relevant threat. Emerging resistance during therapy has been mostly related to AmpC mutations associated with overexpression of the enzyme (81, 93). Importantly, this mechanism may result in cross-resistance to ceftazidime-avibactam, making the treatment of infections caused by organisms with this emerging resistance even more difficult (94).

Meropenem-vaborbactam. Meropenem-vaborbactam is another novel β-lactam–β-lactamase inhibitor combination, exerting potent and specific activity against class A carbapenemase (e.g., KPC)-producing CRE but not against those producing MBLs or class D β-lactamases (e.g., OXA-48) (95). It has already been approved for use in adults, but it has not been approved for use in children. Currently, a study evaluating the pharmacokinetics of meropenem-vaborbactam in patients <18 years of age with serious bacterial infections is under way (https://clinicaltrials.gov/ct2/show/NCT02687906). The Tango II trial compared meropenem-vaborbactam to the best available therapy in patients with serious CRE infections and showed a trend toward a lower rate of mortality and a significantly higher rate of clinical cure in the group that received meropenem-vaborbactam (97). So far, a 4-year-old patient has been treated for a KPC-producing *K. pneumoniae* BSI with meropenem-vaborbactam, with microbiological and clinical resolution (98).

Polymyxins. Since the advent of a growing number of MDR infections, polymyxins have been studied in pediatric populations of different ages (99, 100). Nephrotoxicity is one of the main concerns (99), with a higher risk being seen among adolescents (101). The huge diversity of doses used among the studies and the resulting diversity of recommendations make it hard to establish the optimal dose for children.

Although colistin (polymyxin E) is more broadly used than polymyxin B, polymyxin B may offer some advantages (102), such as a lower risk of nephrotoxicity. Although both antibiotics may need drug adjustment in patients with renal impairment, since polymyxin B clearance is not affected by renal function, polymyxin B may not require such a drastic adjustment for renal impairment. However, no differences in mortality have been observed when treatment with these antibiotics was compared (102), and there is less experience with the use of polymyxin B than with the use of polymyxin E for the treatment of MDR infections.

Most of the observational studies in children described a favorable outcome in >70% of pediatric patients treated with polymyxins for MDR infections (101, 103, 104). Colistin has also been shown to be effective and safe against MDR infections in neonates (104).

Some studies have suggested that traditional lower doses of colistin may be suboptimal (99). This seems especially relevant when treating MDR infections located in tissues where the level of penetration of colistin is low (e.g., the lungs). In the case of central nervous system infections, other routes for colistin administration (e.g., intraventricular/intrathecal) may be considered (105). In critically ill patients with life-

threatening infections, it is recommended that treatment be started with a loading dose in order to achieve therapeutic concentrations more quickly (100, 106), although no data support this recommendation in children.

In a pediatric study, patients receiving an antibiotic regimen containing colistin for the treatment of CRE infections had an increased risk of mortality (18). This, together with evidence from studies with adults (55, 86, 107), makes it recommendable to use colistin as an alternative to β-lactams only in combination treatment for infections caused by CRO until enough evidence regarding the optimal dose in children can be ascertained through appropriate clinical trials.

Emerging polymyxin resistance is considered a serious public health problem. Polymyxin resistance is mainly mediated by modifications in lipopolysaccharides, which can be acquired chromosomally or by a gene transfer mechanism (transfer of the plasmid-mediated *mcr* gene) (108).

Tigecycline. Tigecycline has excellent *in vitro* activity against a significant proportion of pediatric CRO isolates (17, 18, 37, 42, 53, 104, 109, 110), but some concerns exist about poorer outcomes compared to those achieved with other alternatives (111). Some reasons given have been the pharmacokinetics of the drug, which has a large volume of distribution with low serum levels (112). However, some studies have suggested that these therapeutic failures may be due to tigecycline underdosing (113).

Due to a higher risk of mortality in adults when prescribed as monotherapy (114), it is mostly used in combination therapy in children. Alarmingly, mortality among children who received tigecycline for MDR/extensively drug resistant (XDR) infections was 86% among those with BSIs and 24% among those with nonbacteremic infections (115). The dose of tigecycline in children is based on one PK study conducted in children aged 8 to 11 years (116). The use of higher doses led to lower rates of mortality among ICU adult cases (114), and observational studies suggest a similar impact in critically ill children (115). These results altogether suggest the need for higher doses in both adults and children with severe infections, particularly pneumonia and BSIs (3, 115, 117); nevertheless, its use for these infections should be avoided if other antibiotics are available. In addition, tigecycline might have adverse effects in children $<$8 years of age (tooth discoloration and enamel hypoplasia) (118), and therefore, it should be used only when other alternatives do not exist.

Fosfomycin. Fosfomycin retains activity against numerous pediatric CRO isolates (15, 40, 119, 120), and its use should be considered in the absence of other alternatives, based on some experience with its use for the treatment of CRO infections in children (26, 120). Interestingly, fosfomycin has shown synergistic *in vitro* activity with meropenem against MBL-producing *P. aeruginosa* strains (121). All 28 neonates from a center in China who were treated with fosfomycin-containing regimens in combination with meropenem for CR-producing *K. pneumoniae* infections (in which resistance was mediated by NDM-1) survived (26).

Due to the concern over the development of resistance while on therapy (122), it is recommended that it be used in combination therapy (2). The doses of fosfomycin recommended for use in pediatric patients vary widely. A PK study concluded that the currently recommended doses may be suboptimal in children and neonates, suggesting the need for more frequent dosing intervals and higher dosages (123). Oral fosfomycin has been proposed for use for the treatment of uncomplicated lower UTIs due to fosfomycin-susceptible MDR Gram-negative bacteria in older children and adolescents (1, 124).

Imipenem-cilastatin-relebactam. Imipenem-cilastatin-relebactam has recently been approved by the FDA for use in adults. It has good activity against KPCs but poor activity against OXA-48-like carbapenemases and lacks activity against MBLs (125, 126). This combination enhances the activity of imipenem against *P. aeruginosa* isolates (127). Notably, it restores activity against mutated KPC-3, which increases the MIC of ceftazidime-avibactam (125). The RESTORE-IMI 1 trial demonstrated a better clinical response and lower nephrotoxicity for imipenem-cilastatin-relebactam than for imi-

penem combined with colistin in patients with imipenem-nonsusceptible bacterial infections (107). A phase I study and a phase II/III study are currently investigating the use of imipenem-cilastatin-relebactam in children <18 years of age (128, 129).

Other antibiotics. Aminoglycosides and, less frequently, fluoroquinolones are used with a backbone drug for combination therapy for the treatment of CRO infections in children (17, 18, 26, 32, 34–36, 38, 40, 51, 52). CRO isolates among children frequently maintain susceptibility to aminoglycosides (mostly amikacin), and a variable proportion of isolates maintain susceptibility to fluoroquinolones (18, 26, 27, 37, 42, 51). Among the aminoglycosides, plazomicin is a semisynthetic aminoglycoside that was recently approved by the FDA for use in adults and that is active against most CRE isolates, except strains producing New Delhi MBLs (70).

The limited experience with fluoroquinolones for the treatment of CRO infections makes this option less recommendable. Eravacycline is a novel fluorocycline with *in vitro* activity against carbapenemase-producing *Enterobacterales* and CR *A. baumannii* but not against *P. aeruginosa* (70, 130).

Aztreonam is not efficiently hydrolyzed by MBLs; however, these strains usually coproduce other β-lactamases (i.e., ESBLs, AmpC), making them nonsusceptible to this antibiotic. The combination with avibactam frequently restores its activity (131, 132) and is an alternative against MBL-producing *Enterobacterales* when the meropenem MIC is >8 mg/liter, due to the lack of therapeutic possibilities. The combination of aztreonam-avibactam is currently undergoing two phase III clinical trials in adults evaluating the treatment of serious Gram-negative bacterial infections (133, 134). Several case reports describing aztreonam combined with ceftazidime-avibactam have shown promising results (135). However, there is no published experience with this combination in children.

Cefiderocol is a siderophore cephalosporin with broad activity against broad-spectrum MDR Gram-negative bacteria, including those producing serine carbapenemases (i.e., KPC or OXA-48-like carbapenemases) and MBL-producing *Enterobacterales*, *P. aeruginosa*, and *A. baumannii* (136, 137). It has recently been approved by the FDA for the treatment of cUTIs in adults. There are some concerns due to the higher mortality reported in a clinical trial (CREDIBLE-CR) when it was used for the treatment of BSIs and pneumonia; therefore, caution should be used when it is prescribed for severe infections (138). To date, the company (Shionogi Inc.) has provided information about the compassionate use of cefiderocol in nine patients under 18 years old who did not have other options, with six of the patients surviving (138). Pediatric trials with cefiderocol have yet to be initiated, and no specific pharmacokinetic information is known for this population.

Inhaled antibiotics. Some inhaled antibiotics, mainly tobramycin and colistin, have successfully been used in pediatric cystic fibrosis and no-cystic fibrosis populations as an adjunctive therapy for the treatment of Gram-negative bacterial lung infections (139–141). Currently, there is insufficient information to recommend the systematic use of inhaled antibiotics for the therapy of lung infections caused by CRO. However, it is reasonable to consider adjunctive inhaled antibiotic treatment as a treatment of last resort for lung infections caused by CRO in children who are not responding to intravenous antibiotics.

CARBAPENEM-RESISTANT ORGANISMS

Carbapenem-resistant *Enterobacterales*. Most of the data about the treatment of CRO infections have focused on CRE, and the majority of information in this review may apply to this group of microorganisms. Notably, almost all of the new developed antibiotics are focused on the treatment of infections due to *Enterobacterales*. However, epidemiological surveillance will be useful to assay potential clonal changes and to improve the development of new drugs, as the emergence of resistance to newer antibiotics will probably occur when these new agents are used more broadly.

Carbapenem-resistant *P. aeruginosa*. *P. aeruginosa* exhibits a huge diversity in its distribution throughout the world, with different clones that harbor a high diversity of

the mechanisms involved in resistance against carbapenems circulating. This means an even greater challenge for treatment. The prevalence of isolates susceptible to different drugs *in vitro* shows a broad variability. Ceftolozane-tazobactam has good *in vitro* and clinical activity against several CR *P. aeruginosa* isolates in which resistance is not mediated by carbapenemases (e.g., OprD deficiency). Ceftazidime-avibactam is a good alternative for the treatment of infections caused by CR *P. aeruginosa* isolates harboring class A carbapenemases (e.g., GES enzymes). Other newer β-lactam–β-lactamase inhibitor combinations, such as imipenem-cilastatin-relebactam, may play an important role against CR *P. aeruginosa* infections, but few data on their activity against MDR/XDR *P. aeruginosa* isolates have been published.

For isolates resistant to all β-lactams, classic drugs, such as polymyxins or aminoglycosides, and synergistic combinations (142, 143) may be considered. Among the agents commented on in this review, tigecycline and eravacycline do not exhibit relevant activity against *P. aeruginosa*. Although the extended infusion of a high dose of carbapenems combined with a second active antibiotic may be considered for the treatment of CR *P. aeruginosa* infections (2, 142–144), less is known about CR *P. aeruginosa* than about CRE, making this option less attractive.

Carbapenem-resistant *A. baumannii*. Sulbactam provides an additional option against CR *A. baumannii* infections, with some reports suggesting better outcomes compared to those achieved with alternatives for susceptible isolates (145, 146). Higher doses have been suggested in the adult population, taking into account a PK/pharmacodynamic benefit (147). Other alternatives are polymyxins, aminoglycosides, and tigecycline (148). Additionally, co-trimoxazole may be an optimal option for UTIs. The debate about combination therapy versus monotherapy deserves the same considerations for CR *A. baumannii* infections as for *Enterobacterales* infections, but with even less evidence being available for CR *A. baumannii* infections. Generally, for severe infections or immunosuppressed patients, combination therapy should be considered. Cefiderocol is being used on a compassionate-use basis to treat infections caused by pan-drug-resistant isolates against which other options do not exist (148).

CONCLUSIONS

The rate of CRO infections has greatly increased in the last few years, representing a major public health problem. These infections are difficult to treat, leading to high rates of mortality. The evaluation of risk factors for developing a CRO infection may permit individualized empirical broad-spectrum antibiotic therapy, according to the local epidemiology. Clinical evidence regarding the treatment of CRO infections remains scarce, and it mainly comes from observational studies, which are even more limited in children. New antibiotics may open the door to highly effective treatments, but the delay in conducting pediatric trials is leading to off-label use in this population. Antibiotic stewardship programs remain a key element in preserving current antibiotic activity through a rational approach to antimicrobial treatment.

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Staphylococcus aureus Community-acquired Pneumonia in Children After 13-Valent Pneumococcal Vaccination (2008–2018): Epidemiology, Clinical Characteristics and Outcomes

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Background: The epidemiology of community-acquired pneumonia (CAP) has changed, influenced by sociosanitary conditions and vaccination status. We aimed to analyze the recent epidemiology of bacterial CAP in hospitalized children in a setting with high pneumococcal vaccination coverage and to describe the clinical characteristics of pediatric *Staphylococcus aureus* CAP.

Methods: Children <17 years old hospitalized from 2008 to 2018 with bacterial CAP in 5 tertiary hospitals in Spain were included. Cases with pneumococcal CAP were randomly selected as comparative group following a case-control ratio of 2:1 with *S. aureus* CAP.

Results: A total of 313 bacterial CAP were diagnosed: *Streptococcus pneumoniae* CAP (n = 236, 75.4%), *Streptococcus pyogenes* CAP (n = 43, 13.7%) and *S. aureus* CAP (n = 34, 10.9%). Throughout the study period, the prevalence of *S. pyogenes* increased (annual percentage change: +16.1% [95% CI: 1.7–32.4], $P = 0.031$), *S. pneumoniae* decreased (annual percentage change: –4.4% [95 CI: –8.8 to 0.2], $P = 0.057$) and *S. aureus* remained stable. Nine isolates of *S. aureus* (26.5%) were methicillin-resistant. Seventeen cases (50%) with *S. aureus* CAP had some pulmonary complication and 21 (61.7%) required intensive care. *S. pneumoniae* CAP showed a trend toward higher prevalence of pulmonary complications compared with *S. aureus* CAP (69.1% vs. 50.0%, $P = 0.060$), including higher frequency of pulmonary necrosis (32.4% vs. 5.9%, $P = 0.003$).

Conclusions: The incidence of *S. aureus* CAP in children remained stable, whereas the prevalence of pneumococcal CAP decreased and *S. pyogenes* CAP increased. Patients with *S. aureus* presented a high frequency of severe outcomes, but a lower risk of pulmonary complications than patients with *S. pneumoniae*.

Key Words: pneumonia, community-acquired pneumonia, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*

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Community-acquired pneumonia (CAP) is one of the leading causes of morbidity and mortality in children under 5 years old worldwide.[1] The epidemiology of CAP differs remarkably according to the country and is influenced by social and health care conditions and vaccination status. Traditionally, *Streptococcus pneumoniae* has been the most common causative microorganism in childhood CAP. The advent of pneumococcal vaccination modified the spectrum of vaccine-preventable respiratory bacteria, leading to a decrease in the incidence of *S. pneumoniae* CAP, mostly because of a reduction in the incidence of serotypes included in the 7-, 10- and 13-valent pneumococcal conjugate vaccines (PCV).[2,3] Additionally, a relative increase seems to have occurred in the prevalence of other bacteria, such as *Streptococcus pyogenes* and *Staphylococcus aureus*, thus diminishing the relevance of *S. pneumoniae*.[4–7]

Recognition and management of *S. aureus* CAP in children is challenging. Most national guidelines on pediatric CAP do not recommend routine empirical coverage of *S. aureus*.[8,9] Moreover, methicillin-resistant *S. aureus* (MRSA) further increases the risk of inadequate empirical therapy. Consequently, surveillance of *S. aureus* CAP, including changes in resistance patterns, is very important. However, few data have been reported to date on the epidemiology and characteristics of *S. aureus* CAP in children after the implementation of PCV.

The aims of this study were to analyze the recent epidemiology of bacterial CAP in hospitalized children in a setting with high PCV coverage, focusing on the clinical characteristics and outcomes of pediatric *S. aureus* CAP.

MATERIALS AND METHODS

We performed a retrospective, multicenter, observational, cross-sectional, case-control study. The study population comprised

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children younger than 17 years of age who were hospitalized with bacterial CAP in 5 tertiary hospitals in Spain between January 1, 2008, and December 31, 2018.

Definitions

Bacterial CAP was defined as cases with radiographic evidence of pneumonia and a microbiologically confirmed bacterial infection. The radiographic criteria were the presence of consolidation (a lung opacity with or without air bronchograms), other infiltrate (alveolar or interstitial densities) or pleural effusion. Chest radiography findings were interpreted by a radiologist. Pneumonia was considered to be community-acquired if onset of symptoms/signs was outside the hospital or during the first 48 hours after admission, in contrast with the definition of hospital-acquired pneumonia.[10,11]

Microbiologic confirmation of bacterial CAP was defined as detection of *S. pneumoniae*, *S. pyogenes* or *S. aureus* in blood culture, pleural effusion or bronchoalveolar lavage after culture or by polymerase chain reaction (PCR) in a sterile fluid. Other bacteria (eg, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella* spp.) were not considered in this definition because of their atypical manifestations. Patients were recruited from the databases of the microbiology laboratories included in the study. Antibiotic treatment was judged to be adequate based on the in vitro susceptibility of the organism isolated and the degree of lung penetration.

The hospitals included in the study had 226, 120, 112, 76 and 32 pediatric beds, with 8800, 2400, 7800, 2800 and 1200 annual pediatric admissions during the study period, respectively. Samples were obtained at the physicians' discretion and the hospital laboratories performed cultures of respiratory samples and blood, including antimicrobial susceptibility testing of the organisms isolated using standard techniques. Minimum inhibitory concentration breakpoints were interpreted following the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in place at the time.[12]

The characteristics of *S. aureus* CAP, including demographic information, medical history, chest imaging results and clinical data, were systematically collected from the medical chart using standardized definitions and data collection instruments. We used pneumococcal CAP, the most common bacterial CAP detected in children, as the comparison group. We randomly selected cases with pneumococcal CAP following a case-control ratio of 2:1. The information collected from *S. pneumoniae* cases was the same as that collected from *S. aureus* CAP cases. The study data were collected using the REDCap electronic data capture tools hosted at Gregorio Marañón University Hospital.

Statistics

Continuous variables are expressed as medians and interquartile ranges (IQR), since the data were non-normally distributed, and categorical variables are expressed as absolute values and percentages. Differences between categorical data were evaluated using the χ^2 or Fisher Exact test, and differences between continuous variables were assessed using the Kruskal-Wallis test. To characterize trends, the annual percentage change (APC) was estimated with its corresponding 95% confidence interval (CI). We applied the joinpoint modeling percent change calculation to our monthly data by using log-transformed data. For all analyses, a 2-tailed P value <0.05 was considered statistically significant. STATA software version 17 (StataCorp., College Station, TX: StataCorp LLC) and Joinpoint Regression software version 4.9.0.0 (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute) were used for the statistical analysis.

Ethical Approvals

The study was approved by the Clinical Research Ethics Committee at Hospital La Paz (study code PI-3352). The STROBE statement for reporting observational studies was followed.[13]

RESULTS

Epidemiology of Bacterial CAP

From 2008 to 2018, a total of 313 episodes of bacterial CAP were diagnosed in children at the study centers (median age, 18 months; 95% CI: 6–30 months). The most common causative microorganism was *S. pneumoniae* (236 cases; 75.4%), followed by *S. pyogenes* (43 cases; 13.7%) and *S. aureus* (34 cases; 10.9%). Patients with *S. aureus* CAP were younger (median age 9 months, 95% CI: 6–31 months) than patients with *S. pneumoniae* CAP (median age 18 months, 95% CI: 6–34 months) and *S. pyogenes* CAP (median age: 18 months, 95% CI: 6–21 months) ($P = 0.047$).

The prevalence of *S. pyogenes* increased during the study period (APC: +16.1% [95% CI: 1.7–32.4], $P = 0.031$), from 7.0% in 2008 to 26.9% in 2018. The prevalence of *S. pneumoniae* decreased (APC: –4.4% [95% CI: –8.8 to 0.2], $P = 0.057$), from 88.4% in 2008 to 65.4% in 2018 (Fig. 1). The prevalence of *S. aureus* remained stable (APC: +6.1% [95% CI: –11.4 to 27.1], $P = 0.474$), peaking in 2017.

The annual rate of hospitalized children with CAP decreased from 2008 to 2013 (APC: –18.2% [95% CI: –32.6 to –0.7], $P = 0.044$) and then remained stable (Fig. 2). This decrease was mainly due to the decline in *S. pneumoniae* CAP from 2008 to 2011 (APC: –31.6% [95% CI: –54.8 to 3.5], $P = 0.066$). Of note, there was an increase in the annual rate of *S. pyogenes* CAP from 2013 to 2018 (APC: +56.2% [95% CI: 10.4–121], $P = 0.020$). The annual rate of *S. aureus* CAP remained stable (average of 1.3 cases/10,000 admissions/year).

S. aureus CAP

Table 1 shows the characteristics of the 34 patients with *S. aureus* CAP. Twenty (58.8%) were males and 11 (32.4%) had a relevant chronic medical condition. *S. aureus* was isolated in pleural fluid in 18 cases (52.9%), blood culture in 17 (50.0%), bronchoalveolar lavage in 1 (2.9%) and in both blood culture and pleural fluid in 2 cases. In 9 cases (26.4%), *S. aureus* was detected by PCR in pleural fluid (positive culture in only 2/9). The number of cases was similar in autumn, spring and winter (11, 10 and 9 cases, respectively), compared with a lower number of cases in summer (4 cases).

The median hospital stay was 14 days (IQR: 9–21 days). Seven patients (20.6%) had begun antibiotic therapy for CAP before admission, with 5/7 cases (71.4%) not receiving appropriate therapy according to the antimicrobial susceptibility of *S. aureus*. The most common antibiotic used after *S. aureus* was identified and its antibiotic susceptibility known (see Figure, Supplemental Digital Content 1; http://links.lww.com/INF/E687) was cloxacillin (14 cases), followed by clindamycin (9 cases) and vancomycin (9 cases). Twenty-one patients (61.8%) received a single antibiotic as definitive treatment, 10 (29.4%) received a combination of 2 antibiotics, most commonly with toxin-inhibitor antibiotics (clindamycin in 7 cases and linezolid in 2 cases) and 3 (8.8%) received 3 antibiotics. Twenty-seven patients (79.4%) completed their treatment as outpatients with oral antibiotics (median duration, 10.5 days; IQR: 8–18 days). The median total duration of antibiotic therapy was 22 days (IQR: 12–33 days). The most common outpatient oral antibiotic (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/E687) was amoxicillin-clavulanate (9 cases), followed by cloxacillin (5 cases) and cefuroxime (4 cases). Twenty-six of these patients (96.3%) received a single antibiotic.

Diagnostic testing for viruses was performed in a respiratory specimen in 20 cases of *S. aureus* CAP (58.8%), with detection of virus in 9 cases (45.0%). The most common virus was respiratory syncytial virus (4 cases), followed by influenza (2 cases), rhinovirus (2 cases) and parainfluenza (1 case). The presence of Panton-Valentine leukocidin genes (lukS-PV and lukF-PV) was

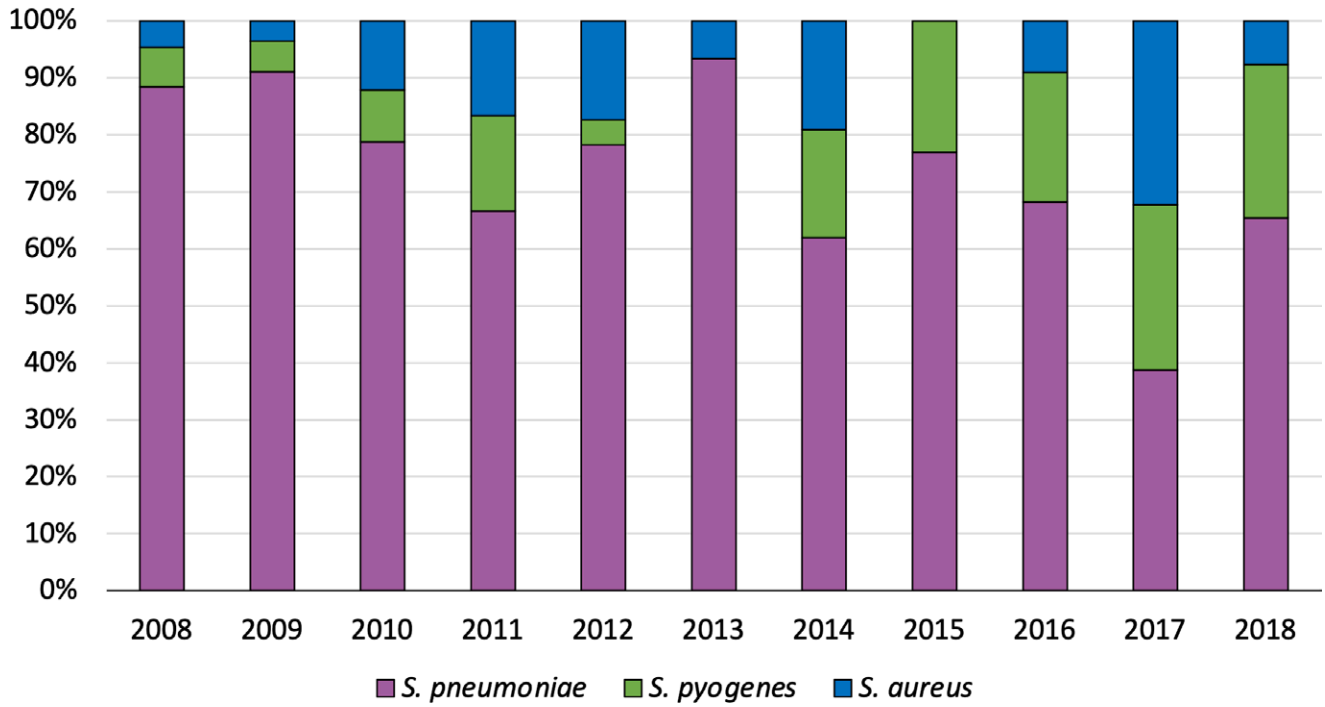

FIGURE 1. Prevalence of bacterial community-acquired pneumonia throughout the study period.

evaluated using PCR in 9 patients. Results were positive in 5/9 cases (55.6%) (positive in 33.3% [2/6] methicillin-susceptible *S. aureus* [MSSA] vs. 100% [3/3] MRSA, $P = 0.058$).

Methicillin-resistant *S. aureus* CAP

Of the 34 cases of *S. aureus* CAP, 25 (73.5%) were caused by MSSA and 9 (26.5%) by MRSA. Figure (Supplemental Digital Content 2, http://links.lww.com/INF/E687) shows the distribution of MRSA throughout the study period. The prevalence of MRSA remained stable (APC: –0.2% [95% CI: –14.3 to 16.1], $P = 0.973$). However, in 2017, there was a peak of 10 cases of *S. aureus* CAP, of which 5 (50.0%) were MRSA. Table 1 shows the comparison of the characteristics between MRSA and MSSA CAP. Compared with MSSA, patients with MRSA were more frequently male (88.9% vs. 48.0%, $P = 0.033$) and more frequently had a relevant chronic medical condition (66.7% vs. 20.0%, $P = 0.010$). Additionally, the empirical antibiotic on admission was not active against the bacterial isolate in a higher proportion of cases (64.0% vs. 22.2, $P = 0.031$), with a higher

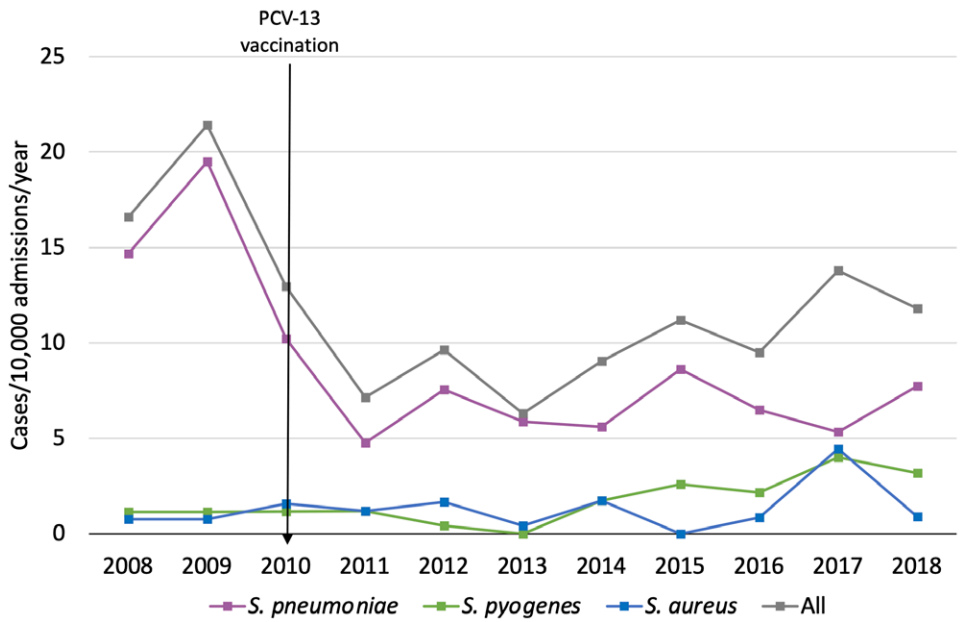

FIGURE 2. Annual rate of children hospitalized with bacterial community-acquired pneumonia.

TABLE 1. Clinical Characteristics of Children Hospitalized With Bacterial Community-acquired Pneumonia According to the Etiology

	S. aureus CAP (N = 34)	MSSA CAP (N = 25)	MRSA CAP (N = 9)	*P* (MSSA vs. MRSA CAP)	*S. pneumoniae* CAP (N = 68)	*P* (*S. aureus* vs. *S. pneumoniae* CAP)
Demographics						
Gender (male)	20/34 (58.8%)	12/25 (48.0%)	8/9 (88.9%)	**0.033**	32/68 (47.1%)	0.263
Age at diagnosis (years)	0.7 (0.5–2.6)	1.0 (0.5–2.1)	0.6 (0.2–3.6)	0.470	2.9 (1.7–4.6)	**<0.001**
Born abroad	2/34 (5.9%)	1/25 (4.0%)	1/9 (11.1%)	0.437	5/68 (7.4%)	0.782
Foreign parents	11/26 (42.3%)	6/18 (33.3%)	5/8 (62.5%)	0.165	13/52 (25.0%)	0.118
Medical chronic condition	11/34 (32.4%)	5/25 (20.0%)	6/9 (66.7%)	**0.010**	21/68 (30.9%)	0.880
Hospitalized during previous 6 months	8/34 (23.5%)	4/25 (16.0%)	4/9 (44.4%)	0.085	9/68 (13.2%)	0.188
Travel abroad during previous 6 months	3/34 (8.8%)	2/25 (8.0%)	1/9 (11.1%)	0.778	4/56 (7.1%)	0.773
Antibiotic therapy						
Antibiotic before admission	7/34 (20.6%)	5/25 (20.0%)	2/9 (22.2%)	0.888	7/68 (10.3%)	0.150
Adequate empirical antibiotic	18/34 (52.9%)	16/25 (64.0%)	2/9 (22.2%)	**0.031**	67/68 (98.5%)	**<0.001**
Delay of adequate antibiotic (days)	0.5 (0.0–3.0)	0.0 (0.0–2.0)	3.0 (1.0–4.0)	**0.033**	0.0 (0.0–0.0)	**<0.001**
Duration of active antibiotic during the admission (days)	12.0 (9.0–21.0)	11.5 (6.5–19.0)	12.0 (10.0–22.0)	0.570	11.0 (5.0–21.0)	0.538
Total duration of active antibiotic (days)	22.0 (12.0–33.0)	21.0 (12.0–34.0)	23.0 (15.0–27.0)	0.969	14.0 (10.0–29.0)	**0.037**
Blood test						
C-reactive protein at admission (mg/dl)	12.1 (2.5–22.3)	14.2 (2.5–24.0)	11.1 (2.9–18.6)	0.711	35.9 (24.9–211.1)	**<0.001**
Highest PCR (mg/dL)	17.5 (6.9–28.8)	21.3 (6.0–29.5)	14.0 (10.2–17.6)	0.777	35.9 (25.9–230.5)	**<0.001**
PCT at admission (ng/mL)	1.5 (0.6–3.2)	3.1 (0.9–3.2)	0.5 (0.4–0.9)	**0.020**	6.6 (2.6–14.0)	**<0.001**
Highest PCT (ng/mL)	2.6 (0.8–4.1)	3.2 (0.9–4.4)	1.0 (0.7–3.1)	0.322	4.0 (1.9–13.5)	0.033
Leukocytes count at admission (x10^9/L)	16.9 (12.0–19.3)	17.0 (11.8–19.3)	16.8 (13.0–18.1)	0.891	16.7 (12.0–24.8)	0.537
Neutrophils count at admission (x10^9/L)	9.1 (7.7–15.2)	9.4 (6.7–15.3)	9.1 (8.3–11.7)	0.746	13.4 (8.1–19.5)	0.068
Highest neutrophils count (x10^9/L)	12.8 (8.9–1.8)	13.1 (8.4–18.7)	12.8 (9.1–18.4)	0.891	15.4 (10.1–23.3)	0.116
Support						
PICU admission	21/34 (61.8%)	15/25 (60.0%)	6/9 (66.7%)	0.724	41/68 (60.3%)	0.886
Duration of PICU admission	5.0 (2.0–10.0)	4.0 (2.0–10.0)	6.5 (2.0–15.0)	0.695	5.5 (3.5–10.5)	0.432
Oxygen therapy	30/34 (88.2%)	21/25 (84.0%)	9/9 (100.0%)	0.201	55/68 (80.9%)	0.348
Duration of oxygen therapy (days)	7.5 (3.0–10.0)	7.5 (3.0–10.0)	7.5 (4.5–11.5)	0.472	6.5 (3.0–11.0)	0.926
Invasive mechanical ventilation	3/34 (8.8%)	3/25 (12.0%)	0/9 (0.0%)	0.276	3/68 (4.4%)	0.372
Duration of invasive mechanical ventilation (days)	4.0 (1.0–12.0)	4.0 (1.0–12.0)	–	–	3.0 (2.0–4.0)	0.658
Noninvasive mechanical ventilation	10/34 (29.4%)	8/25 (32.0%)	2/9 (22.2%)	0.581	7/68 (10.3%)	**0.015**
Duration of noninvasive mechanical ventilation (days)	5.0 (1.0–5.0)	5.0 (1.0–5.0)	4.0 (2.0–6.0)	0.585	11.0 (4.0–12.0)	0.060
Virus						
Respiratory virus diagnostic test	20/34 (58.8%)	15/25 (60.0%)	5/9 (55.6%)	0.816	27/68 (39.7%)	0.068
Virus coinfection	9/20 (45.0%)	6/15 (40.0%)	3/5 (60.0%)	0.436	5/27 (18.5%)	**0.050**
Influenza detected	2/20 (10.0%)	1/15 (6.6%)	1/5 (20.0%)	0.389	3/27 (11.1%)	0.903
RSV detected	4/20 (20.0%)	3/15 (20.0%)	1/5 (20.0%)	1.000	2/27 (7.4%)	0.201
Complications						
Lung complications	17/34 (50.0%)	13/25 (52.0%)	4/9 (44.4%)	0.697	47/68 (69.1%)	0.060
Pleural effusion	16/34 (47.1%)	12/25 (48.0%)	4/9 (44.4%)	0.855	44/68 (64.7%)	0.088
Pulmonary necrosis	2/34 (5.9%)	1/25 (4.0%)	1/9 (11.1%)	0.437	22/68 (32.4%)	**0.003**
Lung abscess	0/34 (0.0%)	0/25 (0.0%)	0/9 (0.0%)	–	2/68 (2.9%)	0.313
Pneumothorax	1/34 (2.9%)	1/25 (4.0%)	0/9 (0.0%)	0.543	11/68 (16.2%)	**0.050**
Pleural drainage	15/34 (44.1%)	12/25 (48.0%)	3/9 (33.3%)	0.447	39/68 (57.4%)	0.207
Intrapleural fibrinolytics	9/15 (60.0%)	7/12 (58.3%)	2/3 (66.7%)	0.792	23/38 (60.5%)	0.972
Videothoracoscopy	3/34 (8.8%)	3/25 (12.0%)	0/9 (0.0%)	0.276	10/68 (14.7%)	0.401
Panton-Valentine leukocidin	5/9 (55.6%)	2/6 (33.3%)	3/3 (100%)	0.058	–	–
Outcome						
Days of admission	14.0 (9.0–21.0)	13.0 (9.0–18.0)	16.0 (13.0–27.0)	0.291	12.0 (5.5–23.0)	0.341
30-day mortality	0/34 (0.0%)	0/25 (0.0%)	0/9 (0.0%)	–	2/68 (2.9%)	0.313
30-day readmission	3/34 (8.8%)	1/25 (4.0%)	2/9 (22.2%)	0.098	4/68 (5.9%)	0.580

CRP indicates C-reactive protein; PCT, procalcitonin; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus.
Significant (<0.05) or almost significant (0.05) *P*-values are shown in bold.

delay in days until adequate antibiotic therapy was given (median of 3 days [IQR: 1–4] vs. 0 days [0–2], $P = 0.033$). However, the length of stay and the frequency of pediatric intensive care unit (PICU) admission or hospital readmissions were not significantly different.

Figure 3 shows the overall proportion of *S. aureus* isolates resistant to various antibiotics and according to methicillin susceptibility. Data on antibiotic susceptibility were not available for all isolates. None of the isolates were resistant to rifampicin, vancomycin or linezolid. Notably, 12.5% of the isolates (4/32) were clindamycin-resistant, which increased to 22.2% (2/9) in the case of MRSA ($P = 0.298$). Furthermore, 14.3% (4/28) of the isolates were levofloxacin-resistant, increasing to 44.4% (4/9) in the case of MRSA ($P = 0.002$).

Clinical Severity in Children With *S. aureus* CAP

A total of 17 children (50.0%) had a pulmonary complication, including pleural effusion in 16 (47.1%), pulmonary necrosis

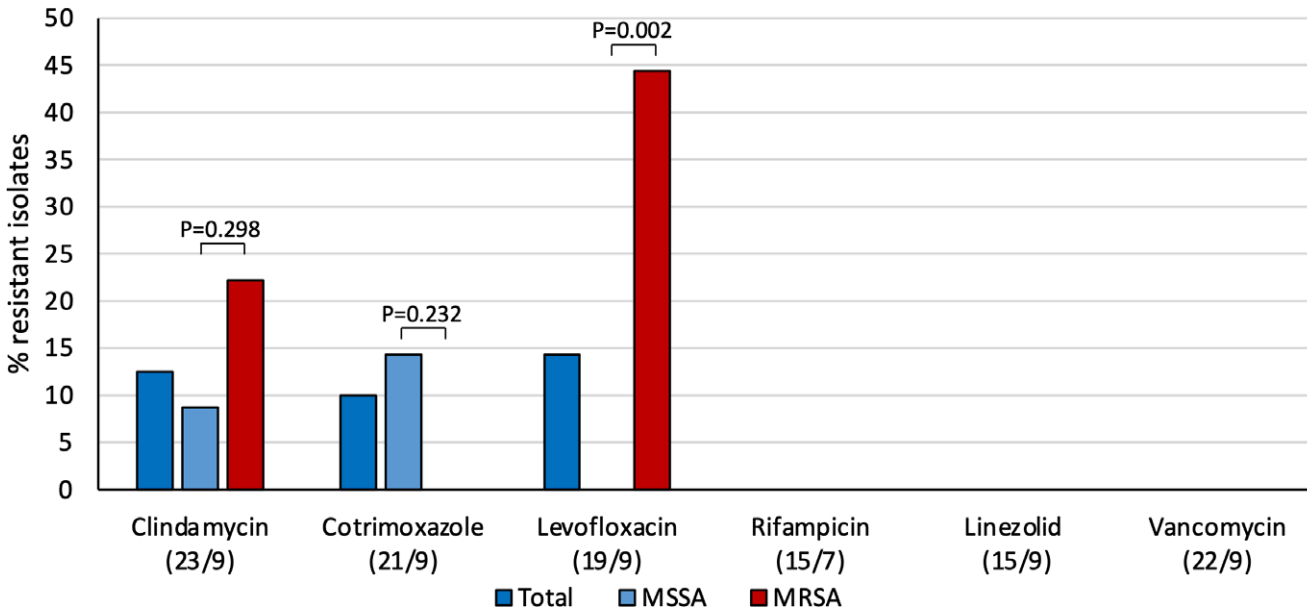

FIGURE 3. Antibiotic resistance among *Staphylococcus aureus* isolates according to methicillin susceptibility. Antibiotic susceptibility was not available for all isolates. The number of isolates evaluated for each antibiotic is shown in parentheses (MSSA/MRSA). MRSA indicates methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

in 2 (5.9%), pneumatoceles in 1 (2.9%) and pneumothorax in 1 (2.9%).

Twenty-one patients (61.7%) were admitted to the PICU, requiring noninvasive mechanical ventilation in 10 cases (29.4%) and invasive mechanical ventilation in 3 (8.8%). Table 2 compares patients admitted with those not admitted to the PICU. Patients admitted to the PICU were younger (median age: 6 months vs. 2.1 years, $P = 0.045$) and less frequently had relevant chronic clinical conditions (19.0% vs. 53.8%, $P = 0.035$). They more frequently had pleural effusion (61.9% vs. 23.1%, $P = 0.028$) and a higher maximum level of C-reactive protein (median: 22.9 vs. 6.4 mg/dL, $P = 0.004$). There were no differences in severity according to methicillin susceptibility (Table 1). None of the patients with *S. aureus* CAP died.

Comparison With *S. pneumoniae* CAP

A total of 68 patients with *S. pneumoniae* CAP were randomly selected and compared with the 34 cases with *S. aureus* CAP (Table 1). The patients with *S. aureus* CAP were younger (median age: 8.4 vs. 34.8 months, $P < 0.001$), with more frequent detection of a concomitant virus (45.0% [9/20] vs. 18.5% [5/27], $P = 0.050$). Although patients with *S. pneumoniae* CAP more frequently received adequate empirical antibiotic therapy (98.5% vs. 50.0%, $P < 0.001$), a trend toward higher prevalence of pulmonary complications was observed (69.1% vs. 50.0%, $P = 0.060$), including a higher prevalence of pulmonary necrosis (32.4% vs. 5.9%, $P = 0.003$). Furthermore, patients with *S. pneumoniae* CAP had higher acute phase reactant values (C-reactive protein and procalcitonin), although they received antibiotics for shorter periods.

DISCUSSION

We evaluated the epidemiology of bacterial CAP in children hospitalized after implementation of PCV13, showing a global decrease in bacterial CAP, mainly associated with a reduction in *S. pneumoniae* CAP. However, the annual rate of *S. pyogenes* CAP increased after 2013, representing 26.9% of bacterial CAP in 2018. *S. aureus* CAP, including MRSA isolates, remained stable throughout the 11-year period. Globally, one-third of cases of *S. aureus* CAP were MRSA, with a high prevalence of resistance to clindamycin. Children with *S. aureus* CAP were younger than those with other causes of bacterial CAP. Patients with *S. aureus* CAP had a high prevalence of complications, although morbidity was even higher in patients with *S. pneumoniae* CAP.

PCV7 was implemented in the Community of Madrid (Spain) in 2006 as part of the publicly funded immunization program. In 2010, it was replaced by PCV13 but was later temporarily excluded in 2012. From 2012 to 2015, the vaccine was available privately for purchase by parents. PCV13 was eventually reintroduced as a publicly funded vaccine in 2015. During the free universal vaccination period, pneumococcal vaccine coverage reached 95% and dropped to 67%–82% during the nonfunded years.[2] This study shows a decrease in the annual rate of CAP cases hospitalized from 2008 to 2013 owing mainly to the decline in *S. pneumoniae* CAP. This annual rate remained stable. The decreased incidence of *S. pneumoniae* CAP has also been reported, mostly because of a reduction in the frequency of those serotypes included in the PCV.[2,3,14] Of note, the incidence of *S. pyogenes* increased after 2013. An increment in the frequency of invasive diseases caused by *S. pyogenes*, including pneumonia, has been reported in several countries.[6,15–17] In a study conducted in France on the epidemiology of community-acquired pleural empyema, the frequency of pneumococcal infection declined from 79.1% in 2009 to 36.4% in 2017 ($P < 0.001$), with *S. pyogenes* being the leading cause in the later years of the study period (2015–2017, 45.5%).[4] Because of the stable prevalence of *S. aureus* CAP, recent updates to guidelines recommend maintaining aminopenicillins as first-line treatment for most cases of CAP, since they remain highly active against *S. pyogenes* and *S. pneumoniae*.[8,9,18]

The prevalence of MRSA among children with *S. aureus* CAP in our study (26.5%) was comparable to that seen in childhood CAP in various European countries,[4,6,7] but lower than reported in other studies performed in countries with a higher burden of MRSA.[19–22] A recent study describing the epidemiology of Spanish children colonized by *S. aureus* reported a prevalence of MRSA of 4.4% among *S. aureus* isolates.[23] Considering only invasive isolates (blood and cerebrospinal fluid), data from the European Centre for

TABLE 2. Clinical Characteristics of Children Hospitalized With *Staphylococcus aureus* Community-acquired Pneumonia According to the Admission to the Pediatric Intensive Care Unit

	Total N = 34	No PICU N = 25	PICU N = 9	*P*
Demographics				
Gender (male)	20/34 (58.8%)	6/13 (46.2%)	14/21 (66.7%)	0.238
Age at diagnosis (years)	0.7 (0.5–2.6)	2.1 (1.0–3.6)	0.5 (0.4–1.1)	**0.045**
Born abroad	2/34 (5.9%)	1/13 (7.7%)	1/21 (4.8%)	0.724
Foreign parents	11/26 (42.3%)	2/11 (18.2%)	9/15 (60.0%)	**0.033**
Underlying disease	11/34 (32.4%)	7/13 (53.8%)	4/21 (19.0%)	**0.035**
Hospitalized during previous 6 months	8/34 (23.5%)	3/13 (23.1%)	5/21 (23.8%)	0.961
Travel abroad during previous 6 months	3/34 (8.8%)	0/13 (0.0%)	3/21 (14.3%)	0.154
Antibiotic therapy				
Antibiotic before admission	7/34 (20.6%)	3/13 (23.1%)	4/21 (19.0%)	0.778
Adequate empirical antibiotic	17/33 (51.5%)	5/13 (38.5%)	12/20 (60.0%)	0.486
Delay of adequate antibiotic (days)	0.5 (0.0–3.0)	1.0 (0.0–4.0)	0.0 (0.0–2.0)	0.203
Duration of active antibiotic during the admission (days)	12.0 (9.0–21.0)	9.5 (5.0–18.0)	12.0 (11.0–21.0)	0.124
Total duration of active antibiotic (days)	22.0 (12.0–33.0)	19.0 (11.0–30.0)	23.0 (12.0–35.0)	0.263
Blood test				
CRP on admission (mg/dl)	12.1 (2.5–22.3)	5.1 (1.7–17.5)	19.7 (3.6–22.9)	0.127
Highest CRP (mg/dL)	17.5 (6.9–28.8)	6.4 (3.8–13.9)	22.9 (14.0–30.3)	**0.004**
PCT at admission (ng/mL)	1.5 (0.6–3.2)	0.9 (0.9–3.2)	2.0 (0.5–3.1)	0.841
Highest PCT (ng/mL)	2.6 (0.8–4.1)	1.6 (0.9–3.2)	3.1 (0.7–5.5)	0.760
Leukocytes count at admission ($x10^9$)	16.9 (12.0–19.3)	16.5 (11.8–19.2)	17.0 (13.6–19.4)	0.547
Neutrophils count at admission ($x10^9$)	9.1 (7.7–15.2)	8.8 (7.7–11.7)	10.7 (7.4–16.3)	0.713
Highest neutrophils count ($x10^9$)	12.8 (8.9–18.5)	9.9 (7.9–15.5)	13.6 (11.1–18.7)	0.156
Support				
Oxygen therapy	30/34 (88.2%)	10/13 (76.9%)	20/21 (95.2%)	0.107
Duration of oxygen therapy (days)	7.5 (3.0–10.0)	3.0 (1.0–10.0)	8.0 (3.0–12.0)	0.117
Invasive mechanical ventilation	3/34 (8.8%)	0/13 (0.0%)	3/21 (14.3%)	0.154
Duration of invasive mechanical ventilation (days)	4.0 (1.0–12.0)		4.0 (1.0–12.0)	
Noninvasive mechanical ventilation	10/34 (29.4%)	1/13 (7.7%)	9/21 (42.9%)	**0.029**
Duration of noninvasive mechanical ventilation (days)	5.0 (1.0–5.0)	1.0 (1.0–1.0)	5.0 (2.0–5.0)	0.203
Virus				
Virus respiratory diagnostic test	20/34 (58.8%)	8/13 (61.5%)	12/21 (57.1%)	0.800
Virus coinfection	9/34 (26.5%)	2/13 (15.4%)	7/21 (33.3%)	0.249
Influenza detected	2/2 (100.0%)	1/1 (100.0%)	1/1 (100.0%)	1.000
RSV detected	4/34 (11.8%)	1/13 (7.7%)	3/21 (14.3%)	0.562
Complications				
Lung complications	17/34 (50.0%)	3/13 (23.1%)	14/21 (66.7%)	**0.013**
Pleural effusion	16/34 (47.1%)	3/13 (23.1%)	13/21 (61.9%)	**0.028**
Pulmonary necrosis	2/34 (5.9%)	1/13 (7.7%)	1/21 (4.8%)	0.720
Lung abscess	0/34 (0.0%)	0/13 (0.0%)	0/21 (0.0%)	1.000
Pneumothorax	1/34 (2.9%)	1/13 (7.7%)	0/21 (0.0%)	0.206
Pleural drainage	15/34 (44.1%)	3/13 (23.1%)	12/21 (57.1%)	0.052
Intrapleural fibrinolytics	9/15 (60.0%)	0/3 (0.0%)	9/12 (75.0%)	**0.018**
Videothoracoscopy	3/34 (8.8%)	2/13 (15.4%)	1/21 (4.8%)	0.290
Panton-Valentine leukocidin	5/9 (55.6%)	1/1 (100%)	4/8 (100%)	0.340
Methicillin resistance	9/25 (36.0%)	12/25 (48.0%)	6/9 (66.7%)	0.724
Outcome				
Days of admission	14.0 (9.0–21.0)	11.0 (6.0–16.0)	15.0 (13.0–21.0)	0.092
30-days mortality	0/34 (0.0%)	0/13 (0.0%)	0/21 (0.0%)	1.000
30-days readmission	3/34 (8.8%)	1/13 (7.7%)	2/21 (9.5%)	0.850

CRP indicates C-reactive protein; PCT, procalcitonin; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus.
Significant (<0.05) *P*-values are shown in bold.

Disease Prevention and Control (ECDC, EARS-Net)[24] show that the prevalence of MRSA in children with 0–4 years and 5–18 years of age in 2019 in Spain was 12% and 15.7%, respectively. Despite the low prevalence of MRSA among children in Spain, *S. aureus* isolates from patients with CAP were associated with a higher prevalence of methicillin resistance. A similar prevalence of methicillin resistance among *S. aureus* CAP in adults in our setting was recently reported.[25]

Another relevant finding in our study is the prevalence of clindamycin resistance in MRSA (22.2%), which was much higher than in MSSA (8.7%). This difference has also been described in isolates from children colonized with *S. aureus* in Spain (26% vs. 16.9%).[23] Such a high prevalence calls into question the suitability of clindamycin as empirical treatment of children with suspected MRSA CAP in our region, as recommended by several guidelines.[8,18,26] Alternatives include vancomycin, linezolid and trimethoprim-sulfamethoxazole.

Regarding clinical outcomes, several studies have compared the severity of CAP caused by the most common bacterial agents in childhood CAP.[7,27–31] Bacteremic pneumonia caused by *S. aureus* and *S. pyogenes* in children in the United States was characterized by higher morbidity, with a higher frequency of hospitalization, PICU admission and mechanical ventilation than in children with *S. pneumoniae*.[28] Other studies in children and adults have shown similar results.[25,30,30] A Spanish study showed results similar to ours, with comparable outcomes among children with *S. pneumoniae* and *S. aureus* CAP, whereas *S. pyogenes* was associated with a higher risk for complications.[7] This higher morbidity associated with *S. pyogenes* CAP than with *S. pneumoniae* CAP was also reported in Israel.[31] In our study, it is noteworthy that patients with *S. aureus*

CAP, which mainly affect infants, were younger than those with CAP caused by other bacteria. This finding was also highlighted in other, similar studies, which report a higher prevalence of *S. aureus* CAP in infants.[20,22,32]

S. aureus bacteremia is a leading cause of mortality. In a study carried out in the United States on *S. aureus* bloodstream infections in children, 8/394 (2%) patients died because of *S. aureus* bacteremia, 5 of whom (62.5%) had pneumonia.[33] Despite the fact that none of the patients with *S. aureus* CAP died in our study, other studies evaluating the outcome of pediatric *S. aureus* CAP have reported a mortality of 0.9–4.9%.[21,22,29,34] A 12-year-old girl living in our region during the study period died suddenly at home; the autopsy revealed the cause of death to be multiple organ failure after MRSA bilateral abscess pneumonia.[35] If she had been hospitalized, the mortality rate of *S. aureus* CAP in our study would have been 2.9%.

We found that disease severity in patients with MRSA was not significantly greater than in those with MSSA CAP. Methicillin resistance in *S. aureus* infection has traditionally been considered a risk factor for adverse outcomes and is probably associated, at least in part, with a delay in the start of active antibiotic therapy. A study that included 394 episodes of *S. aureus* bloodstream infections in children showed that methicillin resistance was associated with a higher risk of complications (aOR 3.31; 95% CI: 1.60–6.85).[33] However, in another study including 152 children with invasive community-acquired *S. aureus* infections, MRSA was not associated with a severe outcome.[37] Additionally, other studies focusing on pediatric *S. aureus* CAP did not show higher morbidity in children with MRSA.[21,22,27] A recent large, prospective study evaluating 552 children with *S. aureus* bacteremia found that whereas developing necrotizing pneumonia increased mortality, the isolation of MRSA did not.[34] Several factors, such as previous MRSA infection or colonization, recurrent skin infections and long-term hemodialysis have been associated with MRSA CAP in adults.[30,38] We found that children with MRSA were more frequently male and more frequently had relevant chronic clinical conditions than those with MSSA.

Our study has several limitations. First, its retrospective design limits the evaluation of factors not routinely considered, including molecular analysis of the isolates (eg, sequence type of *S. aureus* strains or toxin genes) and days of antibiotic therapy before admission. Second, our data can be extrapolated only to populations with a similar epidemiology and comparable vaccination coverage. Finally, *S. pneumoniae* serotypes were not routinely collected. As a strength, our study is one of the largest cohorts of children with bacterial CAP in the post-PCV era. In addition, the patients were included over a long period of time, with a focus on *S. aureus* CAP.

In conclusion, the incidence of *S. aureus* CAP in children remained stable in our study, whereas that of *S. pneumoniae* CAP decreased and that of *S. pyogenes* CAP increased. The prevalence of severe outcomes was high in patients with *S. aureus*, although the risk of pulmonary complications was lower than in patients with *S. pneumoniae*. The relevant prevalence of clindamycin resistance in *S. aureus* CAP, especially in that caused by MRSA, should be monitored closely. Clinical guidelines should be updated if necessary.

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Staphylococcus aureus Community-Acquired Pneumonia in Children After 13-Valent Pneumococcal Vaccination (2008-2018): Epidemiology, Clinical Characteristics, and Outcomes

SUPPLEMENTARY DOCUMENT

Figure S1. Definitive antibiotic treatment (blue bars) and oral outpatient treatment (red bars) in children with *Staphylococcus aureus* community-acquired pneumonia.

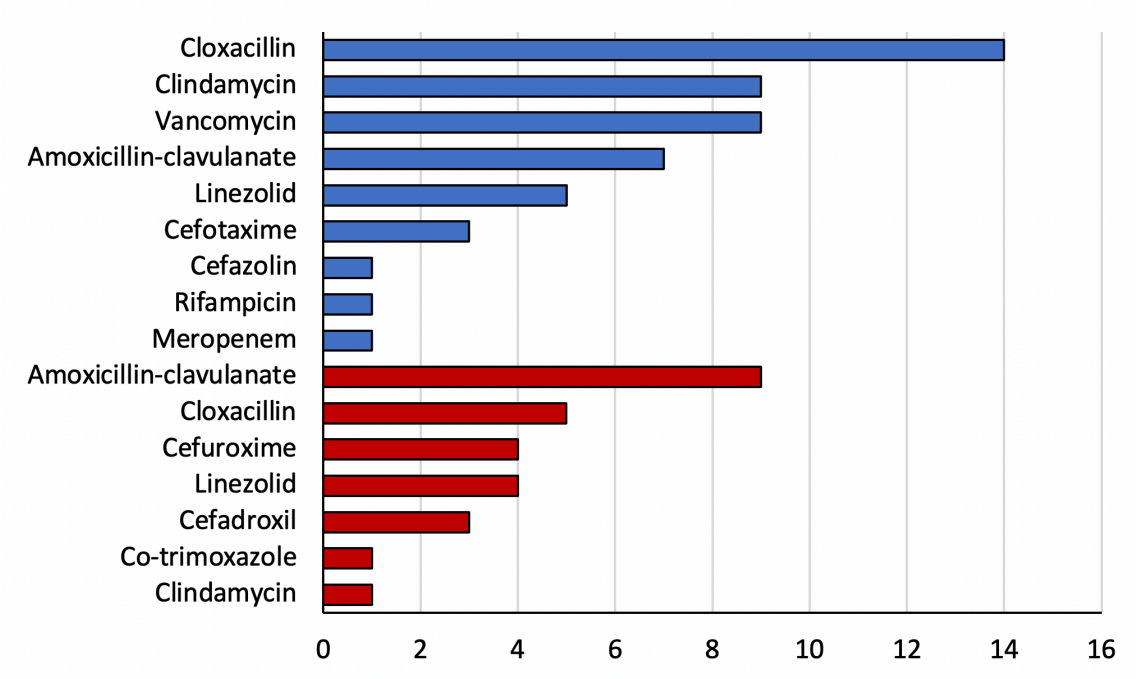
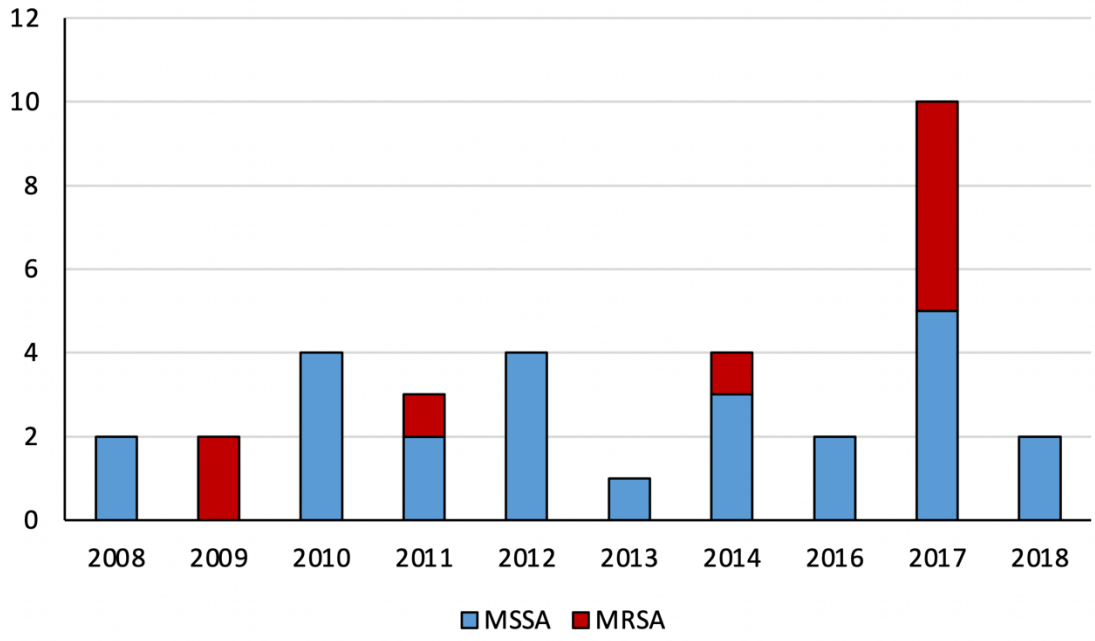


Figure S2. Number of children with *Staphylococcus aureus* community-acquired pneumonia throughout the study period.



Journal of the Pediatric Infectious Diseases Society

BRIEF REPORT

Antibiotic Prescribing in Children Hospitalized With COVID-19 and Multisystem Inflammatory Syndrome in Spain: Prevalence, Trends, and Associated Factors

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The SARS-CoV-2 pandemic has caused an increase in antibiotic use in different settings. We describe the antibiotic prescribing prevalence, associated factors and trends, as well as concomitant bacterial infections in children hospitalized with COVID-19 or multisystemic inflammatory syndrome related to SARS-CoV-2 in Spain.

Key words. antibiotic stewardship; bacterial infections; children; COVID-19; SARS-CoV-2.

The COVID-19 pandemic has had a devastating impact on healthcare systems worldwide. In addition to the high morbidity and mortality associated with SARS-CoV-2 infection, resource prioritization has led to a reduction or interruption in activities related to antimicrobial stewardship programs (ASPs) [1, 2]. This effect has also been described in pediatric settings, with an increase in antibiotic prescribing [3].

While bacterial coinfections or secondary infections have been reported in only 7% to 8% of all patients with COVID-19 [4–6], antibiotic prescribing has been estimated to be 56.6% to 74.6% in different series, but lower in children than in adults (38.5% vs 83.4%) [7, 8]. The substantial difference between antibiotic use and bacterial infections highlights the potential antibiotic overuse in patients with COVID-19.

Specific data on children are scarce [9, 10]. Expanding our knowledge of antibiotic prescribing patterns in the COVID-19 pediatric population could help to develop and implement ASPs, leading to more judicious use of antibiotics. In the present study, the authors sought to analyze the antibiotic prescribing prevalence, risk factors, and trends, as well as bacterial coinfections and secondary infections, in children hospitalized with COVID-19 or multisystem inflammatory syndrome (MIS-C) related to SARS-CoV-2 in Spain.

METHODS

We conducted a multicenter, cohort study of patients < 18 years hospitalized from March 1, 2020, through March 31, 2021, with SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR), rapid antigen test, or fulfilling World Health Organization criteria for MIS-C. The study was conducted nationally across 76 Spanish hospitals included in the Epidemiological Study of Coronavirus in Children in Spain (EPICO-AEP). EPICO-AEP cohort has been previously described [11].

Study Definitions

The prevalence of antibiotic prescribing was considered as the proportion of patients receiving any systemic antibiotic during admission. The length of therapy (LOT) was defined as the number of days that a patient received systemic antibiotics

during admission, using 100 patient days of admission as the denominator. Patients were classified according to 2 diagnoses: (1) acute COVID-19 (symptoms and/or signs of acute SARS-CoV-2 infection) and (2) MIS-C. After central review, bacterial infections were considered based upon microbiological isolation (positive culture or PCR) and clinical relevance.

Statistics

Data are summarized as frequency and percentage for categorical variables and median and interquartile range (IQR) for continuous variables. The monthly percentage change (MPC) was estimated to characterize trends. We used Joinpoint regression modeling of MPC calculations with log-transformed data models to calculate trends in antibiotic prescribing. Categorical variables were compared with χ^2 or Fisher's test, and continuous variables were compared with the Mann-Whitney test. To identify factors associated with the prescribing of systemic antibiotics in patients with COVID-19, all factors with a *P*-value < .05 in bivariate analysis were included in a multivariate logistic regression model. Laboratory blood results were not included in multivariate analysis because of the high number of patients without these tests. All calculated *P*-values were 2-sided and an alpha level of 0.05 was used for assessing significance. Data were analyzed using Joinpoint Regression software v4.9.0.0 (Surveillance Research Program, National Cancer Institute) and Stata v15 (StataCorp, College Station, TX).

Ethics

This study was approved by the ethics committees of Hospital 12 de Octubre (20/101) and the other participating centers.

RESULTS

A total of 640 children were hospitalized with COVID-19 (n = 505, 78.9%) or MIS-C (n = 135, 21.1%). The median age was 4.3 years (IQR: 0.2-11.3 years), and 367 (57.3%) were males. One hundred and twenty-six children (19.7%) were admitted to the pediatric intensive care unit (PICU); 34 (5.3%) required invasive mechanical ventilation and 59 (9.2%) required inotropic support. Eight (1.3%) patients died.

Bacterial coinfections or secondary infections were detected in 7.0% (45/640) of cases and were more frequent in patients with COVID-19 (8.2%, 42/505) than with MIS-C (2.2%, 3/135) (*P* = .020). Urinary tract infections were the most frequent bacterial infections (40.0%, 18/45), mostly by *Escherichia coli*, followed by bloodstream infections (31.1%, 14/45). Coagulase-negative staphylococci were the most prevalent cause of bacteremia (42.9%, 6/14), followed by *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus mitis*, with 2 cases each. Bacterial infections and isolations are included in Supplementary Table S1. Clinical presentation of patients with COVID-19 and bacterial infection are summarized in Supplementary Table S2.

During admission, 347/640 (54.2%) patients received one or more systemic antibiotic, with a LOT of 38.7 days/100 patient days and a median duration of 4.5 days (IQR: 2.5-7.5). Antibiotic prescribing was more common (*P* < .001) in patients with MIS-C (88.9%, 120/135) than with COVID-19 (45.0%, 227/505). Likewise, the LOT was longer for patients with MIS-C (43.4 days/100 patient days) than those with COVID-19 (36.4 days/100 patient-days) (*P* < .001), as was median antibiotic duration (8.5 days [IQR: 6.5-11.5] for MIS-C vs 3.5 days [IQR: 2.5-6.5] for COVID-19; *P* = .004). The most frequently prescribed antibiotic was cefotaxime/ceftriaxone (53.9%, 187/347), followed by azithromycin (26.5%, 92/347), and amoxicillin-clavulanate (18.4%, 64/347). The list of prescribed antibiotics according to diagnosis is included in Supplementary Figures S1-S3.

Changes in the prevalence of antibiotic prescribing among children hospitalized with COVID-19 are shown in Figure 1. There was a significant decline in the prescription of antibiotics in patients with COVID-19 along the study period (MPC: −5.5% [95% confidence interval (CI): −9.7, −1.0]; *P* = .021), and a similar trend was seen for antibiotics prescribed during the first 48 hours of admission (MPC: −5.1% [95% CI: −9.6, −0.4]; *P* = .004). Individual evaluation of antibiotics in patients with COVID-19 revealed a trend for a decline in azithromycin prescription (MPC: −10.8% [95% CI: −21.9, 1.7]; *P* = .081). The LOT in patients with COVID-19 showed a trend for a decrease (MPC: −6.1% [95% CI: −13.9, 2.4]; *P* = .139). There was also a slight but significant decline in the prescription of antibiotics in patients with MIS-C along the study period (MPC: −1.6% [95% CI: −3.1, −0.1]; *P* = .044), but the LOT remained stable (MPC: +4.0% [95% CI: −4.5, 13.3]; *P* = .330).

Factors associated with antibiotic prescribing in patients with COVID-19 in multivariate analysis (Figure 2) were: fever (adjusted odds ratio [aOR]: 3.66 [95% CI: 2.12, 6.31]; *P* < .001), lung infiltrates (aOR: 3.52 [95% CI: 2.08, 5.97]; *P* < .001), sepsis (aOR: 12.95 [95% CI: 1.20, 140.00]; *P* = .035), malignant neoplasm (aOR: 2.86 [95% CI: 1.18, 6.93]; *P* = .020), and hematologic disease (aOR: 3.22 [95% CI: 1.09, 9.51]; *P* = .034). Additionally, every additional year of age increased the odds of receiving antibiotics (aOR: 1.04 [95% CI: 1.00, 1.08]; *P* = .035).

DISCUSSION

To the best of our knowledge, this is the largest study analyzing antibiotic prescribing and concomitant bacterial infection in hospitalized children with COVID-19 or MIS-C. About half (54.2%) of all patients in our cohort received systemic antibiotics during admission, which is higher than that reported by Yock-Corrales et al [10] (24.5%; 243/990 children) in a Latin American cohort including both outpatients and inpatients. Our reported rate is lower than the 69% (415/601) described by

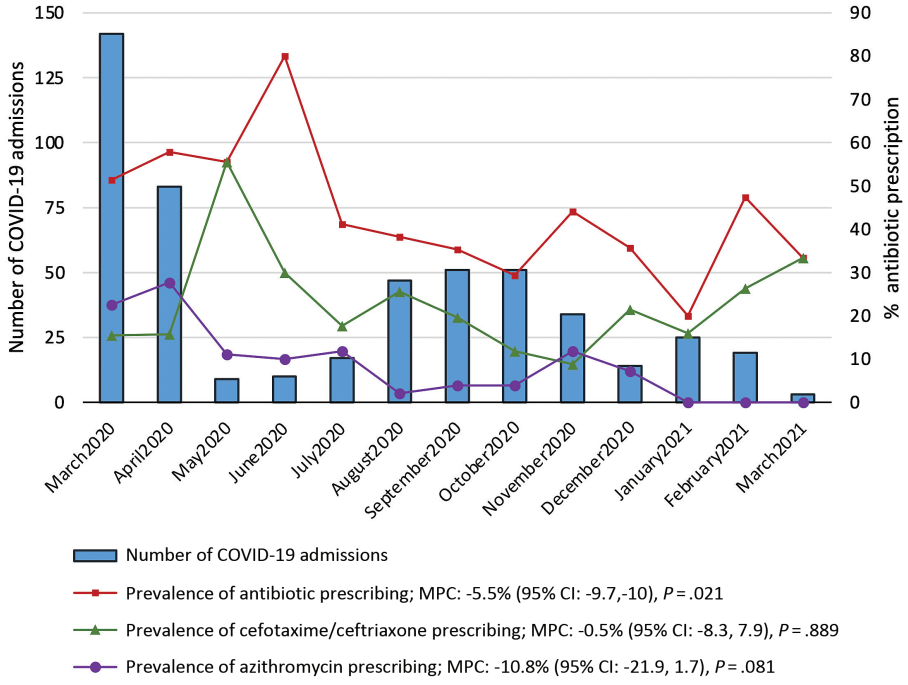

Figure 1. The trend in antibiotic prescribing among children hospitalized with COVID-19. Abbreviation: MPC, monthly percentage change.

Swann et al [9] in hospitalized children in the United Kingdom, perhaps because our study was longer term (until March 2021 vs July 2020), with increasing evidence of low bacterial coinfection in COVID-19. A higher rate has also been described in adults (55%-85%) [7, 8], which is likely explained by the greater severity of SARS-CoV-2 infection in adults than in children.

The severity of acute COVID-19 (eg, fever, lung infiltrates, and PICU admission) and MIS-C was the main reason for antibiotic prescription in our cohort, similar to other adult and pediatric studies [7, 10]. Increasing age has been related to higher antibiotic use in the general population [7] and is confirmed in our study in a pediatric population.

We observed a decline in antibiotic use in COVID-19 cases over time, as reported in adults [7], but not yet described in children [10]. Azithromycin showed the greatest decline in use, likely related to the lack of efficacy in trials [12]. Additionally, a trend toward a reduced LOT was observed in children with COVID-19 but not with MIS-C. Elevated inflammatory markers and the severe clinical presentation in MIS-C overlap with sepsis signs, so empiric antibiotics are usually initiated and later discontinued if MIS-C diagnosis is confirmed.

Notably, we confirm a low rate (7.0%) of bacterial coinfections or secondary infections, especially in MIS-C (2.2%), as described in the aforementioned Latin American cohort (1.3% globally and 0% in MIS-C [10]). Similar to this study, the children in our cohort presented with different bacterial infections when compared with adults, notably urinary tract infections, and all bloodstream infections were due to Gram-positive microorganisms, in contrast to a higher prevalence of Gram-negative bloodstream infections in adults [5, 6].

This considerable difference between the rate of bacterial infections and the prevalence of antibiotic prescribing, especially in MIS-C, underlines the need for a tailored approach to antibiotic use. Antibiotics are likely not needed in the large majority of pediatric admissions for COVID-19. In patients with suspected MIS-C, they can be administered initially after collecting cultures but can be discontinued after 48 to 72 hours of culture incubation if no bacteria are isolated and MIS-C diagnosis is confirmed [13].

Our study has some limitations, including its single-country design. However, a large number of hospitals were included. Also, we focused on hospitalized children, which likely have a higher antibiotic use than outpatients. Because of the nature of our data, we could not distinguish between bacterial coinfections and secondary infections. Further studies are needed to assess this in the pediatric population.

In conclusion, we confirm a high prevalence of antibiotic prescription and low bacterial coinfections or secondary infections in hospitalized children with COVID-19 or MIS-C. A decline in antibiotic use was observed during the first year of the pandemic, but the LOT remained unchanged for MIS-C. Efforts to enhance pediatric ASP actions during the COVID-19 pandemic are needed.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org).

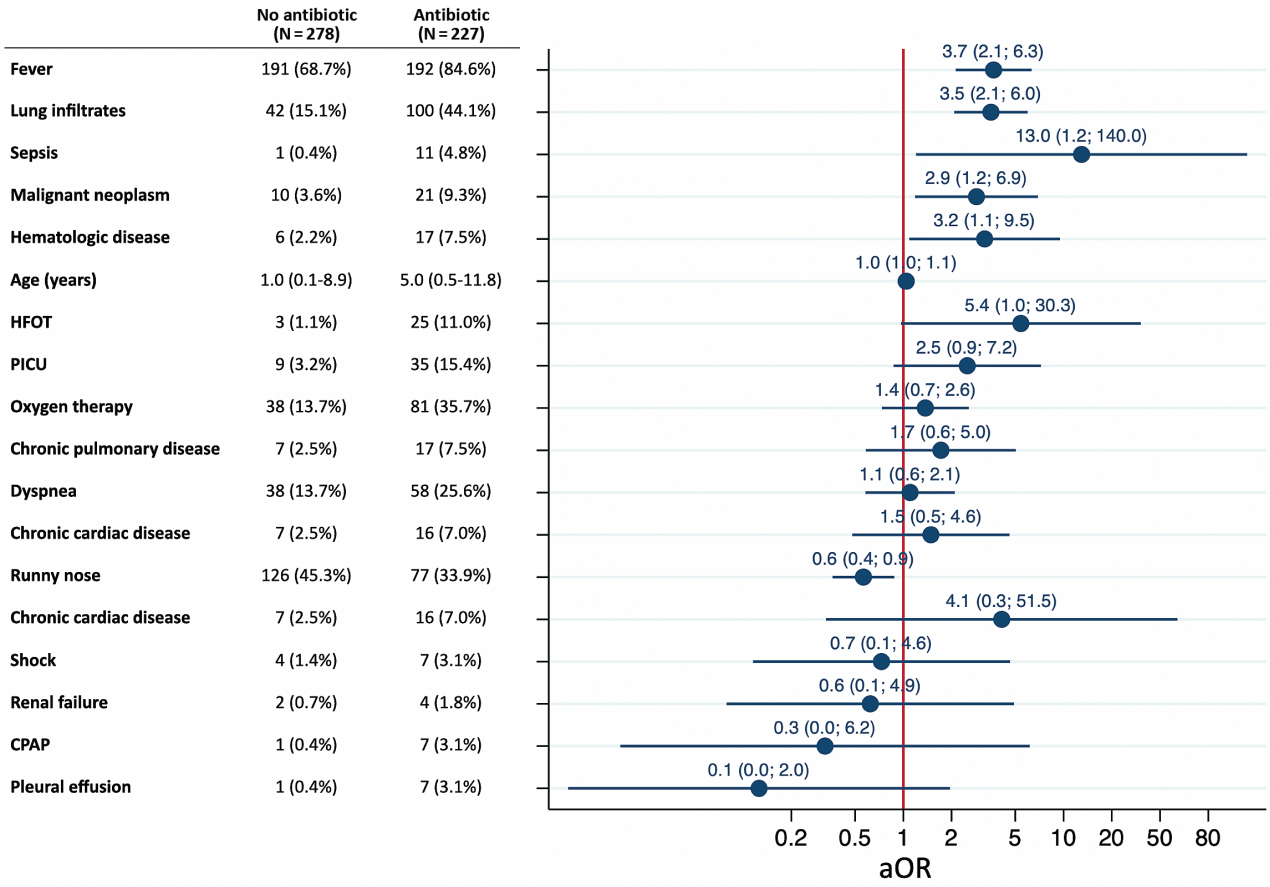

Figure 2. Factors in children hospitalized with COVID-19 associated with antibiotic prescribing in bivariate analysis included in the multivariate analysis. The odds ratio axis is displayed on a logarithmic scale. Abbreviations: aOR, adjusted odds ratio; CPAP, continuous positive airway pressure; HFOT, high-flow oxygen therapy; PICU, pediatric intensive care unit.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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Antibiotic prescribing in children hospitalized with COVID-19 and multisystem Inflammatory syndrome in Spain: prevalence, trends, and associated factors

SUPPLEMENTARY DOCUMENT

Table S1. Bacterial co-infections and secondary infections in children hospitalized with COVID-19 or MIS-C. MIS-C, multisystem Inflammatory syndrome.

Bacterial infection	COVID-19		MIS-C	
	n=42	Microorganisms	n=3	Microorganisms
Bloodstream infection	11	Coagulase-negative staphylococci (3), *Streptococcus pneumoniae* (2), *Staphylococcus aureus* (2), *Enterococcus faecalis* (1), *Enterococcus faecium* (1), *Streptococcus mitis* (2)	3	Coagulase-negative staphylococci (3)
Urinary tract infection	18	*Escherichia coli (14), Enterococcus faecalis (2), Enterobacter cloacae (1), Serratia marcescens (1)*	0	
Gastroenteritis (bacterial)	7	*Campylobacter* spp *(5), Salmonella* spp *(2)*	0	
Whooping cough	2	*Bordetella pertussis* (2)	0	
Bacterial adenitis	1	*Staphylococcus aureus*	0	
Tuberculosis pneumonia	1	*Mycobacterium tuberculosis*	0	
Peritonitis	1	*Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococcus constellatum*	0	
Pelvic inflammatory disease	1	*Neisseria gonorrhoeae*	0	

Table S2. Clinical presentation in patients with COVID-19 and bacterial co-infection or secondary infection. URTI, upper respiratory tract infection.

COVID-19 patients with bacterial co-infection or secondary infection		
Bacterial infection	**n=42**	**Clinical presentation**
Bloodstream infection	11	Pneumonia (6), fever without a source (4), URTI (1)
Urinary tract infection	18	Fever without a source (8), flu-like/URTI (6), pneumonia (2), gastroenteritis (2)
Gastroenteritis (bacterial)	7	Gastroenteritis (5), pneumonia (2)
Whooping cough	2	Bronchiolitis (2)
Bacterial adenitis	1	Gastroenteritis (1)
Tuberculosis pneumonia	1	Pneumonia (1)
Peritonitis	1	Pneumonia (1)
Pelvic inflammatory disease	1	URTI (1)

Figure S1. Systemic antibiotics prescribed during admission in the global cohort (n=640). Percentage of the patients that received some antibiotic (n=347). Some patients received more than one antibiotic.

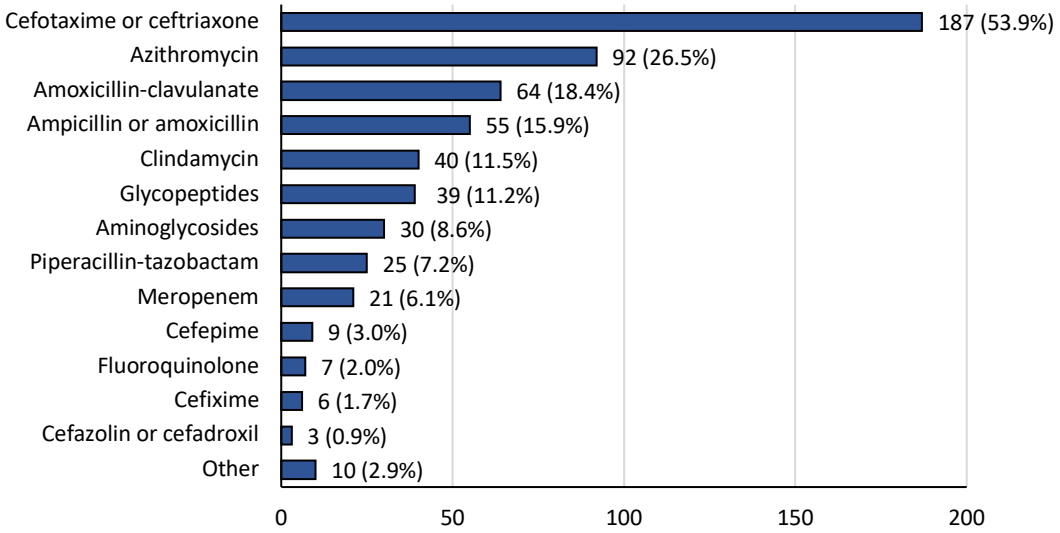


Figure S2. Systemic antibiotics prescribed during admission of patients with COVID-19 (n=505). Percentage of the patients that received some antibiotic (n=227). Some patients received more than one antibiotic.

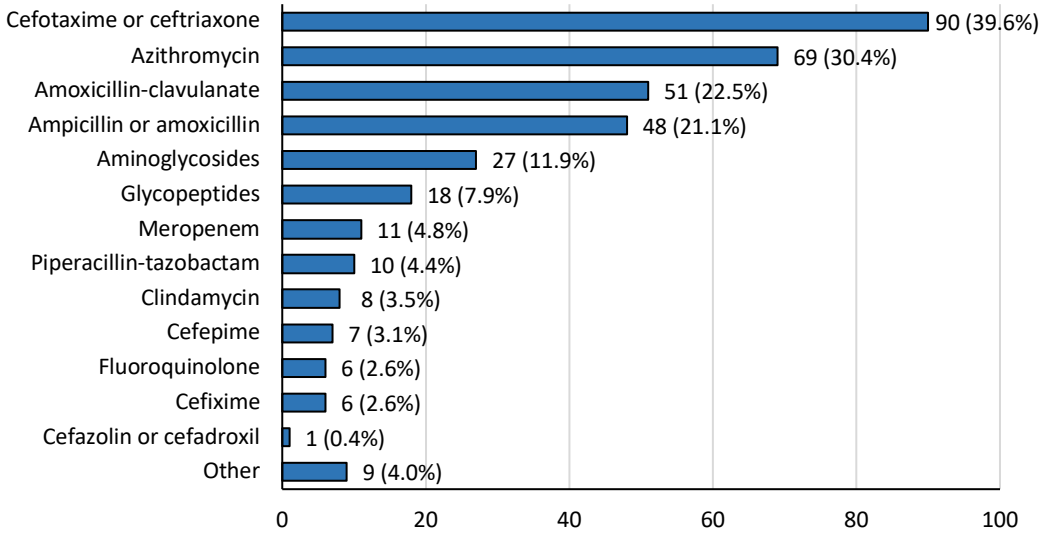
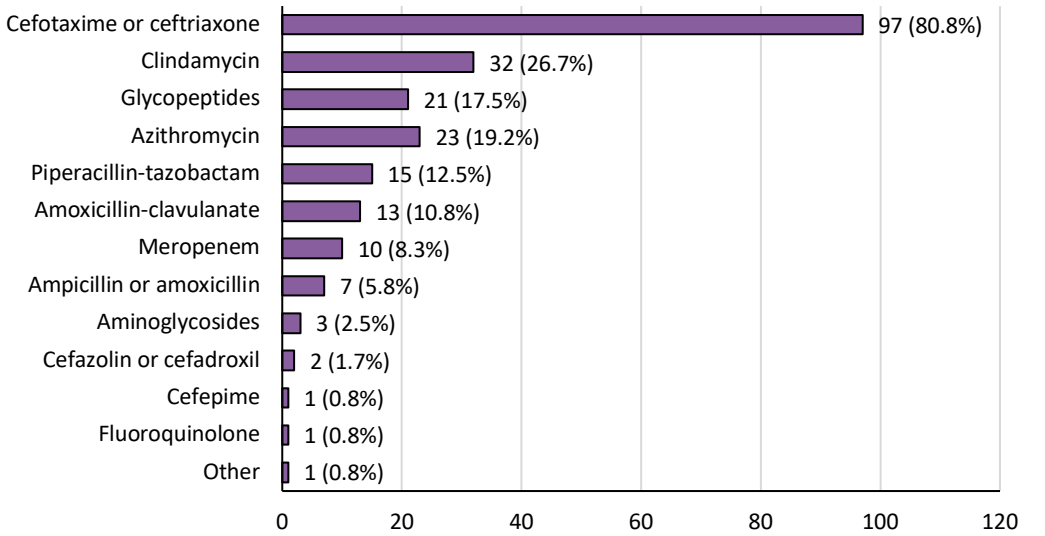


Figure S3. Systemic antibiotics prescribed during admission in patients with MIS-C (n=135). Percentage of patients that received some antibiotic (n=120). Some patients received more than one antibiotic. MIS-C, multisystem Inflammatory syndrome.



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Antibiotic resistance in bloodstream isolates from high-complexity paediatric units in Madrid, Spain: 2013–2021

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SUMMARY

Background: Antimicrobial resistance (AMR) has become a significant challenge in high-complexity healthcare settings.
Aim: To evaluate the prevalence of AMR in bloodstream isolates from high-complexity paediatric units in Spain over a nine-year period.
Methods: A retrospective observational multicentre study was conducted in three tertiary hospitals, analysing bloodstream isolates from patients aged <18 years admitted to the paediatric intensive care, neonatology, and oncology–haematology units between 2013 and 2021. Demographics, antimicrobial susceptibility, and resistance mechanisms were analysed in two periods (2013–2017 and 2017–2021).
Findings: In all, 1255 isolates were included. AMR was more prevalent in older patients and those admitted to the oncology–haematology unit. Multidrug resistance was observed in 9.9% of Gram-negative bacteria (GNB); 20.0% of *P. aeruginosa* vs 8.6% of Enterobacterales ($P < 0.001$), with an increase in Enterobacterales from 6.2% to 11.0% between the first and the second period ($P = 0.021$). Difficult-to-treat resistance was observed in 2.7% of GNB; 7.4% of *P. aeruginosa* vs 1.6% of Enterobacterales ($P < 0.001$), with an increasing trend in Enterobacterales from 0.8% to 2.5% ($P = 0.076$). Carbapenem

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resistance among Enterobacterales increased from 3.5% to 7.2% ($P = 0.029$), with 3.3% producing carbapenemases (67.9% VIM). Meticillin resistance was observed in 11.0% of *S. aureus* and vancomycin resistance in 1.4% of *Enterococcus* spp., with both rates remaining stable throughout the study period.

Conclusion: This study reveals a high prevalence of AMR in high-complexity paediatric units. Enterobacterales showed a concerning increasing trend in resistant strains, with higher rates among older patients and those admitted to oncology—haematology units.

Introduction

The prevalence of antimicrobial resistance (AMR) to common first-line antimicrobials has significantly increased over the past few decades, and it is currently one of the main threats to public health [1]. Infections by multidrug-resistant (MDR) organisms are particularly important in healthcare settings. These infections have a poorer prognosis due to the delay in initiating appropriate antibiotic therapy and the need for alternative antimicrobials, which are usually less effective and less safe [2]. However, the development and introduction in clinical practice of novel β-lactam—β-lactamase inhibitor combinations which are active against many MDR organisms have led to a breakthrough in the treatment of these infections.

Recently, to enhance the classification of AMR isolates with significant clinical impact, the definition of difficult-to-treat resistance (DTR) has been proposed for Gram-negative bacteria (GNB) [3]. Among the risk factors for infection by MDR organisms, most of them are related to high-complexity patients, involving previous broad-spectrum antibiotic administration, invasive devices, or immunosuppression [4,5].

Several surveillance networks have described the epidemiology of AMR across different regions. However, the information classified according to age groups is only reported occasionally, with scarce information on the prevalence of DTR in children. This has remarkable implications since the epidemiology of adults is not always the same in children [6]. Therefore, it is crucial to determine the prevalence of antimicrobial resistance (AMR) in common organisms and infections to establish clinical guidelines for the management of severe infections, such as fever in neutropenic patients or neonatal sepsis.

On the other hand, hospital-acquired infections usually differ in many aspects from community-acquired infections. Thus, the epidemiology in one of these settings is usually not valid for the other. Paediatric intensive care (PICU), oncology—haematology, and neonatal units are among the paediatric units that exhibit the highest prevalence of antimicrobial-resistant isolates [7,8]. Patients admitted to these units are usually exposed to a broad range of risk factors related to resistance acquisition. Furthermore, outbreaks of MDR organisms sometimes occur in these units, with a high nosocomial transmission.

This study aimed to describe the prevalence of AMR among organisms isolated from blood samples in children admitted to high-complexity paediatric units over a nine-year period.

Methods

A retrospective observational multicentre study was conducted in three tertiary hospitals in Madrid (Spain). From January 2013 to December 2021, Enterobacterales (*Escherichia coli*, *Klebsiella* spp., *Serratia* spp., *Enterobacter* spp., and *Proteus* spp.), *Staphylococcus aureus*, *Enterococcus* spp., and *Pseudomonas aeruginosa* isolated from blood cultures in patients aged <18 years admitted to PICU, neonatology or oncology—haematology units from the participating hospitals were evaluated. The same isolate obtained within 14 days of a previous one was excluded. The isolates were identified from the microbiology laboratory databases.

The following data were collected: age, gender, unit of hospitalization, date of isolation, micro-organism isolated and antimicrobial susceptibility, and the enzymatic resistance mechanisms (extended-spectrum β-lactamases (ESBLs) and carbapenemases), if present. The included hospitals have 256, 150, and 140 paediatric beds, with 8800, 2400, and 2800 annual paediatric admissions during the study period.

Microbiology

Blood cultures were processed using semi-automated systems (Bactec FX®; Becton Dickinson, Franklin Lakes, USA; or Bact/Alert Virtuo; bioMérieux, Marcy-l'Etoile, France) and incubated for five days. Gram stain was performed from all positive bottles. In addition, all positive bottles were cultured on to Columbia blood agar (incubation in air), chocolate agar (incubation in 5% CO_2), and Brucella agar (incubation in anaerobic atmosphere) at 35—37 °C for 48 h. Micro-organism identification was performed by matrix-assisted laser desorption—ionization time-of-flight mass spectrometry using the Bruker Biotyper System (Bruker Daltonik GmbH, Bremen, Germany). Antimicrobial susceptibility testing was performed by the automated broth microdilution method (MicroScan; Beckman Coulter, Brea, CA, USA), and, additionally, by Vitek 2 (bioMérieux) in one centre. Interpretation of susceptible, susceptible with increased exposure, and resistant clinical categories was determined following the EUCAST recommendations in 2021 [9]. For the purpose of analysis, we considered isolates that were susceptible as well as those that showed susceptibility with increased exposure as susceptible. ESBLs were detected either by the double-disc diffusion method or by the microdilution method with MicroScan panels, using cefotaxime and ceftazidime in combination with clavulanate, or by Vitek 2. Carbapenemase production (KPC, VIM, NDM, OXA-48, and IMP) was detected by using either immunochromatographic methods

(Coris Bioconcept, Gembloux, Belgium) or by molecular methods using a commercialized polymerase chain reaction (Xpert® Carba-R; Cepheid, CA, Sunnyvale, USA).

The organisms were categorized as carbapenem resistant if they were resistant to imipenem and/or meropenem (and to ertapenem in the case of Enterobacterales) or if carbapenemase production was detected. Resistance to extended-spectrum cephalosporins (ESCs) in Enterobacterales was defined as the presence of resistance to cefotaxime, ceftriaxone, ceftazidime, or cefepime, and for *P. aeruginosa* as the presence of resistance to ceftazidime or cefepime. Resistance to aminoglycosides was defined as the presence of resistance to gentamicin, amikacin, or tobramycin. For *Serratia* spp., only gentamycin was considered for aminoglycoside resistance, since some laboratories reclassified the susceptibility of amikacin and tobramycin as resistant due to intrinsic resistance, independently of the minimum inhibitory concentration [10].

GNB were classified as MDR if they exhibited resistance to at least one antibiotic from three or more distinct antimicrobial groups, excluding intrinsic resistance. The groups evaluated for MDR included ESCs, fluoroquinolones, aminoglycosides, carbapenems, and piperacillin–tazobactam. This definition is similar to the standard MDR definition and it has been used in several studies [11–13]. GNB were classified as having DTR if they exhibited resistance to all β-lactams (including carbapenems, but not new β-lactams, such as ceftazidime–avibactam or ceftolozane–tazobactam) and fluoroquinolones [3]. For DTR and MDR definition, carbapenems were classified as resistant in all carbapenemase-producing organisms (CPO), as they are not the first-line treatment for bloodstream infections (BSIs) caused by CPOs [14].

Statistics

Descriptive statistics were performed and reported in terms of absolute frequencies and percentages for qualitative data and median with interquartile range (IQR) for quantitative data. Patients were classified into two age groups (<1 month and ≥1 month). The median age of the patients included in the sample was used as the criterion to determine the division between the two groups. The study period was divided into two equal periods (the first period from January 2013 to June 2017, and the second period from July 2017 to December 2021). The prevalence of resistance among the different species and groups of organisms was compared according to the age of the patients, periods, and unit and hospital of admission. Age was analysed both categorically, by age groups, and as a continuous variable measured in years. Differences among qualitative data were evaluated using χ^2-test or Fisher's exact test. Additionally, the odds ratios for resistance were calculated by univariate logistic regression and by multivariate logistic regression adjusted for potential confounding factors (unit and hospital). For all calculations, two-tailed $P < 0.05$ was considered statistically significant. Data were analysed using the Stata version 17, College Station, TX, USA.

Ethics

The study was approved by the Clinical Research Ethics Committee of the Gregorio Marañón Hospital.

Results

During the nine-year study period, 1255 isolates from 988 different patients met the inclusion criteria, including 1183 episodes of BSIs. A total of 449/988 (45.5%) of included patients were female. The median age at BSI episode was 1.4 months (IQR: 0.4–7.3). Most BSI episodes (80.0%, 946/1183) were in patients aged <1 year (Supplementary Figure S1). Seventy-one (6.0%) of these episodes were polymicrobial (≥2 isolates). The highest number of isolates was obtained from children admitted to neonatology (736 isolates; 58.7%), followed by PICU (358

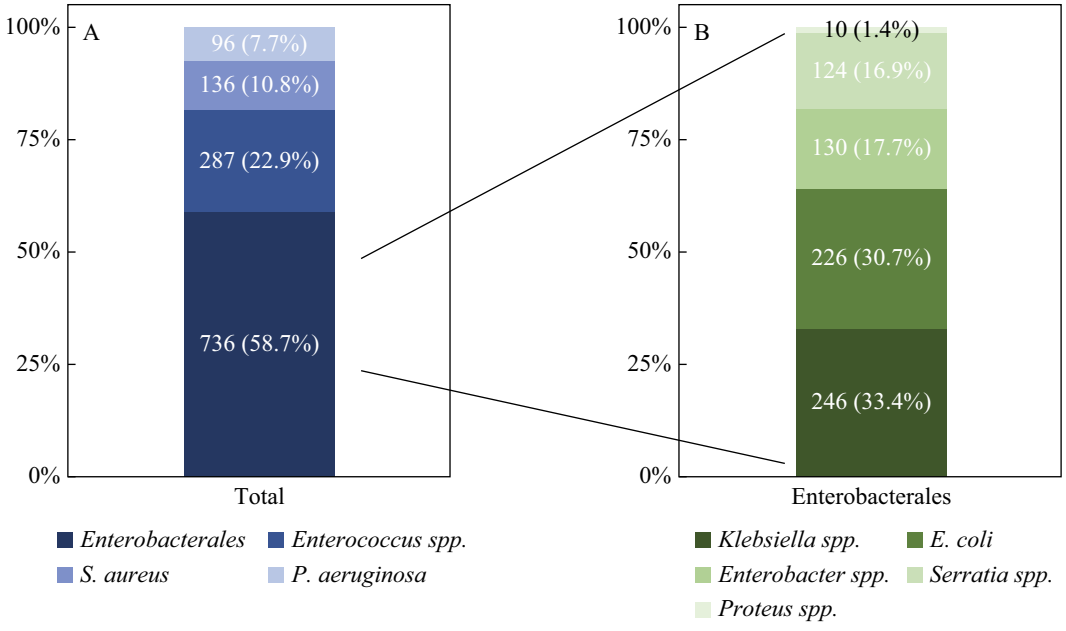

Figure 1. (A) Distribution of isolated bacterial species. (B) Distribution of isolated Enterobacterales (calculated as a percentage of the total number of isolated Enterobacterales).

Table I
Frequency and prevalence of resistance among bloodstream isolates

Micro-organism/antibiotic	No. (%) of isolated tested	No. (%) resistant[a]
Enterobacterales ($N = 736$)		
ESCs	708 (98.6%)	112 (15.4%)
ESBLs	732 (99.5%)	68 (9.3%)
Carbapenems	731 (99.3%)	39 (5.3%)
Meropenem/imipenem	718 (97.6)	18 (2.5)
Carbapenemase	Unknown	24 (3.3%)
Fluoroquinolones	732 (99.5%)	99 (13.5%)
Aminoglycosides	734 (99.7%)	115 (15.7%)
MDR	730 (99.2%)	63 (8.6%)
DTR	730 (99.2%)	15 (1.6%)
Klebsiella spp. ($N = 246$)		
ESCs	240 (97.6%)	44 (18.3%)
ESBLs	240 (97.6%)	32 (13.3%)
Amoxicillin–clavulanate	241 (98.0%)	62 (25.7%)
Carbapenems	245 (99.6%)	20 (8.2%)
Meropenem/imipenem	222 (94.3%)	8 (3.5%)
Carbapenemase	Unknown	16 (6.5%)
Fluoroquinolones	246 (100%)	31 (12.6%)
Aminoglycosides	246 (100%)	41 (16.7%)
MDR	245 (99.6%)	31 (12.7%)
DTR	245 (99.6%)	11 (4.5%)
E. coli ($N = 226$)		
ESCs	223 (98.7%)	30 (13.5%)
ESBLs	223 (98.7%)	27 (12.1%)
Amoxicillin–clavulanate	223 (98.7%)	61 (27.4%)
Carbapenems	223 (98.7%)	3 (1.4%)
Meropenem/imipenem	223 (98.7%)	1 (0.5%)
Carbapenemase	Unknown	0
Fluoroquinolones	222 (98.2%)	58 (26.1%)
Aminoglycosides	224 (99.1%)	58 (25.9%)
MDR	222 (98.2%)	15 (6.8%)
DTR	222 (98.2%)	0
Enterobacter spp. ($N = 130$)		
ESCs	129 (99.2%)	24 (18.6%)
ESBLs	128 (99.2%)	8 (6.2%)
Carbapenems	129 (99.2%)	9 (7.0%)
Meropenem/imipenem	129 (100%)	5 (3.9%)
Carbapenemases	Unknown	5 (3.9%)
Fluoroquinolones	130 (100%)	8 (6.2%)
Aminoglycosides	130 (100%)	14 (10.8%)
MDR	129 (99.2%)	15 (11.6%)
DTR	129 (99.2%)	0
Serratia spp. ($N = 124$)		
ESCs	124 (100%)	14 (11.3%)
ESBLs	124 (100%)	1 (0.8%)
Carbapenems	124 (100%)	7 (5.7%)
Meropenem/imipenem	124 (100%)	4 (3.2%)
Carbapenemase	Unknown	3 (2.4%)
Fluoroquinolones	124 (100%)	1 (0.8%)
Aminoglycosides	124 (100%)	2 (1.6%)
MDR	124 (100%)	2 (1.6%)
DTR	124 (100%)	0
Proteus spp. ($N = 10$)		
ESCs	9 (100%)	0
ESBLS	9 (100%)	0
Amoxicillin–clavulanate	7 (77.8%)	0
Carbapenems	9 (100%)	0
Meropenem/imipenem	9 (100%)	0
Carbapenemase	Unknown	0
Fluoroquinolones	9 (100%)	1 (11.1%)
Aminoglycosides	9 (100%)	0
MDR	9 (100%)	0
DTR	9 (100%)	0
S. aureus ($N = 136$)		
Meticillin	136 (100%)	15 (11.0%)
P. aeruginosa ($N = 96$)		
ESCs	96 (100%)	25 (26.0%)
Carbapenems	96 (100%)	28 (29.2%)
Carbapenemase	Unknown	5 (5.2%)
Fluoroquinolones	95 (99.0%)	26 (27.4%)
Aminoglycosides	96 (100%)	19 (19.8%)
Piperacillin–tazobactam	96 (100%)	21 (22.1%)
MDR	95 (99.0%)	19 (20.0%)
DTR	95 (99.0%)	7 (7.3%)
Enterococcus spp. ($N = 287$)		
Vancomycin	282 (98.2%)	4 (1.4%)

DTR, difficult-to-treat resistance; ESBL, extended-spectrum β-lactamases; ESCs, extended-spectrum cephalosporins; MDR, multidrug-resistant.

[a] Percentage calculated using as denominator the total of isolates with any susceptibility test for that antibiotic/resistance mechanism. Carbapenemase percentages were calculated out of the total of isolates in each organism/group.

isolates; 28.5%) and oncology–haematology unit (161 isolates; 12.8%). The number of isolates from the different hospitals was similar: 461, 398, and 396, respectively.

The distribution of the isolated bacterial species is shown in Figure 1. The majority (58.7%, 736/1255) were Enterobacterales. Among these, the most frequent organism was *Klebsiella* spp. (33.4%, 246/736; 74.4% *Klebsiella pneumoniae*, 19.5% *Klebsiella oxytoca*, and 6.1% other species), followed by *E. coli* (30.7%, 226/736). The prevalence of AMR among the different bacterial species is shown in Table I. ESBLs were identified in 68/736 (9.3%) Enterobacterales, more frequently in *Klebsiella* spp. (13.3%, 32/246), and carbapenemase production in 29/828 (3.5%) GNB. The most common carbapenemase was VIM, in 20/29 (67.9%) CPOs, followed by OXA-48 in 6/29 (20.7%) CPOs. In a single isolate, KPC and VIM were simultaneously detected. The distribution of CPOs is shown in Supplementary Table S1. The most frequent CPO was *Klebsiella* spp. (55.2%, 16/29), followed by *Enterobacter* spp. and *P. aeruginosa* (17.2%, 5/29 each), and *Serratia* spp. (10.3%, 3/29). The epidemiology of the carbapenemases detected among CPOs changed from the first to the second period: VIM significantly decreased ($P = 0.002$) from 87.5% (14/16) to 46.2% (6/13) and OXA-48 increased ($P < 0.001$) from 0% (0/16) to 46.2% (6/13).

A total of 82/825 (9.9%) GNB were classified as MDR (20.0% of *P. aeruginosa* vs 8.6% of Enterobacterales, $P < 0.001$), and 22/825 (2.7%) GNB as having DTR (7.3% of *P. aeruginosa* vs 1.6% of Enterobacterales, $P < 0.001$). DTR in Enterobacterales

affected mostly to *Klebsiella* spp. (91.7% of all DTR Enterobacterales isolates, 4.5% of *Klebsiella* spp. isolates).

The prevalence of meticillin-resistant *S. aureus* (MRSA) among *S. aureus* isolates was 11.0% ($N = 15/136$). The prevalence of vancomycin resistance among *Enterococcus* spp. isolates was 1.4% (4/287; 0% in *Enterococcus faecalis* and 8.6% in *Enterococcus faecium*).

Resistance according to the units

Enterobacterales isolated from oncology–haematology units had the highest prevalence of AMR (Table II, Supplementary Table S2). The isolates from neonatology, including Enterobacterales, *P. aeruginosa*, *S. aureus*, and *Enterococcus* spp., had the lowest prevalence of AMR. *P. aeruginosa* isolates from PICU had a trend towards higher resistance rates compared to other units. Older children had higher odds of resistant isolates, including all evaluated organisms except *S. aureus* (Table III). Comparison of the prevalence of resistant isolates according to the hospital can be seen in Supplementary Table S3.

Resistance according to the study period

Throughout the study period, there was an overall increase in the prevalence of resistant Enterobacterales, including resistance to ESCs, carbapenems, and fluoroquinolones (Figure 2, Table IV, Supplementary Table S4), mostly because of an increase in the prevalence of AMR in *Klebsiella* spp., *Enterobacter* spp., and *Serratia* spp., but not in *E. coli*. Thus, the prevalence of ESC-, carbapenem- and fluoroquinolone-resistant Enterobacterales increased from the first to the second period, from 12.5% (46/368) to 18.4% (66/358; aOR: 1.66; 95% CI: 1.08–2.55), from 3.5% (13/368) to 7.2% (26/363; aOR: 2.15; 95% CI: 1.07–4.30), and from 10.9% (40/368) to 16.2% (59/364; aOR: 1.66; 95% CI: 1.06–2.61), respectively. In addition, there was a significant increase in the prevalence of MDR Enterobacterales comparing the first with the second period, from 6.2% (23/368) to 11.0% (40/362; aOR: 1.93; 95% CI: 1.10–3.37), and a non-significant increase of DTR from 0.8% (3/368) to 2.5% (9/362; aOR: 3.12; 95% CI: 0.83–11.67).

The prevalence of carbapenemase-producing and aminoglycoside-resistant *P. aeruginosa* isolates decreased from 9.4% (5/53) to 0% (0/43) ($P = 0.039$), and from 28.3% (15/53) to 9.3% (4/43; aOR: 0.24; 95% CI: 0.07–0.80), respectively. Despite the decrease of carbapenemase-producing *P. aeruginosa*, the prevalence of carbapenem-resistant *P. aeruginosa* isolates remained stable. The prevalence of MRSA and vancomycin-resistant *Enterococcus* spp. also remained stable.

Discussion

The present multicentre study, involving three referral tertiary hospitals in Spain, describes the epidemiology of AMR among bacterial isolates from blood samples in children admitted to high-complexity paediatric units. The prevalence of resistant GNB was high, showing an increasing trend within the study period in the AMR of Enterobacterales against commonly used antibiotics, such as ESCs, carbapenems, or fluoroquinolones. Older patients had a higher prevalence of resistant isolates in almost all the evaluated micro-organisms, and Enterobacterales from oncology–haematology units had the highest

Table II
Number and percentage of resistant bloodstream isolates from the different units

Micro-organism/ resistance	Total	Neonatology (N)	PICU (P)	Oncology–haematology (OH)	*P*-value	N vs P	N vs OH	P vs OH
Enterobacterales	$N = 736$	$N = 449$	$N = 187$	$N = 100$				
ESCs	112/726 (15.4%)	33/443 (7.4%)	45/184 (24.5%)	34/99 (34.3%)	<0.001	<0.001	<0.001	ns
ESBLs	68/732 (9.3%)	21/448 (4.7%)	22/185 (11.9%)	25/99 (25.3%)	<0.001	0.001	<0.001	0.004
Carbapenems	39/731 (5.3%)	9/445 (2.0%)	18/186 (9.7%)	12/100 (12.0%)	<0.001	<0.001	<0.001	ns
Carbapenemase	24/732 (3.3%)	4/448 (0.9%)	12/185 (6.5%)	8/99 (8.1%)	<0.001	<0.001	<0.001	ns
Fluoroquinolones	99/732 (13.5%)	36/446 (8.1%)	27/186 (14.5%)	36/100 (36.0%)	<0.001	0.014	<0.001	<0.001
Aminoglycosides	115/734 (15.7%)	46/448 (10.3%)	36/186 (19.4%)	33/100 (33.0%)	<0.001	0.002	<0.001	0.010
MDR	71/730 (9.7%)	16/444 (3.6%)	31/186 (16.7%)	24/100 (24.0%)	<0.001	<0.001	<0.001	ns
DTR	12/730 (1.6%)	1/444 (0.2%)	9/186 (4.8%)	2/100 (2.0%)	<0.001	<0.001	0.030	ns
P. aeruginosa	$N = 96$	$N = 24$	$N = 51$	$N = 21$				
ESCs	25/96 (26.0%)	4/24 (16.7%)	18/51 (35.3%)	3/21 (14.3%)	ns	ns	ns	ns
Carbapenems	28/96 (29.2%)	4/24 (16.7%)	18/51 (35.3%)	6/21 (28.6%)	ns	ns	ns	ns
Carbapenemase	5/96 (5.2%)	0/24 (0.0%)	3/51 (5.9%)	2/21 (9.5%)	ns	ns	ns	ns
Fluoroquinolones	26/95 (27.4%)	2/24 (8.3%)	19/51 (37.3%)	5/20 (25.0%)	0.031	0.009	ns	ns
Aminoglycosides	19/96 (19.8%)	2/24 (8.3%)	14/51 (27.5%)	3/21 (14.3%)	ns	ns	ns	ns
MDR	19/95 (20.0%)	3/24 (12.5%)	13/51 (25.5%)	3/20 (15.0%)	ns	ns	ns	ns
DTR	7/95 (7.4%)	1/24 (4.2%)	4/51 (7.8%)	2/20 (10.0%)	ns	ns	ns	ns
S. aureus	$N = 136$	$N = 79$	$N = 33$	$N = 24$				
Meticillin	15/136 (11.0%)	6/79 (7.6%)	4/33 (12.1%)	5/24 (20.8%)	ns	ns	ns	ns
Enterococcus spp.	$N = 287$	$N = 184$	$N = 87$	$N = 16$				
Vancomycin	4/282 (1.4%)	0/181 (0.0%)	2/85 (2.4%)	2/16 (12.5%)	<0.001	0.038	<0.001	ns

DTR, difficult-to-treat resistance; ESCs, extended-spectrum cephalosporins; MDR, multidrug-resistant; PICU, paediatric intensive care unit; ns, non-significant.

Table III
Comparison of resistant isolates according to age group

Micro-organism/resistance	Total	<1 month	≥1 month	*P*-value	OR (95% CI)	OR years of age (95% CI)[a]
Enterobacterales	*N* = 736	*N* = 338	*N* = 398			
ESCs	112/726 (15.4%)	19/336 (5.7%)	93/390 (23.8%)	<0.001	5.22 (3.07–9.28)	1.12 (1.07–1.17)
ESBLs	68/732 (9.3%)	12/338 (3.6%)	56/394 (14.2%)	<0.001	4.50 (2.33–9.38)	1.12 (1.06–1.18)
Carbapenems	39/731 (5.3%)	4/335 (1.2%)	35/396 (8.8%)	<0.001	8.02 (2.82–31.34)	1.11 (1.04–1.18)
Carbapenemase	24/732 (3.3%)	2/338 (0.6%)	22/394 (5.6%)	<0.001	9.94 (2.41–87.60)	1.11 (1.02–1.20)
Fluoroquinolones	99/732 (13.5%)	27/336 (8.0%)	72/396 (18.2%)	<0.001	2.54 (1.56–4.23)	1.18 (1.12–1.24)
Aminoglycosides	115/734 (15.7%)	34/338 (10.1%)	81/396 (20.5%)	<0.001	2.30 (1.47–3.65)	1.10 (1.05–1.16)
MDR	63/730 (8.6%)	6/334 (1.8%)	57/396 (14.4%)	<0.001	9.19 (3.89–26.39)	1.13 (1.07–1.20)
DTR	12/730 (1.6%)	1/334 (0.3%)	11/396 (2.8%)	0.009	9.51 (1.37–410.66)	1.13 (1.02–1.25)
Klebsiella spp.	*N* = 246	*N* = 99	*N* = 147			
ESCs	44/240 (18.3%)	6/99 (6.1%)	38/141 (27.0%)	<0.001	5.72 (2.25–17.20)	1.22 (1.08–1.36)
ESBLs	32/246 (13.0%)	5/99 (5.1%)	27/147 (18.4%)	0.002	4.23 (1.52–14.53)	1.16 (1.05–1.29)
Carbapenems	20/245 (8.2%)	1/98 (1.0%)	19/147 (12.9%)	<0.001	14.40 (2.20–604.20)	1.18 (1.06–1.32)
Carbapenemase	16/246 (6.5%)	1/99 (1.0%)	15/147 (10.2%)	0.004	11.14 (1.65–473.42)	1.20 (1.08–1.35)
Fluoroquinolones	31/246 (12.6%)	5/99 (5.1%)	26/147 (17.7%)	0.003	4.04 (1.45–13.92)	1.18 (1.06–1.31)
Aminoglycosides	41/246 (16.7%)	7/99 (7.1%)	34/147 (23.1%)	<0.001	3.95 (1.62–11.01)	1.19 (1.07–1.33)
MDR	31/245 (12.7%)	3/98 (3.1%)	28/147 (19.0%)	<0.001	7.45 (2.19–39.20)	1.23 (1.10–1.37)
DTR	11/245 (4.5%)	1/98 (1.0%)	10/147 (6.8%)	0.032	7.08 (0.97–310.32)	1.18 (1.04–1.33)
E. coli	*N* = 226	*N* = 127	*N* = 99			
ESCs	30/223 (13.5%)	6/126 (4.8%)	24/97 (24.7%)	<0.001	6.58 (2.45–20.44)	1.11 (1.03–1.19)
ESBLs	27/223 (12.1%)	5/127 (3.9%)	22/96 (22.9%)	<0.001	7.25 (2.52–25.36)	1.10 (1.02–1.18)
Amoxicillin-clavulanate	61/223 (27.4%)	26/126 (20.6%)	35/97 (36.1%)	0.010	2.17 (1.14–4.13)	1.04 (0.97–1.11)
Carbapenem	3/223 (1.3%)	1/126 (0.8%)	2/97 (2.1%)	ns	2.63 (0.13–156.46)	0.92 (0.60–1.41)
Carbapenemase	0/223 (0.0%)	0/127 (0.0%)	0/96 (0.0%)	–	–	–
Fluoroquinolones	58/222 (26.1%)	21/125 (16.8%)	37/97 (38.1%)	<0.001	3.05 (1.57–6.00)	1.19 (1.11–1.29)
Aminoglycosides	58/224 (25.9%)	25/127 (19.7%)	33/97 (34.0%)	0.015	2.10 (1.10–4.04)	1.03 (0.96–1.10)
MDR	15/222 (6.8%)	2/125 (1.6%)	13/97 (13.4%)	<0.001	9.52 (2.06–88.25)	1.10 (1.01–1.21)
DTR	0/222 (0.0%)	0/125 (0.0%)	0/97 (0.0%)	–	–	–
P. aeruginosa	*N* = 96	*N* = 19	*N* = 77			
ESCs	25/96 (26.0%)	1/19 (5.3%)	24/77 (31.2%)	ns	8.15 (1.13–353.46)	1.17 (1.06–1.30)
Carbapenem	28/96 (29.2%)	2/19 (10.5%)	26/77 (33.8%)	0.046	4.33 (0.90–41.03)	1.17 (1.05–1.29)
Carbapenemase	5/96 (5.2%)	0/19 (0.0%)	5/77 (6.5%)	0.254	–	1.45 (1.16–1.80)
Fluoroquinolones	26/95 (27.4%)	1/19 (5.3%)	25/76 (32.9%)	0.016	8.82 (1.23–382.01)	1.22 (1.09–1.36)
Aminoglycosides	19/96 (19.8%)	1/19 (5.3%)	18/77 (23.4%)	0.076	5.49 (0.75–241.28)	1.12 (1.01–1.24)
MDR	19/95 (20.0%)	0/19 (0.0%)	19/76 (25.0%)	0.015	–	1.17 (1.06–1.31)
DTR	7/95 (7.4%)	0/19 (0.0%)	7/76 (9.2%)	0.169	–	1.17 (1.02–1.34)
S. aureus	*N* = 136	*N* = 55	*N* = 81			
Meticillin	15/136 (11.0%)	4/55 (7.3%)	11/81 (13.6%)	0.249	1.67 (0.48–6.57)	1.11 (0.99–1.25)
Enterococcus spp.	*N* = 287	*N* = 124	*N* = 163			
Vancomycin	4/282 (1.4%)	0/123 (0.0%)	4/159 (2.5%)	0.073	–	1.23 (0.98–1.54)

OR, odds ratio; CI, confidence interval; DTR, difficult-to-treat resistance; ESCs, extended-spectrum cephalosporins; MDR, multidrug-resistant; PICU, paediatric intensive care unit; ns, non-significant.
[a] Includes the odds ratio of resistance calculated using the years of age as an independent continuous variable.

prevalence of AMR. To the best of our knowledge, this study includes one of the largest samples of bloodstream isolates from high-complexity paediatric patients published so far, which is a group of patients with a high risk of AMR.

As shown in other studies, the prevalence of BSIs in our population was higher among younger children [6,15,16]. However, younger children, especially those admitted to neonatal units, had a lower prevalence of AMR, which is in agreement with other studies performed in high-income countries. A recent study that evaluated BSIs in children in Japan showed a lower prevalence of MDR in GNB in the neonatal unit (14.4%) compared to other units, such as oncology–haematology (35.1%) or PICU (22.4%) [8]. With a similar trend, the resistance rates of different GNB were lower in children aged <1 year (e.g. to fluoroquinolones in *E. coli* or to carbapenems in *K. pneumoniae*) than in patients aged ≥1 year in the European ARPEC study [6]. Nevertheless, data from low- and middle-income countries showed a similar or even higher prevalence of AMR among neonates compared with older children [17,18]. Therefore, there seem to be relevant

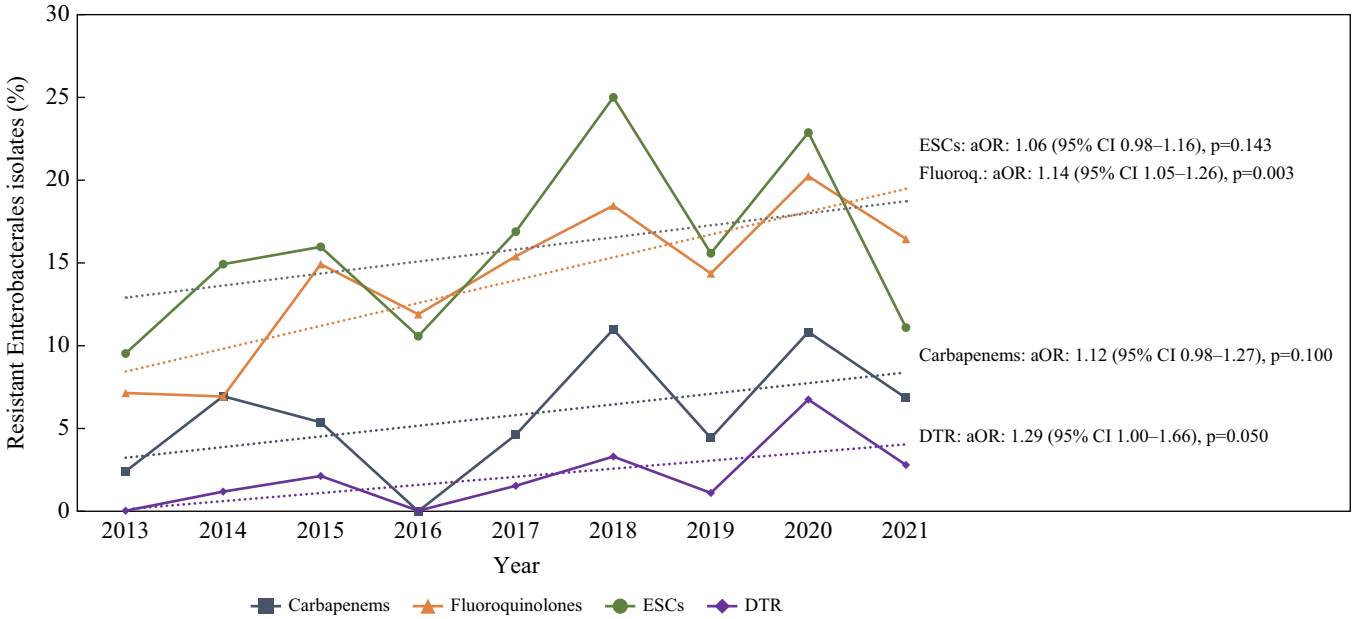

Figure 2. Annual trend of antibiotic resistance among Enterobacterales isolates. The dotted lines represent the modelled trend of each antibiotic resistance. The odds ratio of resistance was adjusted for potential confounding factors (unit and hospital), including the year of isolation as an independent variable. ESCs, extended-spectrum cephalosporins; aOR, adjusted odds ratio; CI, confidence interval; DTR, difficult-to-treat resistance.

geographical differences in AMR in neonates in high-income countries compared with low and middle-income countries. Although first-line antibiotic treatments are effective against most of the neonatal sepsis episodes in the UK, including early- and late-onset sepsis, bloodstream isolates from neonates in countries such as India, Bangladesh, or Nigeria show an impressive AMR prevalence [17,19,20].

When considering the unit of admission, the prevalence of resistance among Enterobacterales was found to be higher in the oncology–haematology unit compared to the PICU or neonatal units. A multicentre national study in the USA analysing isolates from healthcare-associated infections in children from 2011 to 2014 described a similar distribution of AMR among Enterobacterales [7]. In that study, *E. coli* and *Klebsiella* spp. isolates from the paediatric oncology ward also had a higher prevalence of AMR to most antibiotics than other units. A multicentre study including 25 countries described the epidemiology of AMR among GNB causing BSIs in haematopoietic stem-cell transplant (HSCT) recipients [21]. In this study, the resistance rates were similar in adults and children, except for a higher fluoroquinolone and β-lactam/β-lactamase inhibitors resistance rates among children with allogenic-HSCT. Patients with oncological conditions are exposed to a high number of antibiotic treatments due to the higher risk of infections. This increases the risk of colonization and infection by resistant organisms [22,23]. Of note, prophylaxis with fluoroquinolones for high-risk children with cancer has become an indication in the oncology units included in this study during recent years. This could be associated with the higher prevalence of resistance to fluoroquinolones among Enterobacterales (37.4%) compared with the neonatal units (8.4%) and PICUs (14.8%) in the present study. The prevalence of fluoroquinolone-resistant Enterobacterales isolated in the oncology–haematology unit increased from 28.0% (14/50) to 44.0% (22/50) ($P = 0.096$) from the first to the second study period. Notably, there is an increasing concern about the risk of developing AMR in patients under fluoroquinolone prophylaxis [21]. Considering the high prevalence of resistance to fluoroquinolones, antibiotic prophylaxis in these patients might not be effective and may be associated with more risks than advantages [24].

The prevalence of ESC carbapenem- and fluoroquinolone-resistant Enterobacterales increased in our population over the study period. This was mostly due to an increase in the prevalence of AMR among *Klebsiella* spp. and *Enterobacter* spp. Several studies have described an increasing trend in carbapenem- and ESC-resistant Enterobacterales and carbapenem-resistant and MDR *P. aeruginosa* in children in recent years [18,25–31]. This phenomenon, which is in agreement with our study results, highlights the relevance of surveying AMR and having well-structured antimicrobial stewardship programmes coordinated with infection, prevention, and control programmes. On the other hand, since 2005, multiple American and European populations have reported a decrease in MRSA infections, including adults and children, but this has not been observed in our study [25,32–34].

Carbapenem resistance among Enterobacterales in children from countries with a low global incidence of carbapenem-resistant Enterobacterales is relatively low [35]. We have recorded similar findings, with a prevalence of carbapenem-resistant Enterobacterales of 5.3%. However, we have found a significant increase in this resistance during the study period, with a two-fold increase from 3.5% to 7.2% ($P = 0.029$) from the first to the second study period. Among carbapenem-resistant Enterobacterales, 61.5% (24/39) were found to be mediated by carbapenemase production. Remarkably, the epidemiology of carbapenemases during the first period of our study (2013–2017) differs notably from that found in adult studies performed in Spain. Several studies have shown that OXA-48-

Table IV
Comparison of resistant isolates among periods

Micro-organism/resistance	Total	2013–2017	2017–2021	*P*-value	OR (95% CI)	aOR[a] (95% CI)
Enterobacterales	*N* = 736	*N* = 369	*N* = 367			
ESC	112/726 (15.4%)	46/368 (12.5%)	66/358 (18.4%)	0.027	1.58 (1.03–2.44)	1.66 (1.08–2.55)
ESBL	68/732 (9.3%)	30/366 (8.2%)	38/366 (10.4%)	ns	1.30 (0.76–2.22)	1.31 (0.78–2.21)
Carbapenem	39/731 (5.3%)	13/368 (3.5%)	26/363 (7.2%)	0.029	2.11 (1.02–4.54)	2.15 (1.07–4.30)
Carbapenemase	24/732 (3.3%)	11/366 (3.0%)	13/366 (3.6%)	ns	1.19 (0.48–2.97)	1.18 (0.52–2.71)
Fluoroquinolones	99/732 (13.5%)	40/368 (10.9%)	59/364 (16.2%)	0.035	1.59 (1.01–2.51)	1.66 (1.06–2.61)
Aminoglycosides	115/734 (15.7%)	57/368 (15.5%)	58/366 (15.8%)	ns	1.03 (0.68–1.56)	1.05 (0.69–1.57)
MDR	63/730 (8.6%)	23/368 (6.2%)	40/362 (11.0%)	0.021	1.86 (1.06–3.33)	1.93 (1.10–3.37)
DTR	12/730 (1.6%)	3/368 (0.8%)	9/362 (2.5%)	ns	3.10 (0.76–17.93)	3.12 (0.83–11.67)
Klebsiella spp.	*N* = 246	*N* = 120	*N* = 126			
ESC	44/240 (18.3%)	16/120 (13.3%)	28/120 (23.3%)	0.045	1.98 (0.96–4.17)	1.74 (0.84–3.59)
ESBL	32/246 (13.0%)	11/120 (9.2%)	21/126 (16.7%)	ns	1.98 (0.86–4.78)	1.71 (0.76–3.84)
Carbapenem	20/245 (8.2%)	7/120 (5.8%)	13/125 (10.4%)	ns	1.87 (0.66–5.75)	1.50 (0.55–4.09)
Carbapenemase	16/246 (6.5%)	6/120 (5.0%)	10/126 (7.9%)	ns	1.64 (0.52–5.66)	1.30 (0.44–3.88)
Fluoroquinolones	31/246 (12.6%)	8/120 (6.7%)	23/126 (18.3%)	0.006	3.13 (1.27–8.42)	2.88 (1.21–6.88)
Aminoglycosides	41/246 (16.7%)	18/120 (15.0%)	23/126 (18.3%)	ns	1.27 (0.61–2.65)	1.05 (0.51–2.14)
MDR	31/245 (12.7%)	11/120 (9.2%)	20/125 (16.0%)	ns	1.89 (0.81–4.58)	1.52 (0.65–3.55)
DTR	11/245 (4.5%)	3/120 (2.5%)	8/125 (6.4%)	ns	2.67 (0.62–15.93)	2.31 (0.59–9.09)
E. coli	*N* = 226	*N* = 110	*N* = 116			
ESC	30/223 (13.5%)	14/109 (12.8%)	16/114 (14.0%)	ns	1.11 (0.48–2.60)	1.22 (0.54–2.76)
ESBL	27/223 (12.1%)	13/108 (12.0%)	14/115 (12.2%)	ns	1.01 (0.42–2.47)	1.11 (0.48–2.61)
Amoxicillin–clavulanate	61/223 (27.4%)	26/109 (23.9%)	35/114 (30.7%)	ns	1.41 (0.75–2.68)	1.55 (0.84–2.85)
Carbapenem	3/223 (1.3%)	1/109 (0.9%)	2/114 (1.8%)	ns	1.93 (0.10–114.80)	2.06 (0.19–23.33)
Carbapenemase	0/223 (0.0%)	0/108 (0.0%)	0/115 (0.0%)	–	–	–
Fluoroquinolones	58/222 (26.1%)	26/109 (23.9%)	32/113 (28.3%)	ns	1.26 (0.66–2.41)	1.47 (0.76–2.82)
Aminoglycosides	58/224 (25.9%)	31/109 (28.4%)	27/115 (23.5%)	ns	0.77 (0.41–1.47)	0.82 (0.44–1.50)
MDR	15/222 (6.8%)	6/109 (5.5%)	9/113 (8.0%)	ns	1.49 (0.45–5.25)	1.55 (0.50–4.79)
DTR	0/222 (0.0%)	0/109 (0.0%)	0/113 (0.0%)	–	–	–
P. aeruginosa	*N* = 96	*N* = 53	*N* = 43			
ESC	25/96 (26.0%)	13/53 (24.5%)	12/43 (27.9%)	ns	1.19 (0.43–3.28)	1.23 (0.49–3.10)
Carbapenem	28/96 (29.2%)	16/53 (30.2%)	12/43 (27.9%)	ns	0.90 (0.33–2.37)	0.90 (0.36–2.20)
Carbapenemase	5/96 (5.2%)	5/53 (9.4%)	0/43 (0.0%)	0.039	–	–
Fluoroquinolones	26/95 (27.4%)	18/53 (34.0%)	8/42 (19.0%)	ns	0.46 (0.15–1.30)	0.44 (0.17–1.18)
Aminoglycosides	19/96 (19.8%)	15/53 (28.3%)	4/43 (9.3%)	0.020	0.26 (0.06–0.93)	0.24 (0.07–0.80)
MDR	19/95 (20.0%)	12/53 (22.6%)	7/42 (16.7%)	ns	0.68 (0.20–2.14)	0.69 (0.24–1.95)
DTR	7/95 (7.4%)	4/53 (7.5%)	3/42 (7.1%)	ns	0.94 (0.13–5.93)	0.95 (0.20–4.56)
S. aureus	*N* = 136	*N* = 60	*N* = 76			
Meticillin	15/136 (11.0%)	5/60 (8.3%)	10/76 (13.2%)	ns	1.67 (0.48–6.57)	2.82 (0.84–9.50)
Enterococcus spp.	*N* = 287	*N* = 177	*N* = 110			
Vancomycin	4/282 (1.4%)	4/172 (2.3%)	0/110 (0.0%)	ns	–	–

OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; DTR, difficult-to-treat resistance; ESCs, extended-spectrum cephalosporins; MDR, multidrug-resistant; PICU, paediatric intensive care unit; ns, non-significant.
The 2013–2017 period includes isolates from January 2013 to June 2017 and the 2017–2015 period from July 2017 to December 2021.
[a] Odds ratio adjusted for potential confounding factors (unit and hospital).

type carbapenemase is the most common carbapenemase in Spain among adults [36,37]. However, in our paediatric population, 81.8% of carbapenemases in Enterobacterales were VIM during the first five years. The same epidemiology with a predominance of VIM in children in Spain has been described in previous studies [38,39]. Moreover, several centres across different countries have reported distinct epidemiological patterns among paediatric populations, including variations in bacterial clones compared to those found in adult units within the same centre, as well as differences in regional epidemiology between children and adults [40,41]. Despite this unique circumstance, over the last five years of our study, the epidemiology of carbapenemases appears to be converging towards that observed in adults in Spain, with an increase in the prevalence of OXA-48 among carbapenem-producing Enterobacterales, from 0% to 46.2% ($P = 0.001$). However, transient outbreaks cannot be ruled out, which could affect the epidemiology.

Recently, a novel classifier of AMR – DTR – has been proposed, which integrates the impact of resistance on antibiotic selection and the resulting clinical outcomes [3]. It may be easier to evaluate than previous proposed AMR definitions, such as MDR, which shows a large variability since all antibiotics included in the MDR definition are not always evaluated. DTR

has shown a higher mortality risk than other AMR profiles, such as MDR or carbapenem resistance [42]. To the best of our knowledge, our study is the first performed on children including this new definition. The prevalence of DTR in Enterobacterales was 1.6%, involving mostly *Klebsiella* spp., with an increase from 0.8% in 2013—2017 to 2.5% in 2017—2021. As previously described in adults, the prevalence of DTR was higher in *P. aeruginosa* than in Enterobacterales isolates (7.4% vs 1.6%, $P \leq 0.001$) [3]. The prevalence of DTR among adults with BSIs caused by GNB has been reported to be as high as 11% (42.3% in *K. pneumoniae* isolates) in an Italian study [43].

Our study has some limitations. First, we have focused on a specific population, paediatric patients admitted to high-complexity units from three referral hospitals in Madrid. Therefore, these data may not be generalizable to other populations, such as children with community-acquired infections or those residing in countries other than Spain. However, this is an intrinsic limitation of most epidemiological studies on AMR. Second, owing to the lack of clinical data, we were unable to analyse information such as risk factors for bacterial resistance, or clinical outcomes (e.g. mortality).

As a strength, our study includes a large number of bloodstream isolates collected over an extended period, enabling us to provide updated insights into the epidemiology of AMR in children. Additionally, by focusing on high-complexity units, such as PICU, oncology—haematology, and neonatology, we were able to provide a comprehensive overview of AMR epidemiology in specific populations with unique clinical needs, as community-acquired infections generally show a different pattern of AMR.

In conclusion, our study highlights the high prevalence of BSIs caused by GNB with AMR in high-complexity paediatric units in Spain. Of particular concern is the increasing trend in the prevalence of carbapenem, ESC, and fluoroquinolone resistance among Enterobacterales. Our findings also suggest that older children and patients from non-neonatal units are at the highest risk for resistant isolates.

To effectively monitor changes in the epidemiology of AMR and to optimize antibiotic therapy, it is imperative to establish surveillance networks within paediatric units. Such networks would allow for ongoing monitoring of AMR trends and facilitate the timely implementation of appropriate infection prevention and control measures.

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Author contributions

D.A.-A., J.S.L., L.E.G., and C.E. conceptualized and designed the study. D.A.-A. performed the data management. D.A.-A. and J.S.L. drafted the manuscript. All authors enrolled participants and participated in the collection of data. All authors were involved in the preparation and review of the final manuscript. All authors participated and were involved in the critical review of the final manuscript.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2023.05.021.

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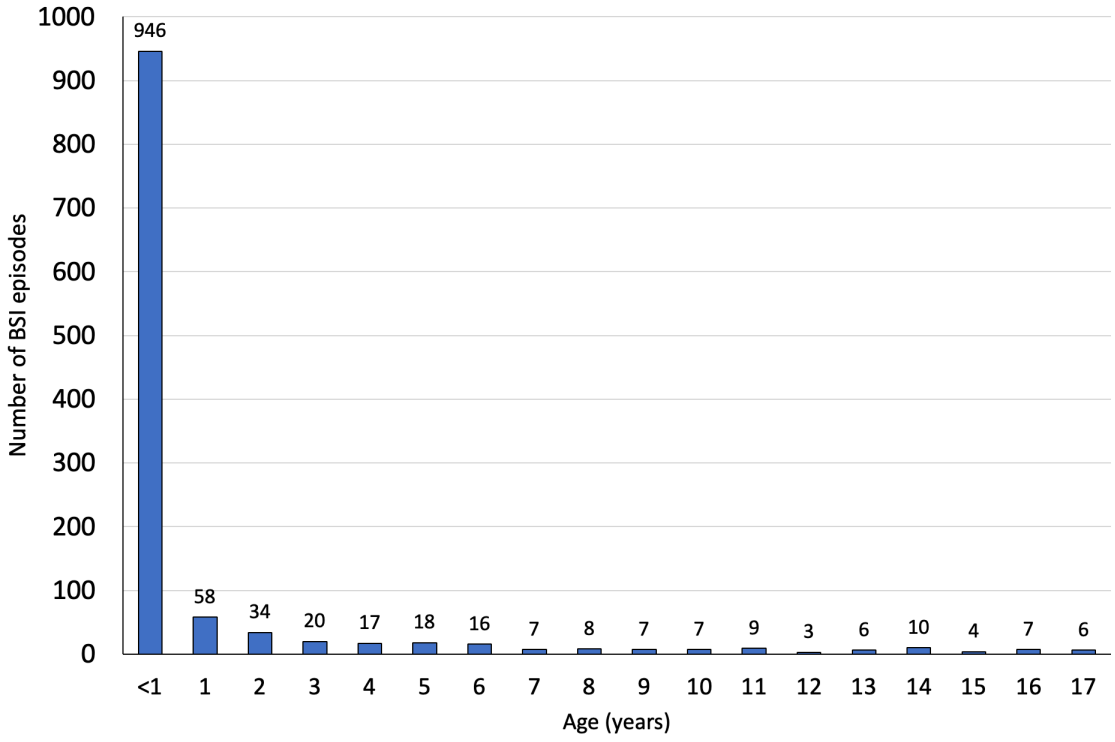
Supplementary document

Supplementary Figure S1. Distribution of bloodstream infections according to the age of patients. BSI, bloodstream infection.



Supplementary Table S1. List of isolated carbapenem-producing organisms sorted by year of isolation. KPC, Klebsiella pneumoniae carbapenemase; ND, Not determined; VIM, Verona integron–encoded metallo-β-lactamase

N.	Year	Microorganism	Carbapenemase
1	2013	*Serratia* spp.	VIM
2	2014	*Serratia* spp.	ND
3	2014	*P. aeruginosa*	VIM
4	2014	*K. pneumoniae*	VIM
5	2014	*Enterobacter* spp.	VIM
6	2014	*K. pneumoniae*	VIM
7	2014	*Serratia* spp.	VIM
8	2015	*P. aeruginosa*	VIM
9	2015	*P. aeruginosa*	VIM
10	2015	*Enterobacter* spp.	VIM
11	2015	*K. pneumoniae*	VIM
12	2015	*K. oxytoca*	VIM+KPC
13	2015	*K. pneumoniae*	VIM
14	2015	*K. pneumoniae*	ND
15	2016	*P. aeruginosa*	VIM
16	2016	*P. aeruginosa*	VIM
17	2017	*Enterobacter* spp.	VIM
18	2017	*Enterobacter* spp.	VIM
19	2017	*K. pneumoniae*	VIM
20	2018	*K. pneumoniae*	VIM
21	2018	*K. pneumoniae*	OXA-48
22	2019	*K. pneumoniae*	ND
23	2020	*K. pneumoniae*	OXA-48
24	2020	*K. pneumoniae*	OXA-48
25	2020	*K. pneumoniae*	OXA-48
26	2020	*K. pneumoniae*	OXA-48
27	2021	*K. pneumoniae*	OXA-48
28	2021	*Enterobacter* spp.	VIM
29	2021	*K. oxytoca*	VIM

Supplementary Table S2. Number and percentage of resistant bloodstream isolates from the different units. DTR, Difficult-to-treat resistance; ESCs, extended-spectrum cephalosporins; MDR, Multidrug-resistant; PICU, Paediatric Intensive Care Unit. Significant differences ($p<0.05$) are highlighted. The last columns show the p-value of the following comparisons: Neonatology vs PICU (N vs P), Neonatology vs Oncology-Haematology (N vs OH) and PICU vs Oncology-Haematology (P vs H).

	Total	Neonatology	PICU	Oncology-haematology	p-value	N vs P	N vs OH	P vs OH
***Klebsiella* spp.**	N=246	N=147	N=70	N=29				
ESCs	44/240 (18.3%)	11/144 (7.6%)	20/68 (29.4%)	13/28 (46.4%)	**<0.001**	**<0.001**	**<0.001**	0.111
ESBLs	32/246 (13.0%)	9/147 (6.1%)	13/70 (18.6%)	10/29 (34.5%)	**<0.001**	**0.005**	**<0.001**	0.088
Carbapenems	20/245 (8.2%)	2/146 (1.4%)	12/70 (17.1%)	6/29 (20.7%)	**<0.001**	**<0.001**	**<0.001**	0.677
Carbapenemase	16/246 (6.5%)	1/147 (0.7%)	11/70 (15.7%)	4/29 (13.8%)	**<0.001**	**<0.001**	**<0.001**	0.808
Fluoroquinolones	31/246 (12.6%)	9/147 (6.1%)	15/70 (21.4%)	7/29 (24.1%)	**<0.001**	**<0.001**	**0.002**	0.768
Aminoglycosides	41/246 (16.7%)	12/147 (8.2%)	17/70 (24.3%)	12/29 (41.4%)	**<0.001**	**0.001**	**<0.001**	0.089
MDR	31/245 (12.7%)	5/146 (3.4%)	15/70 (21.4%)	11/29 (37.9%)	**<0.001**	**<0.001**	**<0.001**	0.089
DTR	11/245 (4.5%)	1/146 (0.7%)	9/70 (12.9%)	1/29 (3.4%)	**<0.001**	**<0.001**	0.201	0.157
E. coli	N=226	N=155	N=24	N=47				
ESCs	30/223 (13.5%)	10/153 (6.5%)	6/23 (26.1%)	14/47 (29.8%)	**<0.001**	**0.002**	**<0.001**	0.748
ESBLs	27/223 (12.1%)	9/154 (5.8%)	4/23 (17.4%)	14/46 (30.4%)	**<0.001**	**0.048**	**<0.001**	0.245
Amoxicillin-clavulanate	61/223 (27.4%)	31/153 (20.3%)	13/23 (56.5%)	17/47 (36.2%)	**<0.001**	**<0.001**	**0.026**	0.106
Carbapenems	3/223 (1.3%)	1/153 (0.7%)	1/23 (4.3%)	1/47 (2.1%)	0.312	0.119	0.374	0.600
Carbapenemase	0/223 (0.0%)	0/154 (0.0%)	0/23 (0.0%)	0/46 (0.0%)	**-**	-	-	-
Fluoroquinolones	58/222 (26.1%)	24/152 (15.8%)	8/23 (34.8%)	26/47 (55.3%)	**<0.001**	**0.028**	**<0.001**	0.106
Aminoglycosides	58/224 (25.9%)	30/154 (19.5%)	11/23 (47.8%)	17/47 (36.2%)	**0.003**	**0.003**	**0.018**	0.350
MDR	15/222 (6.8%)	3/152 (2.0%)	4/23 (17.4%)	8/47 (17.0%)	**<0.001**	**<0.001**	**<0.001**	0.969
DTR	0/222 (0.0%)	0/152 (0.0%)	0/23 (0.0%)	0/47 (0.0%)	**-**	-	-	-

Supplementary Table S3. Comparison of resistant isolates among hospitals. Significant differences (p<0.05) are highlighted in bold. DTR, Difficult-to-treat resistance; ESBLs, Extended Spectrum Beta-Lactamases; ESCs, extended-spectrum cephalosporins; MDR, multidrug-resistant; MRSA, methicillin-resistant *S. aureus*.

	Total	**Hospital A**	**Hospital B**	**Hospital C**	**p-value**
Enterobacterales	N=736	N=233	N=301	N=202	
ESCs	112/726 (15.4%)	37/232 (15.9%)	50/295 (16.9%)	25/199 (12.6%)	0.402
ESBLs	68/732 (9.3%)	23/233 (9.9%)	36/301 (12.0%)	9/198 (4.5%)	**0.019**
Carbapenemss	39/731 (5.3%)	8/232 (3.4%)	23/300 (7.7%)	8/199 (4.0%)	0.062
Carbapenemase	24/732 (3.3%)	3/233 (1.3%)	19/301 (6.3%)	2/198 (1.0%)	**<0.001**
Fluoroquinolones	99/732 (13.5%)	38/233 (16.3%)	44/300 (14.7%)	17/199 (8.5%)	**0.047**
Aminoglycosides	115/734 (15.7%)	41/233 (17.6%)	50/301 (16.6%)	24/200 (12.0%)	0.235
MDR	71/730 (9.7%)	20/232 (8.6%)	35/300 (11.7%)	16/198 (8.1%)	0.330
DTR	12/730 (1.6%)	1/232 (0.4%)	10/300 (3.3%)	1/198 (0.5%)	**0.011**
***Klebsiella* spp.**	N=246	N=72	N=108	N=66	
ESCs	44/240 (18.3%)	11/72 (15.3%)	25/103 (24.3%)	8/65 (12.3%)	0.108
ESBLs	32/246 (13.0%)	6/72 (8.3%)	20/108 (18.5%)	6/66 (9.1%)	0.075
Carbapenems	20/245 (8.2%)	3/72 (4.2%)	14/108 (13.0%)	3/65 (4.6%)	0.051
Carbapenemase	16/246 (6.5%)	2/72 (2.8%)	12/108 (11.1%)	2/66 (3.0%)	**0.035**
Fluoroquinolones	31/246 (12.6%)	7/72 (9.7%)	20/108 (18.5%)	4/66 (6.1%)	**0.038**
Aminoglycosides	41/246 (16.7%)	7/72 (9.7%)	24/108 (22.2%)	10/66 (15.2%)	0.082
MDR	31/245 (12.7%)	6/72 (8.3%)	20/108 (18.5%)	5/65 (7.7%)	**0.049**
DTR	11/245 (4.5%)	1/72 (1.4%)	9/108 (8.3%)	1/65 (1.5%)	**0.036**
E. coli	N=226	N=101	N=75	N=50	
ESCs	30/223 (13.5%)	16/101 (15.8%)	11/74 (14.9%)	3/48 (6.2%)	0.252
ESBLs	27/223 (12.1%)	13/101 (12.9%)	12/75 (16.0%)	2/47 (4.3%)	0.146
Amoxicillin-clavulanate	61/223 (27.4%)	33/101 (32.7%)	17/74 (23.0%)	11/48 (22.9%)	0.269
Carbapenems	3/223 (1.3%)	2/101 (2.0%)	0/74 (0.0%)	1/48 (2.1%)	0.469
Carbapenemase	0/223 (0.0%)	0/101 (0.0%)	0/75 (0.0%)	0/47 (0.0%)	
Fluoroquinolones	58/222 (26.1%)	28/101 (27.7%)	20/74 (27.0%)	10/47 (21.3%)	0.692
Aminoglycosides	58/224 (25.9%)	31/101 (30.7%)	15/75 (20.0%)	12/48 (25.0%)	0.274
MDR	15/222 (6.8%)	11/101 (10.9%)	2/74 (2.7%)	2/47 (4.3%)	0.077
DTR	0/222 (0.0%)	0/101 (0.0%)	0/74 (0.0%)	0/47 (0.0%)	
P. aeruginosa	N=96	N=16	N=45	N=35	
ESCs	25/96 (26.0%)	5/16 (31.2%)	14/45 (31.1%)	6/35 (17.1%)	0.322
Carbapenems	28/96 (29.2%)	6/16 (37.5%)	14/45 (31.1%)	8/35 (22.9%)	0.523
Carbapenemase	5/96 (5.2%)	0/16 (0.0%)	5/45 (11.1%)	0/35 (0.0%)	0.050
Fluoroquinolones	26/95 (27.4%)	5/16 (31.2%)	13/44 (29.5%)	8/35 (22.9%)	0.747
Aminoglycosides	19/96 (19.8%)	2/16 (12.5%)	8/45 (17.8%)	9/35 (25.7%)	0.491
MDR	19/95 (20.0%)	3/16 (18.8%)	11/44 (25.0%)	5/35 (14.3%)	0.492
DTR	7/95 (7.4%)	1/16 (6.2%)	5/44 (11.4%)	1/35 (2.9%)	0.350
S. aureus	N=136	N=69	N=27	N=40	
Methicillin	15/136 (11.0%)	9/69 (13.0%)	5/27 (18.5%)	1/40 (2.5%)	0.091

***Enterococcus* spp.**	N=287	N=80	N=88	N=119	
Vancomycin	4/282 (1.4%)	0/80 (0.0%)	4/88 (4.5%)	0/114 (0.0%)	**0.011**

Supplementary Table S4. Comparison of resistant isolates (*Enterobacter* spp. and *Serratia* spp.) among periods. The 2013-2017 period includes isolates from January 2013 to June 2017 and the 2017-2015 period from July 2017 to December 2021. aOR, adjusted Odds ratio; OR, Odds ratio. *Odds ratio adjusted for potential confounding factors (unit and hospital). Significant differences (p<0.05) are highlighted in bold.

	Total	**2013-2017**	**2017-2021**	**p-value**	**OR (95% CI)**	**aOR (95% CI)**
***Enterobacter* spp.**	N=130	N=69	N=61			
ESC	24/129 (18.6%)	10/69 (14.5%)	14/60 (23.3%)	0.198	1.80 (0.67-4.95)	2.29 (0.88-6.00)
ESBL	8/129 (6.2%)	6/68 (8.8%)	2/61 (3.3%)	0.192	0.35 (0.03-2.07)	0.39 (0.07-2.15)
Carbapenem	9/129 (7.0%)	2/69 (2.9%)	7/60 (11.7%)	0.051	4.42 (0.79-44.88)	**5.63 (1.04-30.47)**
Carbapenemase	5/129 (3.9%)	2/68 (2.9%)	3/61 (4.9%)	0.561	1.71 (0.19-21.01)	2.04 (0.31-13.58)
Fluoroquinolones	8/130 (6.2%)	4/69 (5.8%)	4/61 (6.6%)	0.857	1.14 (0.20-6.41)	1.31 (0.30-5.80)
Aminoglycosides	14/130 (10.8%)	7/69 (10.1%)	7/61 (11.5%)	0.807	1.15 (0.32-4.10)	1.33 (0.42-4.23)
MDR	15/129 (11.6%)	5/69 (7.2%)	10/60 (16.7%)	0.096	2.56 (0.73-10.10)	2.99 (0.91-9.76)
DTR	1/129 (0.8%)	0/69 (0.0%)	1/60 (1.7%)	0.282	-	-
***Serratia* spp.**	N=124	N=66	N=58			
ESC	14/124 (11.3%)	6/66 (9.1%)	8/58 (13.8%)	0.409	1.60 (0.45-5.97)	1.67 (0.52-5.30)
ESBL	1/124 (0.8%)	0/66 (0.0%)	1/58 (1.7%)	0.284	-	-
Carbapenem	7/124 (5.6%)	3/66 (4.5%)	4/58 (6.9%)	0.571	1.56 (0.25-11.05)	1.65 (0.35-7.84)
Carbapenemase	3/124 (2.4%)	3/66 (4.5%)	0/58 (0.0%)	0.100	-	-
Fluoroquinolones	1/124 (0.8%)	1/66 (1.5%)	0/58 (0.0%)	0.347	-	-
Aminoglycosides	2/124 (1.6%)	1/66 (1.5%)	1/58 (1.7%)	0.927	1.14 (0.01-90.87)	1.17 (0.70-19.46)
MDR	10/124 (8.1%)	5/66 (7.6%)	5/58 (8.6%)	0.831	1.15 (0.25-5.29)	1.14 (0.31-4.24)
DTR	0/124 (0.0%)	0/66 (0.0%)	0/58 (0.0%)	-	-	-

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Pseudomonas aeruginosa bloodstream infections in children and adolescents: risk factors associated with carbapenem resistance and mortality

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Keywords:	Pseudomonas aeruginosa, antimicrobial resistance, antibacterial agents, children, epidemiology, bloodstream infections

Pseudomonas aeruginosa bloodstream infections in children and adolescents: risk factors associated with carbapenem resistance and mortality

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40-word summary

Of 151 patients with *Pseudomonas aeruginosa* bloodstream infections, 29.8% were carbapenem-resistant, which was associated with prior carbapenem therapy and solid organ transplantation. The 30-day mortality was 23.2% and was associated with sepsis, inappropriate empirical treatment, and optimal source control as protective factor.

ABSTRACT

Introduction

Pseudomonas aeruginosa bloodstream infections (PA-BSIs) are a serious disease and a therapeutic challenge due to increasing resistance to carbapenems. Our objectives were to describe the prevalence and risk factors associated with carbapenem resistance (CR) and mortality in children with PA-BSI.

Methods

Retrospective, multicenter study including patients aged <20 years with PA-BSI in 4 tertiary hospitals in Madrid (Spain) during 2010-2020. Risk factors for CR PA-BSIs and 30 day-mortality were evaluated in a multivariate logistic regression model.

Results

In total, 151 patients with PA-BSI were included, with a median age of 29 months (IQR: 3.5-87.1). Forty-five (29.8%) cases were CR (26.7% [12/45] producing VIM-type carbapenemase), 9.9% multidrug-resistant, and 6.6% extensively drug-resistant. The prevalence of CR remained stable throughout the study period. Patients with BSIs produced by CR-PA were more likely to receive inappropriate empiric treatment (53.3% vs 5.7%, p<0.001), and to have been previously colonized by CR-PA (8.9% vs 0%, p=0.002) than BSIs caused by carbapenem-susceptible PA. CR was associated with carbapenem treatment in the previous month (adjusted OR [aOR] 11.15) and solid organ transplantation (aOR 7.64). The 30-day mortality was 23.2%, which was associated with mechanical ventilation (aOR 4.24), sepsis (aOR 5.72), inappropriate empiric antibiotic therapy (aOR 5.86), and source control as a protective factor (aOR 0.16).

Conclusion

This study shows a concerning prevalence of CR in children with PA-BSIs, leading to high mortality. Inappropriate empiric treatment and sepsis were associated with mortality. The high prevalence of CR with an increased risk of inappropriate empiric treatment should be closely monitored.

Introduction

Pseudomonas aeruginosa bloodstream infections (PA-BSIs) are an important cause of mortality, especially in patients with comorbidities.[1] The emergence of isolates resistant to carbapenems constitutes a therapeutic challenge. [2] In 2017, the World Health Organization included carbapenem-resistant *P. aeruginosa* (CR-PA) within the critical group of bacteria for which the development of new antibiotics was urgently needed. [3]

An increase in CR-PA isolates has been described in the global population, which appears to be consistent with the data in children[4]. In a Chinese study enrolling children with PA isolates from patients admitted to pediatric intensive care units (PICUs) from 2016 to 2020, the prevalence of CR-PA was 18.4%, with a fluctuating trend that greatly increased in 2021 (24.2%).[5] In Europe, CR rates in children have also increased, oscillating between 20% and 30% in invasive specimens. [6,7] In Spain, according to a multicenter prevalence study in the adult population, the rate of CR-PA isolates was 15%.[8]

Several studies have reported prior exposure to antipseudomonal antibiotics, previous admission to the intensive care unit, sepsis at diagnosis, invasive procedures, immunosuppression, and coexistence of multiple comorbidities as the most frequent risk factors for the development of CR PA-BSI. [9-11] Delays in initiation of active antibiotic therapy, clinical severity, and lack of appropriate empiric antibiotics are well-described predictors of mortality in adults. Monotherapy treatment has also been associated with mortality but not in all studies. [9,12-14] Because of the scarce data about CR-PA BSIs in children, the recommendations for its management have been extrapolated from studies performed in the adult population. [2,15] Identification of risk factors associated with CR-PA BSIs and mortality in children may be beneficial for the proper management of these patients.

The objectives of this study were to describe the characteristics of children with PA-BSIs over the past 11 years, to investigate the risk factors associated with CR and to evaluate the mortality rate in both PA-BSI and CR-PA BSI populations.

METHODS

We performed a retrospective multicenter study in patients younger than 20 years of age with a first episode of PA-BSI evaluated in 4 tertiary hospitals in Madrid, Spain, from January 2010 to December 2020. The cases were identified from the microbiology laboratory database. The participant hospitals had a total of 750 pediatric beds and an average of 28,000 annual pediatric admissions during the study period. The included data comprised epidemiological, microbiological, and clinical variables obtained by reviewing medical charts. Exclusion criteria

were patients with polymicrobial bacteremia, incomplete information, or second and successive episodes of PA-BSI.

Microbiological identification and antibiotic susceptibility tests were performed following standardized protocols implemented in the microbiology laboratory of each center (Supplementary Table S1). Interpretation of susceptibility categories was determined according to EUCAST 2020 breakpoints.[16] In the absence of specific breakpoints for fosfomycin against PA, it was classified following the recommendations for Enterobacterales.

Definitions

CR was defined by the presence of resistance to one or more carbapenems with antipseudomonal activity (doripenem, imipenem, or meropenem), or the identification of carbapenemase production. Multidrug-resistant PA was defined as being resistant to at least 1 agent in 3 or more classes of antipseudomonal antibiotics. Extensively drug-resistant PA was defined as being resistant to at least one agent in all but two or fewer classes of antibiotics.[17]

Sepsis diagnosis was made according to the International Conference on Pediatric Sepsis definitions and catheter-related bloodstream infection according to Infectious Diseases Society of America (IDSA) guidelines.[18,19] Neutropenia was defined as an absolute neutrophil count of fewer than 500 neutrophils/µL.

Empiric therapy was defined as the antibiotics administered until the microorganism was identified and the results of the antibiotic susceptibility test were received, whereas definitive therapy refers to the antibiotic treatment after this information was available. Combined treatment was considered as two or more antibiotics administered simultaneously. Empiric antimicrobial therapy was considered appropriate if the patient received at least one active agent against the isolated bacteria (MIC within the range of susceptibility and antibiotic exposure adequate to the MIC), except for monotherapy treatment with aminoglycosides. For analysis purposes, the study was divided into 4 periods (2010-2012, 2013-2015, 2016-2018, and 2019-2020). Mortality was evaluated up to 30 days after diagnosis.

The study was approved by the Ethics Committee at each participating site.

Statistical analysis

Categorical variables were expressed as frequencies and percentages and quantitative variables as median and interquartile ranges (IQR). Continuous variables were compared using Student's T test or the Mann-Whitney test based on their distributions, and categorical variables were compared employing Pearson's χ^2 or Fisher's exact test. A univariate analysis was conducted to

identify risk factors associated with 30-day mortality in the entire population and in the subgroup of patients with BSIs caused by CR-PA.

All the variables in the entire cohort with a p-value <0.05 in the univariate analysis of 30-day mortality were included in a backward, conditional, stepwise, multivariate, logistic regression model. The general goodness of fit of the final model was analyzed with Nagelkerke's R-square. The predictive ability of the final model was examined by calculating its area under the receiver operating characteristic (AUROC) curve with a 95% confidence interval (CI). Additionally, a multivariate logistic regression was conducted to assess the association between each antibiotic group, including both empiric and definitive therapy, and 30-day mortality, adjusted by all the variables present in the final predictive model for 30-day mortality with a p-value <0.05. Statistical significance was considered as a 2-tailed p-value <0.05. Statistical analyses were performed with STATA 17, College Station, TX, USA.

RESULTS

Clinical and epidemiological characteristics

Of 177 patients diagnosed with PA-BSI, 26 were excluded, ultimately totaling 151 patients included in the final analysis (Figure S1). The annual distribution of cases was uniform, with a slightly higher number of diagnoses in the later study periods (Supplementary Figure S2). The median age at diagnosis was 29 months (IQR 3.5-87.1), with a higher number of cases diagnosed in infants ≤1 year of age (47.0% of cases, Supplementary Figure S3).

The most common source of infection was the central venous catheter (n=35, 23.2%), followed by nosocomial pneumonia (n=20, 13.2%), and unknown in 55 (36.4%) cases. Forty-one (27.1%) patients were born premature, 48 (31.5%) had a hematological disease, and 35 (23.2%) had heart disease. Baseline characteristics are included in Table 1. One hundred and six (72.1%) patients had received a carbapenem in the previous month and 39/149 patients (26.2%) had previous PA colonization/infection. In 98/151 (64.9%) patients, the infection presented with sepsis. A total of 107/151 (70.9%) patients received some antibiotic combination as empiric treatment, and 77/151 (50.1%) as definitive treatment. The empiric and definitive treatment regimens prescribed are shown in Supplementary Table S2.

Microbiology

Of the 151 episodes, 15 (9.9%) were caused by multidrug-resistant PA and 10 (6.6%) by extensively drug-resistant PA. Forty-five isolates were CR-PA (29.8%), 12 (26.7%) of which were VIM carbapenemase producers. Other carbapenemase enzymes were not detected.

The trend in the prevalence of CR throughout the study period is depicted in Supplementary Figure S4, and the CR mechanisms are shown in Supplementary Figure S5. During the first 3 periods, the prevalence of CR decreased from 41.4% to 17.5% (odds ratio [OR] 0.55; 95% CI 0.32-0.95; p=0.031), but in the last study period the prevalence increased to 30.3% (OR 2.05; 95% CI 0.68-6.18; p=0.202). The prevalence of resistance in all isolates to various antibiotics and according to carbapenem susceptibility is presented in Supplementary Figure S6. Among the CR-PA isolates, the lowest resistance prevalence was observed for colistin (4.5%) and amikacin (36.4%).

Risk factors associated with CR.

Several variables were found to be associated with CR in the univariate analysis, including carbapenem treatment in the previous month (OR 8.82) and previous 6 months, and solid organ transplantation (OR 5.05), with an unknown source of infection (OR 0.27) found to be a protective factor (Table 1). Four (8.9%) of 45 patients with CR-PA BSI had been previously identified with CR-PA colonization in the previous 6 months, whereas no cases of colonization were observed among the 106 patients with carbapenem-susceptible PA-BSI (p=0.002). The CR-PA group was more likely to receive inappropriate empiric treatment (5.7% vs 53.3%, p<0.001).

The final predictive model (Table 2) included the following variables associated with CR: carbapenem treatment in the previous month (adjusted OR [aOR] 11.15), solid organ transplantation (aOR 7.64), and unknown source of infection as a protective factor (aOR 0.33). The final model reported an AUROC curve of 0.80 (95% CI 0.71-0.88) for CR (Supplementary Figure S7). Overall, the model displayed acceptable goodness of fit, with a pseudo-R square (Nagelkerke) of 0.373.

The 30-day mortality and risk factors associated with mortality in the whole cohort.

The 30-day mortality rate was 23.2% (n=35 patients, 95% CI 16.7%-30.7%), which was attributable to PA-BSI in 25/35 (71.4%) of the episodes. Sixty percent of patients who died did so within the first 72 hours after being diagnosed with PA-BSI. Among the variables associated with 30-day mortality in the univariate analysis (Table 3) were CR-PA (OR 3.49), neutropenia (OR 2.84), PICU admission at BSI onset (OR 2.92), and sepsis (OR 8.08). The final predictive model for 30-day mortality (Table 4) included the following variables with a p-value <0.05 in the

multivariate model: mechanical ventilation (aOR 4.24), sepsis (aOR 5.72), inappropriate empiric antibiotic therapy (aOR 5.86), and source control as a protective factor (aOR 0.16). The final model reported an AUROC curve of 0.89 (95% CI 0.84-0.94) for 30-day mortality (Supplementary Figure S8). Overall, the model displayed acceptable goodness of fit, with a pseudo-R square (Nagelkerke) of 0.508.

Supplementary Table S3 includes the comparison of 30-day mortality according to the antibiotic treatment. After adjusting for variables included in the final predictive model for 30-day mortality, our analysis found that empiric carbapenem was positively associated with 30-day mortality (aOR 3.16; 95% CI 1.08-9.28; p=0.036), whereas definitive treatment including non-carbapenem β-lactams was negatively associated with 30-day mortality (aOR 0.30; 95% CI 0.11-0.89; p=0.030). In a sensitivity analysis including only those patients who survived after 72 hours of PA-BSI diagnosis (Supplementary Table S4), only definitive treatment with colistin was associated with 30-day mortality, but not in the multivariate analysis.

The 30-day mortality and risk factors associated with mortality in CR-PA BSIs

The 30-day mortality rate in CR-PA BSIs was 40% (n=18/45 patients). The univariate analysis in CR-PA BSIs (Supplementary Table S5) showed that 30-day mortality was associated with neutropenia (OR 7.95), and source control (OR 0.06) as a protective factor. BSI caused by VIM-type carbapenemase-producing PA was associated with 30-day mortality (OR 5.23). Due to the low number of cases with CR-PA BSI, a stepwise multivariate logistic regression model analysis was not performed. Definitive treatment including non-carbapenem β-lactams (aOR 0.09) or aminoglycosides (aOR 0.13), and definitive combined treatment (aOR 0.18) constituted a protective factor for 30-day mortality, after adjusting for variables included in the final predictive model for 30-day mortality in the whole population (Supplementary Table S6). In a sensitivity analysis including only those patients who survived after 72 hours of PA-BSI diagnosis (Supplementary Table S7), only definitive treatment with colistin was associated with 30-day mortality in the univariate analysis, but not in the multivariate analysis.

Discussion

In this study, including 151 patients with PA-BSIs in 4 tertiary hospitals in Spain (2010-2020), we have described the epidemiology, characteristics, mortality, and risk factors for mortality in PA-BSIs. The annual number of cases and the prevalence of CR-PA remained stable throughout the study period, being identified in 30% of isolates. The 30-day mortality was high, with almost one-fourth of patients dying. 30-day mortality was associated with sepsis, inappropriate empiric antibiotic therapy, and lack of source control.

Children from our cohort had at least one underlying disease, multiple invasive procedures, high exposure to antibiotics, and prolonged hospital admission[12,20,21]. The prevalence of CR was higher than the rates reported by the European Centre for Disease Prevention and Control (ECDC) for the general Spanish population during the study period (16.3%-22.7%)[22]. Additionally, compared with a Spanish study in adult patients with PA-BSI, our pediatric cohort had higher resistance rates to amikacin (13% vs 4%) and lower to ciprofloxacin (22% vs 38%), whereas the rate of resistance to other antibiotics was similar[8].

The only carbapenemase detected in our study was the VIM type. Consistent with previous studies, CR was most frequently attributed to mechanisms other than carbapenemase production. [8] In a study including 71 carbapenemase-producing PA isolates, 87% carried the VIM carbapenemase. [23] In our study, the isolation of VIM-producing PA was associated with higher mortality in CR-PSA BSIs, although this association had not been observed in previous studies. [24] Moreover, VIM-producing PA are often resistant to first-line antibiotics, requiring antibiotics not approved for children (e.g., cefiderocol) or complex drug combinations, given that most of the new β-lactams have poor or limited activity against this type of carbapenemase.[25,26]

As previously described, CR was associated with previous carbapenem exposure and solid organ transplantation.[21,27,28] We also found an increased risk for the development of CR PA-BSI among children colonized by CR-PA in the preceding 6 months. A similar result has been reported in a Spanish study in children, in which prior colonization was shown to be a risk factor for developing BSIs caused by CR Enterobacterales.[29] We found a significant proportion of inappropriate empiric treatment in CR PA-BSI, which has been described in previous studies. [11,12,14] Delay in active treatment has also been shown to be a poor prognostic factor in other studies.[27] Inappropriate empiric treatment was associated with higher mortality in patients included in our study. This highlights the importance of developing diagnostic tools to initiate early appropriate treatment.

The mortality in our population was high (23.2%), in accordance with previous data that reported mortality rates of 15%-52% in the pediatric population.[1,9,12,14,20,21] The role of CR-PA as a predictor of mortality is controversial, and there are studies that failed to demonstrate this association.[10,12,13,21,24,27,30] In our univariate analysis, CR-PA was associated with higher mortality, in line with the meta-analysis by Zhang et al,[30] as well as in other recent studies.[12,13] However, this result did not remain significant after adjusting for inappropriate empiric treatment or source control. This outcome could be explained by the fact that CR-PA isolates are not inherently more virulent and, therefore, their higher mortality rates may be attributable to a delay in receiving appropriate antibiotic treatment. Lodise et al [31] evaluated the impact on

mortality of specific variables among patients with serious Enterobacterales infection, demonstrating that a delay in appropriate therapy was found to be a more important predictor of outcomes compared with CR status. They concluded that it is not antibiotic resistance per se that affects clinical outcomes, but whether appropriate antibiotic therapy is promptly administered.

Neutropenia is a relevant predisposing factor for the development of BSIs by Gram-negative microorganisms.[1,11,14,32,33] In our study, neutropenia was associated with 30-day mortality. As in previous studies, other variables, such as kidney failure, parenteral nutrition, and mechanical ventilation were also associated with mortality.[14]

Empiric treatment with carbapenems was found to be associated with higher mortality in our entire population, which could be attributed to a bias toward administering carbapenems to patients with more severe illnesses despite attempts to adjust for confounding factors. More than half of the total cohort presented with sepsis, which, as in other studies, was also associated with mortality.[14,20,33] On the other hand, the use of β-lactams other than carbapenems, and the inclusion of aminoglycosides in definitive treatment for CR PA-BSIs, were protective factors against mortality.

In our study, the use of definitive combined treatment against CR PA-BSI constituted a protective factor against mortality, but the evidence is controversial. Notably, the IDSA guidelines do not recommend combination therapy for difficult-to-treat PA infections when a first-line β-lactam agent is active against the isolated microorganism.[25] However, other guidelines highlight the benefits of combined therapy in some cases, especially as empiric treatment in seriously ill patients at risk of infection by multidrug-resistant microorganisms.[15,26,34] This study was conducted primarily prior to the approval of new β-lactam-β-lactam inhibitor combinations for children, which are now considered the standard of care for infections caused by CR organisms.[25,26,35,36] At the time, various combinations were recommended as the definitive treatment for these infections.[37]

Immortal time bias is a common issue in observational studies evaluating the efficacy of interventions.[38] It is particularly relevant in the evaluation of definitive antibiotic treatments because patients who die before receiving susceptibility results do not have the opportunity to receive optimal treatment. To address this issue, we performed a sensitivity analysis that included only patients who survived for at least 72 hours after the diagnosis of PA-BSI. In this analysis, only colistin showed a significant association with a higher risk of mortality in the univariate analysis. Several studies have raised concerns regarding colistin-based regimens for

the treatment of serious Gram-negative infections due to their prominent toxicity (including both nephrotoxicity and neurotoxicity) and the lack of robust evidence on their pharmacokinetics in children.[39,40]

This study has some limitations, such as its retrospective nature. Additionally, the resistance patterns of each hospital reflect the resistance patterns of individual communities, making it difficult to extrapolate to other scenarios. We could not assess the role of new β-lactam antibiotics, such as ceftazidime-avibactam or ceftolozane-tazobactam, because they were not available during most of the study period. As a strength, this study adds new data regarding PA-BSIs in children, including a large cohort of pediatric patients, focusing on risk factors for mortality and CR, which is very relevant from a clinical point of view.

In conclusion, PA-BSIs were mostly observed in children with underlying diseases and high exposure to antibiotics. Nearly one-third of PA-BSIs were CR associated with recent consumption of carbapenems and solid organ transplantation. 23.2% of patients died within 30 days after diagnosis. Several factors were related to mortality, including inappropriate empiric treatment, neutropenia, and sepsis, with optimal source control being a protective factor. Although CR remained stable throughout the study period, the high prevalence found in our study, coupled with the increased risk of inappropriate empiric treatment for these isolates, which is associated with a poorer prognosis, highlights the need for further investigation.

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TRANSPARENCY DECLARATIONS

None to declare.

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TABLES

Table 1. Characteristics of the entire population and comparison of the characteristics of the episodes according to carbapenem resistance. Categorical variables are presented as frequencies (percentages) and quantitative variables as medians (interquartile ranges). Significant p-values (p<0.05) are highlighted in bold. CR, carbapenem-resistant; HSCT, hematopoietic stem cell transplant; PA, *Pseudomonas aeruginosa*

	Total n=151	CS-PA-BSI n=106	CR-PA-BSI n=45	P value	OR (95% CI)
Demographics					
Sex (female)	83 (55.0)	50 (47.2)	18 (40.0)	0.418	0.75 [0.34-1.60]
Age (months)	29.0 (3.5-87.1)	28.5 (3.3-81.5)	29.3 (6.5-108.1)	0.344	1.00 [0.99-1.01]
Medical background					
Prematurity	41/127 (32.3)	32 (30.2)	9 (20.0)	0.329	0.65 [0.24-1.65]
HSCT	20 (13.2)	10 (9.4)	10 (22.2)	**0.034**	2.74 [0.93-8.00]
Solid organ transplant	14 (9.2)	5 (4.7)	9 (20)	**0.003**	5.05 [1.39-20.25]
Hematological disease	48 (31.8)	30 (28.3)	18 (40)	0.158	1.69 [0.76-3.72]
Chronic lung disease	38 (25.2)	28 (26.4)	10 (22.2)	0.587	0.80 [0.31-1.92]
Heart disease	35 (23.2)	23 (21.7)	12 (26.7)	0.508	0.31 [0.53-3.13]
Neurological disease	22 (14.6)	16 (15.1)	6 (13.3)	0.779	0.87 [0.26-2.55]
Intestinal disease	26 (17.2)	18 (17)	8 (17.8)	0.906	1.06 [0.36-2.83]
Surgical disease	38 (25.2)	29 (27.4)	9 (20)	0.341	0.66 [0.25-1.63]
Carbapenem previous month	106/147 (72.1)	67/103 (65.0)	39/44 (88.6)	**0.003**	8.82 [3.49-22.62]
Carbapenem previous 6 months	45/139 (35.3)	24/100 (22.6)	27/41 (60.0)	**<0.001**	6.11 [2.58-14.63]
PICU admission previous 6 months	75/150 (50.0)	49 (46.2)	26 (57.7)	0.212	1.56 [0.73-3.37]
Microbiology					
PA colonization/infection previous 6 months	39/149 (26.2)	24 (22.6)	15 (33.3)	0.155	1.75 [0.74-4.02]
CR-PA colonization previous 6 months	4 (2.6)	0 (0)	4 (8.9)	**0.002**	-
Characteristics at diagnosis					
Renal failure	25 (16.6)	14 (13.2)	11 (24.4)	0.089	2.13 [0.79-5.59]
Neutropenia	33 (21.9)	24 (22.6)	9 (20)	0.714	0.85 [0.32-2.14]
Sepsis	98 (64.9)	66 (62.3)	32 (71.1)	0.817	0.89 [0.28-2.91]
PICU admission	91 (60.2)	45 (42.4)	24 (53.3)	0.220	1.55 [0.72-3.32]
Central venous catheter	132 (88.0)	89 (83.9)	43 (95.5)	0.062	3.87 [0.84-35.91]
Parenteral nutrition	61 (40.4)	37 (34.9)	24 (53.3)	**0.035**	2.13 [0.99-4.60]
Mechanical ventilation	52 (34.4)	32 (30.2)	20 (44.4)	0.092	1.85 [0.84-4.03]
Source of infection					
Unknown	55 (36.4)	47 (44.3)	8 (17.8)	**0.002**	0.27 [0.10-0.67]
Central venous catheter	35 (23.2)	22 (20.8)	13 (28.9)	0.279	1.55 [0.64-3.67]
Nosocomial pneumonia	20 (13.2)	14 (13.2)	6 (13.3)	0.983	1.01 [0.30-3.06]
Skin and soft tissue infection	12 (7.9)	9 (8.5)	3 (6.7)	0.705	0.77 [0.13-3.30]
Biliary/hepatic	5 (3.3)	1 (0.9)	4 (8.9)	0.013	10.24 [0.96-509.06]
Intestinal	8 (5.3)	4 (3.8)	4 (8.9)	0.199	2.49 [0.44-13.94]
Urinary	8 (5.3)	7 (6.6)	1 (2.2)	0.272	0.32 [0.01-2.64]
Multiple sources	5 (3.3)	4 (3.8)	1 (2.2)	0.626	0.58 [0.01-6.10]

Table 2. Variables included in the final predictive model for carbapenem resistance. aOR, adjusted odds ratio

Variable	aOR (95% CI)	p-value
Solid organ transplantation	7.64 (1.91-30.59)	0.004
Carbapenem administration the previous month	11.15 (4.41-28.19)	<0.001
Unknown source of infection	0.33 (0.12-0.87)	0.026

Table 3. Comparison of the episodes according to 30-day mortality in whole cohort. Categorical variables are presented as frequencies (percentages) and quantitative variables as medians (interquartile ranges). Significant p-values (p<0.05) are highlighted in bold. BSI, bloodstream infection; CR, carbapenem resistant; HSCT, hematopoietic stem cell transplant; PA, *Pseudomonas aeruginosa*

	Survived n=116	**Died** n=35	**P value**	**OR** (95% CI)
Demographics				
Sex (female)	53 (45.7)	15 (42.9)	0.768	0.89 [0.42-1.91]
Age (months)	29.9 (6.5-84.7)	21.2 (1.1-101.9)	0.289	0.99 [0.42-1.01]
Medical background				
Prematurity	33 (28.4)	8 (22.8)	0.634	0.80 [0.27-2.15]
HSCT	12 (10.3)	8 (22.8)	0.056	2.57 [0.82-7.61]
Solid organ transplant	8 (6.9)	6 (17.1)	0.067	2.79 [0.73-9.96]
Solid organ tumor	5 (4.3)	1 (2.8)	0.700	0.65 [0.01-6.13]
Hematological disease	33 (28.4)	15 (42.9)	0.109	1.89 [0.79-4.41]
Chronic lung disease	25 (21.5)	13 (37.1)	0.062	2.15 [0.86-5.20]
Heart disease	25 (21.5)	10 (28.6)	0.388	1.46 [0.55-3.66]
Neurological disease	16 (13.8)	6 (17.1)	0.622	1.29 [0.38-3.88]
Intestinal disease	21 (18.1)	5 (14.3)	0.600	0.75 [0.20-2.30]
Surgical disease	32 (27.6)	6 (17.1)	0.212	0.54 [0.17-1.51]
Carbapenem previous 6 months	33 (28.4)	18 (51.4)	**0.007**	2.96 [1.22-7.22]
PICU admission previous 6 months	56 (48.2)	19 (54.2)	0.562	1.25 [0.55-2.88]
Surgery	39 (33.6)	7 (20.0)	0.125	0.49 [0.17-1.30]
Microbiology				
Carbapenem resistance	27 (23.2)	18 (51.4)	**0.001**	3.49 [1.46-8.28]
VIM type carbapenemase	6 (5.2)	6 (17.1)	0.062	3.79 [1.14-12.63]
Previous CR-PA colonization/infection	27 (23.2)	12 (34.2)	0.169	1.78 [0.70-4.33]
Characteristics at diagnosis				
Renal failure	14 (12.1)	11 (31.4)	**0.007**	3.34 [1.20-9.01]
Neutropenia	20 (17.2)	13 (37.1)	**0.013**	2.84 [1.11-7.05]
Sepsis	66 (56.9)	32 (91.4)	**<0.001**	8.08[2.30- 43.09]
PICU admission	64 (55.1)	27 (77.1)	**0.020**	2.74 [1.09-7.55]
Central venous catheter	100 (86.2)	32 (91.4)	0.476	1.69 [0.41-9.14]
Parenteral nutrition	40 (34.4)	21 (60.0)	**0.007**	2.85 [1.22-6.72]
Mechanical ventilation	33 (28.4)	19 (54.3)	**0.005**	2.99 [1.27-7.00]
Source of infection				
Unknown	41 (35.3)	14 (40.0)	0.616	1.22 [0.51-2.82]
Central venous catheter	29 (25.0)	6 (17.1)	0.334	0.62 [0.19-1.74]
Nosocomial pneumonia	14 (12.1)	6 (17.1)	0.438	1.51 [0.43-4.64]
Skin and soft tissue	8 (6.9)	4 (11.4)	0.385	1.74 [0.36-7.01]
Biliary/hepatic	3 (2.5)	2 (5.7)	0.365	2.28 [0.18-20.68]
Intestinal	2 (5.7)	6 (5.1)	0.900	1.11 [0.10-6.60]
Urinary	8 (6.9)	0 (0.0)	0.110	0.00 [0.00-1.53]
Multiple sources	4 (3.4)	1 (2.9)	0.864	1.0.82 [0.02-8.70]
Treatment				
Inappropriate empiric treatment	16 (13.8)	14 (40.0)	**<0.001**	4.17 [1.60-10.65]
Source control	72 (62.1)	5 (14.3)	**<0.001**	0.10 [0.03-0.30]
Delay of active antibiotic treatment	12/114 (10.5)	11/29 (37.9)	**<0.001**	5.19. [1.76-14.99]

Table 4. Variables included in the final predictive model for 30-day mortality. aOR, adjusted odds ratio

Variable	aOR (95% CI)	P value
Mechanical ventilation	4.24 (1.45-12.34)	0.008
Sepsis	5.72 (1-42-22.97)	0.014
Inappropriate empiric antibiotic therapy	5.86 (1.89-18.16)	0.002
Source control	0.16 (0.53-50.00)	0.002
Neutropenia	2.64 (0.84-8.30)	0.096

Supplementary appendix

Table S1. Microbiological identification and antibiotic susceptibility tests performed in each centre.

Hospital Gregorio Marañon	Blood cultures were processed using the Bactec FX® automated system (Becton Dickinson, Franklin Lakes, NJ, USA) and incubated for 5 days. Gram stain was performed from all positive bottles. In addition, all positive bottles were cultured onto Columbia blood agar (incubation in air), chocolate agar (incubation in 5% CO2), and Brucella agar (incubation in anaerobic atmosphere) at 35-37 °C for 48 h. Microorganism identification was performed by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) using the Bruker Biotyper System (Bruker Daltonik GmbH, Bremen, Germany). Antimicrobial susceptibility testing was performed by the automated broth microdilution method (MicroScan, Beckman Coulter, CA, USA). Interpretation of susceptible, susceptible with increased exposure, and resistant clinical categories were determined following the EUCAST recommendations in 2021. For the purpose of analysis, isolates susceptible and susceptible with increased exposure were considered susceptible. Extended-spectrum beta-lactamases were detected either by the double-disc diffusion method or by the microdilution method with MicroScan panels, using cefotaxime and ceftazidime in combination with clavulanate. Carbapenemase production (KPC, VIM, NDM, OXA-48, and IMP) was detected by employing either immunochromatographic methods (Coris Bioconcept®) or a commercial polymerase chain reaction (Xpert® Carba-R, Cepheid).
Hospital La Paz	Blood cultures were processed with the Bactec FX® automated system (Becton Dickinson, Franklin Lakes, NJ, USA) and incubated for 5 days. Gram stain was performed from all positive bottles. In addition, all positive bottles were cultured onto Columbia blood agar (incubation in air), chocolate agar (incubation in 5% CO2), and Brucella agar (incubation in anaerobic atmosphere) at 35-37 °C for 48 h. Microorganism identification was performed by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) using the Bruker Biotyper System (Bruker Daltonik GmbH, Bremen, Germany). Antimicrobial susceptibility testing was performed by the automated broth microdilution method (MicroScan, Beckman Coulter, CA, USA). Interpretation of susceptible, susceptible with increased exposure, and resistant clinical categories were determined following the EUCAST recommendations in 2021. For the purpose of analysis, isolates susceptible and susceptible with increased exposure were considered susceptible. Extended-spectrum beta-lactamases were detected either by the double-disc diffusion method or by the microdilution method with MicroScan panels, using cefotaxime and ceftazidime in combination with clavulanate. Carbapenemase production (KPC, VIM, NDM, OXA-48, and IMP) was detected by employing either immunochromatographic methods (Coris Bioconcept®) or by a commercial polymerase chain reaction (Xpert® Carba-R, Cepheid).

Hospital Niño Jesús	Blood cultures were processed using the Bactec FX® automated system (Becton Dickinson, Franklin Lakes, NJ, USA) and incubated for 5 days. Gram stain was performed from all positive bottles. In addition, all positive bottles were cultured onto Columbia blood agar (incubation in air), chocolate agar (incubation in 5% CO2), and Brucella agar (incubation in anaerobic atmosphere) at 35-37 °C for 48 h. Microorganism identification and antimicrobial susceptibility were performed by the automated broth microdilution method (Vitek 2-compact, bioMérieux España S.A.). Interpretation of susceptible, susceptible with increased exposure, and resistant clinical categories were determined following the EUCAST recommendations in 2022. For the purpose of analysis, isolates susceptible and susceptible with increased exposure were considered susceptible. Extended-spectrum beta-lactamases were detected either by the double-disc diffusion method using cefotaxime and ceftazidime in combination with clavulanate or by the microdilution (Vitek 2-compact, bioMérieux España S.A.). Carbapenemase production (KPC, VIM, NDM, OXA-48, and IMP) was detected by employing molecular methods using a commercial polymerase chain reaction (Xpert® Carba-R, Cepheid).
Hospital 12 de Octubre	Blood cultures were processed in the semi-automated blood culture system BACT/ALERT VIRTUO, (bioMérieux, Marcy-l'Etoile, France) and incubated for 5 days. Gram stain was performed from all positive bottles. In addition, all positive bottles were cultured onto Columbia blood agar (incubation in air), chocolate agar (incubation in 5% CO2), and Brucella agar (incubation in anaerobic atmosphere) at 35-37 °C for 48 h. Microorganism identification was performed by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) using the Bruker Biotyper System (Bruker Daltonik GmbH, Bremen, Germany). Antimicrobial susceptibility testing was performed by the automated broth microdilution method (MicroScan, Beckman Coulter, CA, USA). Interpretation of susceptible, susceptible with increased exposure, and resistant clinical categories were determined following the EUCAST recommendations in 2021. For the purpose of analysis, isolates susceptible and susceptible with increased exposure were considered susceptible. Extended-spectrum beta-lactamases were detected by the microdilution method with MicroScan panels, using cefotaxime and ceftazidime in combination with clavulanate. Carbapenemase production (KPC, VIM, NDM, OXA-48, and IMP) was detected by employing either immunochromatographic methods (Coris Bioconcept®) or by a commercial polymerase chain reaction (Xpert® Carba-R, Cepheid).

Figure S1. Study flow diagram. Carbapenem-resistant *Pseudomonas aeruginosa (*CR-PA).

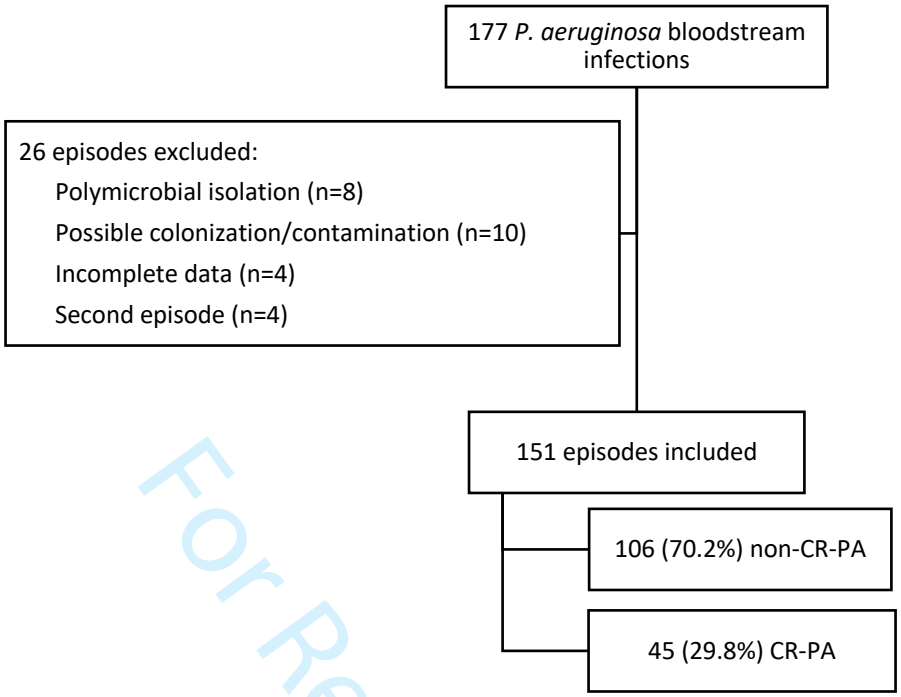

Figure S2. Episodes of *Pseudomonas aeruginosa* bloodstream infections per year

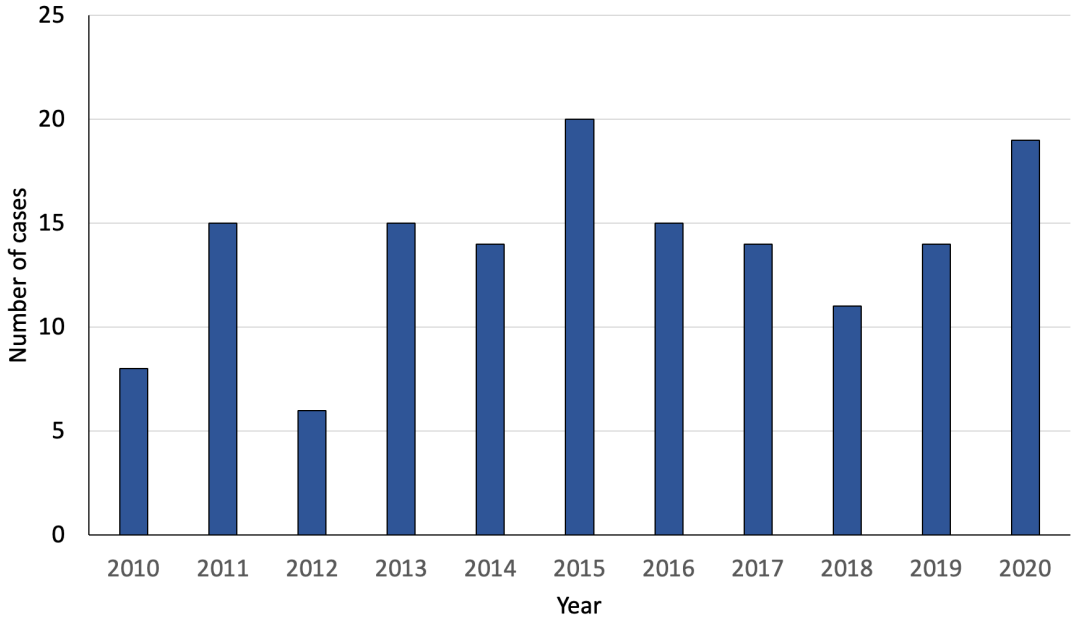

Figure S3. Episodes of *Pseudomonas aeruginosa* bloodstream infections by age

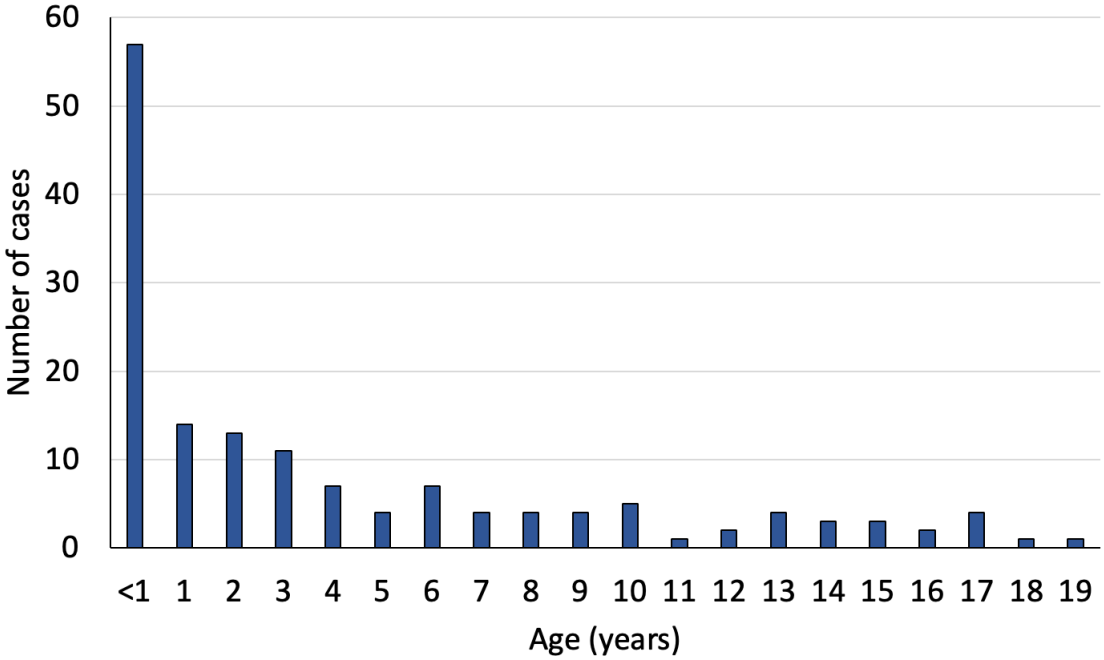

Table S2. Empiric and definitive treatment regimens prescribed in PA-BSIs, sorted by frequency.

Empiric treatment	**Frequency**	**Percentage**
Non-carbapenem β-lactam	26	17.3
Carbapenem + aminoglycoside	21	14.0
Carbapenem + other	16	10.6
Carbapenem + aminoglycoside + other	15	10.0
Non-carbapenem β-lactam + aminoglycoside	11	7.3
Non-carbapenem β-lactam + other	9	6.0
Carbapenem	8	5.3
Non-carbapenem β-lactam + aminoglycoside	7	4.6
Aminoglycoside	5	3.3
Non-carbapenem β-lactam + carbapenem	3	2.0
Non-carbapenem β-lactam + carbapenem + aminoglycoside	3	2.0
Non-carbapenem β-lactam + carbapenem + other	3	2.0
Quinolone	3	2.0
Carbapenem + aminoglycoside + quinolone	2	1.3
Carbapenem + aminoglycoside + quinolone + other	2	1.3
Carbapenem + non-carbapenem β-lactam + aminoglycoside	2	1.3
Carbapenem + quinolone + other	2	1.3
Aminoglycoside + other	1	0.7
Aminoglycoside + quinolone + other	1	0.7
Carbapenem + aminoglycoside + aztreonam	1	0.7
Carbapenem + aminoglycoside + colistin	1	0.7
Carbapenem + aminoglycoside + colistin + other	1	0.7
Carbapenem + colistin + other	1	0.7
Carbapenem + non-carbapenem β-lactam + colistin	1	0.7
Carbapenem + quinolone	1	0.7
Non-carbapenem β-lactam + aminoglycoside	1	0.7
Non-carbapenem β-lactam + quinolone	1	0.7
Non-carbapenem β-lactam + quinolone + other	1	0.7
Other	1	0.7
Definitive treatment	**Frequency**	**Percentage**
Non-carbapenem β-lactam	32	24.1
Non-carbapenem β-lactam + aminoglycoside	15	11.3
Carbapenem	13	10
Carbapenem + aminoglycoside	11	8.3
Quinolone	7	5.3
Carbapenem + aminoglycoside + other	6	4.5
Non-carbapenem β-lactam + quinolone	6	4.5
Non-carbapenem β-lactam + aminoglycoside	4	3.0
Aminoglycoside + colistin	3	2.3
Carbapenem + non-carbapenem β-lactam + aminoglycoside	3	2.3

Non-carbapenem β-lactam + aminoglycoside	3	2.3
Aminoglycoside	2	1.5
Carbapenem + aminoglycoside + quinolone + other	2	1.5
Carbapenem + colistin + aztreonam + other	2	1.5
Carbapenem + non-carbapenem β-lactam + other	2	1.5
Carbapenem + other	2	1.5
Carbapenem + quinolone	2	1.5
Non-carbapenem β-lactam + colistin	2	1.5
Aminoglycoside + aztreonam	1	0.7
Aminoglycoside + other	1	0.7
Aminoglycoside + quinolone	1	0.7
Carbapenem + aminoglycoside + quinolone	1	0.7
Carbapenem + colistin	1	0.7
Carbapenem + colistin + fosfomycin + other	1	0.7
Carbapenem + non-carbapenem β-lactam + aminoglycoside	1	0.7
Carbapenem + quinolone + colistin + other	1	0.7
Colistin	1	0.7
Colistin + aztreonam	1	0.7
Colistin + aztreonam + fosfomycin	1	0.7
Non-carbapenem β-lactam + aminoglycoside	1	0.7
Non-carbapenem β-lactam + other	1	0.7
Non-carbapenem β-lactam + quinolone + colistin	1	0.7
Quinolone + aztreonam + other	1	0.7
Other	1	0.7

Figure S4. Changes in carbapenem resistance within the study period

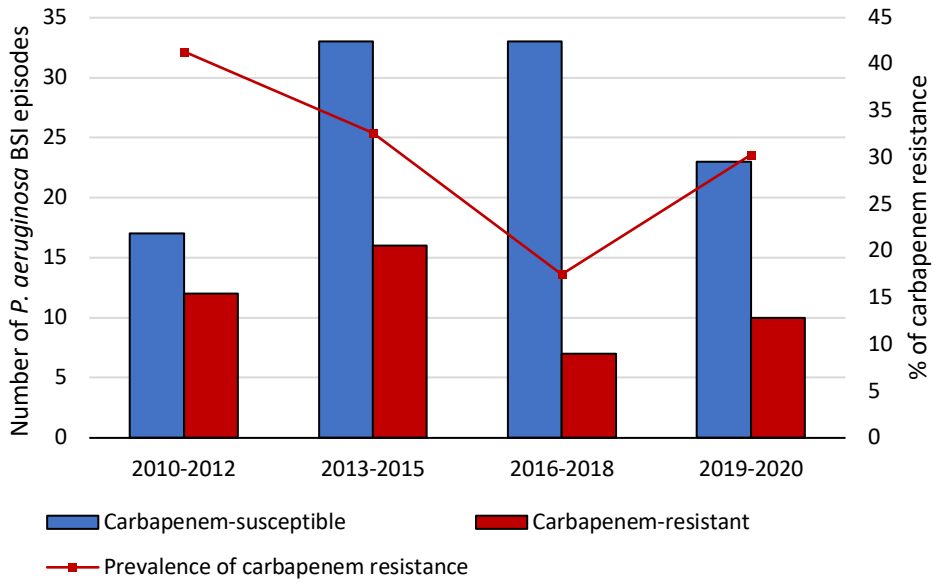

Figure S5. Carbapenem resistance rate and resistance mechanisms within the study periods

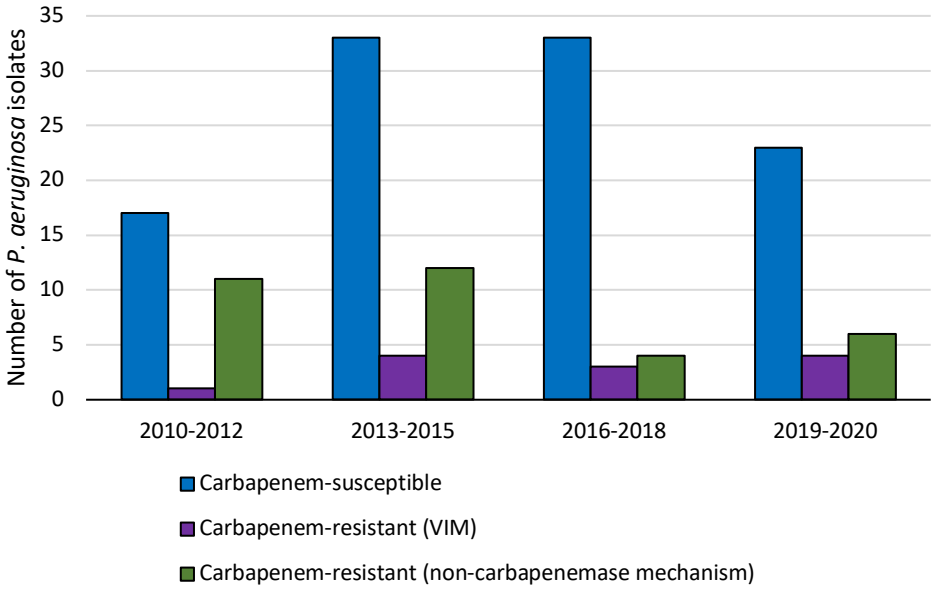

Figure S6. Prevalence of resistance of *P. aeruginosa* isolates to various antibiotics in all isolates and according to carbapenem susceptibility. The number of isolates evaluated for each antibiotic is within parentheses**.** The overall prevalence of CR was 29.6%.

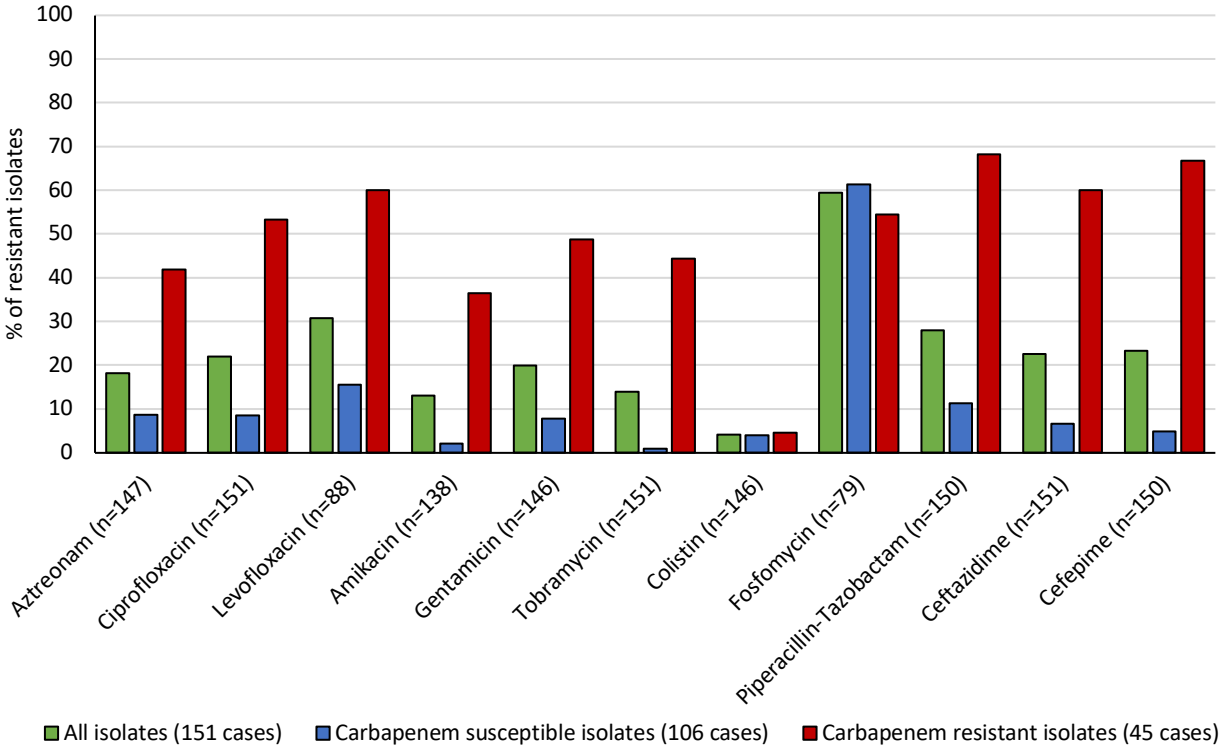

Figure S7. Receiver operating characteristic curve of the final predictive model for carbapenem resistance

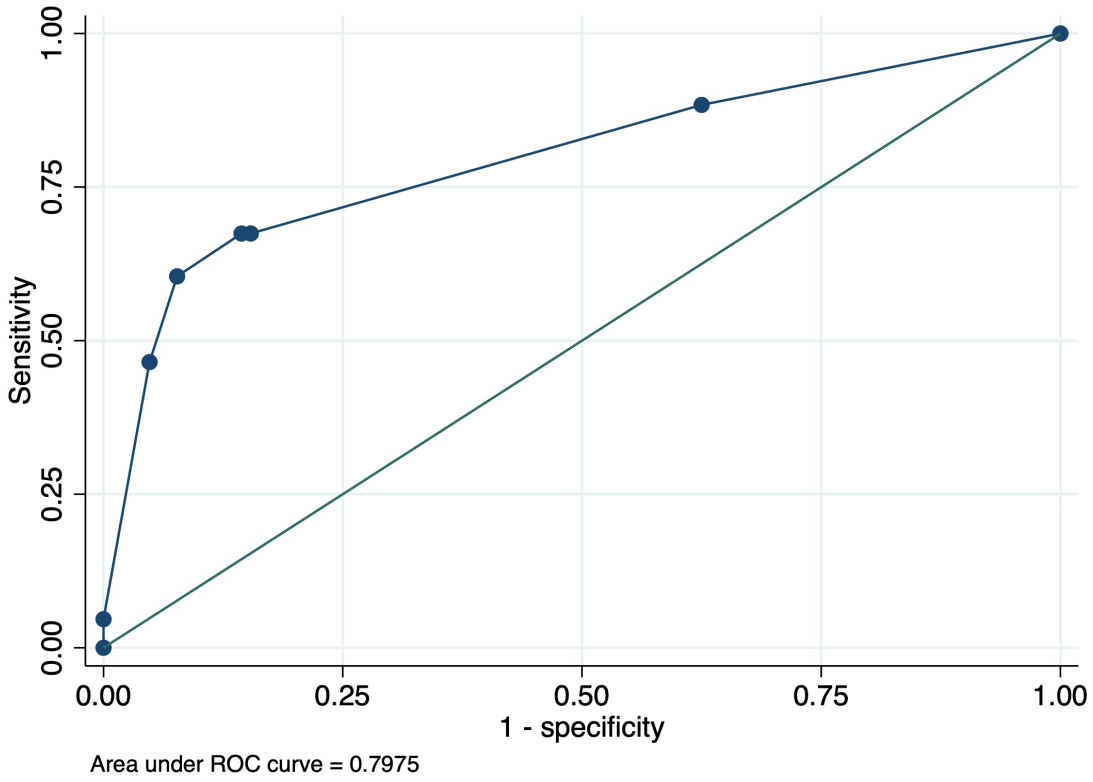

Figure S8. Receiver operating characteristic curve of the final predictive model for 30-day mortality.

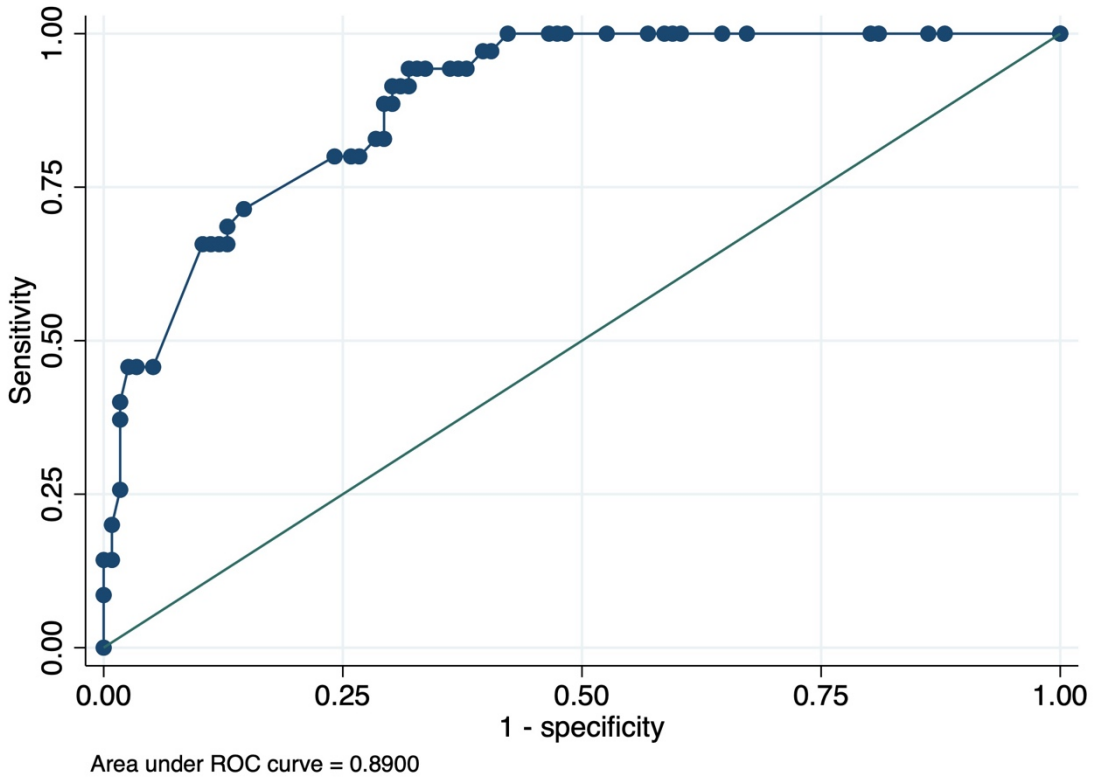

Table S3. Comparison of 30-day mortality according to the antibiotic treatment in the entire population. The adjusted odds ratio was calculated with a multivariate logistic regression including all variables present in the final predictive model for 30-day mortality with a p-value <0.05. aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio

	Total N=151	**Survived** N=116	**Died** N=35	**p-value**	**OR (95% CI)**	**aOR (95% CI)**
Empiric treatment						
Combined treatment	107 (70.9%)	75 (64.7%)	32 (91.4%)	**0.002**	**5.83 (1.68-20.21)**	3.34 (0.84-13.36)
Non-carbapenem β-lactam	68 (45.0%)	57 (49.1%)	11 (31.4%)	0.065	0.47 (0.19-1.12)	0.59 (0.22-1.58)
Carbapenem	83 (55.0%)	55 (47.4%)	28 (80.0%)	**<0.001**	**4.44 (1.70-12.90)**	**3.16 (1.08-9.28)**
Aminoglycosides	74 (49.0%)	55 (47.4%)	19 (54.3%)	0.476	1.32 (0.58-3.03)	1.42(0.55-3.71)
Fluoroquinolone	14 (9.3%)	8 (6.9%)	6 (17.1%)	0.067	2.79 (0.73-9.96)	4.06 (0.97-16.93)
Colistin	5 (3.3%)	3 (2.6%)	2 (5.7%)	0.365	2.28 (0.18-20.68)	1.00 (0.08-11.46)
Aztreonam	1 (0.7%)	0 (0.0%)	1 (2.9%)	0.068	-	-
Fosfomycin	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	-	-
Other antibiotics	64 (42.4%)	42 (36.2%)	22 (62.9%)	**0.005**	**2.98 (1.28-7.11)**	1.92 (0.72-5.06)
Definitive treatment						
Combined treatment	77 (51.0%)	62 (53.5%)	15 (42.9%)	0.272	0.65 (0.30-1.40)	0.53 (0.20-1.41)
Non-carbapenem β-lactam	71 (47.0%)	64 (55.2%)	7 (20.0%)	**<0.001**	**0.20 (0.07-0.53)**	**0.30 (0.11-0.89)**
Carbapenem	48 (31.8%)	40 (34.5%)	8 (22.9%)	0.195	0.56 (0.20-1.43)	0.44 (0.14-1.33)
Aminoglycosides	55 (36.4%)	45 (38.8%)	10 (28.6%)	0.271	0.63 (0.25-1.52)	0.57 (0.20-1.57)
Fluoroquinolone	25 (16.6%)	21 (18.1%)	4 (11.4%)	0.352	0.58 (0.14-1.93)	0.61 (0.14-2.65)
Colistin	16 (10.6%)	9 (7.8%)	7 (20.0%)	**0.039**	**2.97 (0.85-9.79)**	1.53 (0.32-7.15)
Aztreonam	6 (4.0%)	4 (3.4%)	2 (5.7%)	0.547	1.70 (0.15-12.40)	0.74 (0.07-7.15)
Fosfomycin	2 (1.3%)	1 (0.9%)	1 (2.9%)	0.366	3.38 (0.04-267.64)	0.23 (0.01-5.06)
Other antibiotics	25 (16.6%)	19 (16.4%)	6 (17.1%)	0.915	1.06 (0.32-3.09)	0.71 (0.21-2.43)

Table S4. Comparison of 30-day mortality according to definitive antibiotic treatment in the whole cohort of patients who survived after 72 hours of *P. aeruginosa* bloodstream infection diagnosis. The adjusted odds ratio was calculated with a multivariate logistic regression including all variables present in the final predictive model for 30-day mortality with a p-value <0.05. aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio

	Total N=130	**Survived** N=116	**Died** N=14	**p-value**	**OR (95% CI)**	**aOR (95% CI)**
Definitive treatment						
Combined treatment	71 (54.6%)	62 (53.4%)	9 (64.2%)	0.442	1.57 (0.44-6.31)	1.47 (0.37-5.88)
Non-carbapenem β-lactam	71 (54.6%)	64 (55.7%)	7 (50.0%)	0.713	0.81 (0.23-2.91)	1.06 (0.31-3.70)
Carbapenem	44 (33.8%)	40 (34.4%)	4 (28.5%)	0.659	0.76 (0.16-2.86)	0.74 (0.19-2.95)
Aminoglycosides	51 (39.2%)	45 (38.7%)	6 (42.8%)	0.769	1.18 (0.32-4.18)	1.18 (0.33-4.26)
Fluoroquinolone	23 (17.6%)	21 (18.1%)	2 (14.2%)	0.724	0.75 (0.08-3.80)	0.73 (0.12-4.30)
Colistin	14 (10.7%)	9 (7.7%)	5 (35.7%)	**0.001**	**6.60 (1.40-27.75)**	4.74 (0.86-26.16)
Aztreonam	5 (3.8%)	4 (3.4%)	1 (7.1%)	0.497	2.15 (0.04-23.89)	1.37 (0.11-17.04)
Fosfomycin	1 (0.7%)	1 (0.8%)	0 (0.0%)	0.727	-	-
Other antibiotics	21 (16.1%)	19 (16.4%)	2 (14.2%)	0.841	0.85 [0.09-4.33]	0.81 (0.15-4.44)

Table S5. Comparison of the episodes according to 30-day mortality in CR-PA BSIs. Categorical variables are presented as frequencies (percentages) and quantitative variables as medians (interquartile ranges). Significant p-values (p<0.05) are highlighted in bold. HSCT, hematopoietic stem cell transplant; PA, *Pseudomonas aeruginosa*; CR, carbapenem resistant; BSI, blood stream infection

	Survived n=27	**Died** n=18	**P value**	**OR** (95% CI)
Demographics				
Sex (female)	9 (33.3)	9 (50.0)	0.264	2.00 [0.59-6.79]
Age (months)	16.0 (3.6-102.0)	48.3 (12.1-164.0)	0.228	1.00 [0.99-1.01]
Medical background				
Prematurity	8 (29.6)	1 (5.5)	0.089	0.17 [0.00-1.67]
HSCT	4 (14.8)	6 (33.3)	0.143	2.88 [0.54-16.35]
Solid organ transplant	4 (14.8)	5 (27.7)	0.287	2.21 [0.39-13.06]
Solid organ tumor	1(3.7)	1 (5.5)	0.768	1.53[0.02-124.60]
Hematological disease	8 (29.6)	10 (55.5)	0.082	2.97 [0.73-12.33]
Chronic lung disease	5 (18.5)	5 (27.7)	0.464	1.69 [0.32-8.86]
Heart disease	8 (29.6)	4 (22.2)	0.582	0.68 [0.12-3.21]
Neurological disease	4 (14.8)	2 (11.1)	0.720	0.72 [0.06-5.78]
Intestinal disease	5 (18.5)	3 (16.6)	0.874	0.88 [0.12-5.36]
Surgical disease	5 (18.5)	4 (22.2)	0.761	1.26 [0.21-6.98]
Carbapenem previous 6 months	14 (51.8)	13 (72.2)	0.096	3.40 [0.66-22.62]
PICU admission previous 6 months	18 (66.6)	8 (44.4)	0.139	0.40 [0.10-1.61]
Microbiology				
VIM type carbapenemase	6 (22.2)	6 (33.3)	**0.009**	5.23 [1.50-18.17]
CR-PA colonization/infection previous 6 months	7 (25.9)	8 (44.4)	0.228	2.17 [0.51-9.32]
CR-PA colonization previous 6 months	0 (0.0)	4 (22.2)	0.010	-
Characteristics at diagnosis				
Renal failure	5 (18.5)	6 (33.3)	0.257	2.20 [0.44-11.07]
Neutropenia	20 (17.2)	13 (37.1)	**0.010**	7.95 [1.19-85.98]
Sepsis	17 (62.9)	15 (83.3)	0.140	2.94 [0.59- 19.31]
PICU admission	12 (44.4)	12 (66.6)	0.143	2.50 [0.62-10.53]
Central venous catheter	26 (96.3)	17 (94.4)	0.768	0.65 [0.01-54.31]
Parenteral nutrition	13 (48.1)	11 (61.1)	0.393	1.69 [0.43-6.82]
Mechanical ventilation	13 (48.1)	7 (38.9)	0.540	0.69 [0.17-2.68]
Source of infection				
Unknown	5 (18.5)	3 (16.6)	0.874	0.88 [0.12-5.36]
Central venous catheter	8 (29.6)	5 (27.7)	0.893	0.91 [0.19-4.07]
Nosocomial pneumonia	4 (124.8)	2 (11.1)	0.720	0.72 [0.06-5.78]
Skin and soft tissue	1 (63.7)	2 (11.1)	0.329	3.25 [0.15-198.94]
Biliary/hepatic	2 (7.41)	2 (11.1)	0.669	1.56 [0.10-23.35]
Intestinal	3 (11.1)	1 (5.5)	0.521	0.47 [0.01-6.55]
Urinary	1 (3.7)	0 (0.0)	0.409	-
Several sources	1 (3.7)	0 (0.0)	0.409	-
Treatment				
Inappropriate empiric treatment	12 (44.4)	12 (66.6)	0.143	2.50 [0.62-10.53]
Source control	16 (59.2)	4 (22.2)	**<0.001**	0.06 [0.01-0.38]
Delay of active antibiotic treatment	9 (33.3)	10 (55.5)	0.118	2.70 [0.65-11.47]
Outcomes				
PICU admission due to PA-BSI	20 (74.0)	13 (72.2)	0.891	0.91 [0.20-4.48]

Table S6. Comparison of 30-day mortality according to the antibiotic treatment in bloodstream infections by carbapenem-resistant *P. aeruginosa*. The adjusted odds ratio was calculated with a multivariate logistic regression including all variables present in the final predictive model for 30-day mortality with a p-value <0.05. aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio

	Total N=45	**Survived** N=27	**Died** N=18	**p-value**	**OR (95% CI)**	**aOR (95% CI)**
Empiric treatment						
Combined treatment	39 (86.7%)	23 (85.2%)	16 (88.9%)	0.720	1.39 (0.23-8.53)	0.96 (0.13-7.19)
Non-carbapenem β-lactam	15 (33.3%)	10 (37.0%)	5 (27.8%)	0.519	0.65 (0.14-2.74)	0.81 (0.18-3.62)
Carbapenem	33 (73.3%)	17 (63.0%)	16 (88.9%)	0.054	4.71 (0.79-49.13)	3.89 (0.58-26.03)
Aminoglycosides	26 (57.8%)	16 (59.3%)	10 (55.6%)	0.805	0.86 (0.22-3.41)	0.56 (0.12-2.58)
Fluoroquinolone	7 (15.6%)	3 (11.1%)	4 (22.2%)	0.314	2.29 (0.33-17.61)	3.32 (0.44-24.82)
Colistin	5 (11.1%)	3 (11.1%)	2 (11.1%)	1.000	1.00 (0.08-9.79)	0.85 (0.08-8.36)
Aztreonam	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	-	-
Fosfomycin	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	-	-
Other antibiotics	15 (33.3%)	10 (37.0%)	5 (27.8%)	0.393	1.69 (0.43-6.82)	1.27 (0.31-5.18)
Definitive treatment						
Combined treatment	27 (60.0%)	20 (74.1%)	7 (38.9%)	**0.018**	**0.22 (0.06-0.80)**	**0.18 (0.04-0.84)**
Non-carbapenem β-lactam	15 (33.3%)	13 (48.1%)	2 (11.1%)	**0.010**	**0.09 (0.01-0.51)**	**0.12 (0.02-0.76)**
Carbapenem	4 (8.9%)	3 (11.1%)	1 (5.6%)	0.502	0.55 (0.05-3.96)	0.42 (0.05-3.40)
Aminoglycosides	15 (33.3%)	8 (29.6%)	7 (38.9%)	**0.010**	**0.13 (0.01-0.79)**	**0.15 (0.02-0.90)**
Fluoroquinolone	6 (13.3%)	4 (14.8%)	2 (11.1%)	0.521	0.47 (0.01-6.55)	0.18 (0.01-2.55)
Colistin	2 (4.4%)	1 (3.7%)	1 (5.6%)	0.519	1.51 (0.35-6.32)	1.25 (0.28-5.49)
Aztreonam	8 (17.8%)	6 (22.2%)	2 (11.1%)	0.720	0.72 (0.06-5.78)	0.54 (0.07-4.16)
Fosfomycin	7 (15.6%)	5 (18.5%)	2 (11.1%)	0.768	1.53 (0.02-124.60)	0.38 (0.02-7.92)
Other antibiotics	15 (33.3%)	13 (48.1%)	2 (11.1%)	0.340	0.44 (0.04-2.94)	0.36 (0.04-2.71)

IV. Discusión integradora

1. Resistencia a antibióticos en bacilos gramnegativos en pediatría

1.1. Epidemiología de las resistencias en bacilos gramnegativos en pediatría

En concordancia con lo observado en poblaciones adultas, se ha registrado un aumento progresivo durante los últimos años en la incidencia de infecciones por bacilos gramnegativos multirresistentes (MDR) en niños. Destaca un incremento en la prevalencia de resistencia a carbapenemes en bacilos gramnegativos desde finales de los años 90 hasta los primeros años de la segunda década de los años 2000, especialmente notable en el caso de *P. aeruginosa* [100, 101, 102].

Datos europeos más recientes procedentes del registro internacional ATLAS revelaron un aumento en la prevalencia de resistencia a carbapenemes en aislamientos de *K. pneumoniae*, del 2,4% en el período de 2004-2012 al 4,7% en el período de 2013-2018, y de *A. baumannii*, del 14,5% en el período de 2004-2012 al 32,3% en el período de 2013-2018, manteniéndose estable en el caso de *E. coli* (<1%)[104]. De una forma similar, nuestro estudio sobre bacteriemias en pacientes ingresados en unidades de alta complejidad también mostró un incrementó en la prevalencia de resistencia a carbapenemes en Enterobacterales, del 3,5% en 2013-2017 al 7,2% en 2017-2021[225]. Contrario a lo previo, un estudio reciente que analizó los aislamientos bacterianos en diferentes muestras de niños procedentes de 11 hospitales terciarios en China entre 2016 y 2020, encontró una disminución en la prevalencia de resistencia a carbapenemes en *K. pneumoniae* y *A. baumannii* del 23,0% y 54,5% en 2016 al 35,8% y 13,4% en 2020, respectivamente[226].

Respecto a *P. aeruginosa*, nuestro grupo ha llevado a cabo 2 estudios que han analizado la prevalencia de resistencia a carbapenemes: el estudio de aislamientos bacterianos en hemocultivos de pacientes ingresados en unidades de alta complejidad muestra una prevalencia estable (30,2-27,9%) durante el periodo del estudio[225]; el

trabajo de bacteriemias por *P. aeruginosa* en cuatro centros pediátricos, en el que se analiza en periodos de tres años, se observa un descenso inicial del 41,4% en 2010-2012 al 17,5% en 2016-2018, con un posterior aumento al 30,3% en 2019-2020[227].

En cuanto a la resistencia a cefalosporinas de espectro extendido en bacilos gramnegativos, principalmente mediadas por BLEEs en Enterobacterales, encontramos una tendencia similar a la descrita en la resistencia a carbapenemes. Una revisión sobre aislamientos de Enterobacterales productores de BLEEs en hemocultivos pediátricos a nivel mundial demostró un incremento de su prevalencia de 3,5% al 8% desde el 1996 al 2013 [89]. En Europa, los años siguientes al estudio previo en pacientes pediátricos, incluyendo distintos tipos de muestras, se objetivó un incremento sostenido en la prevalencia de *K. pneumoniae* productor de BLEEs del 35,0% en 2013-2017 al 39,2% en 2017-2021, con un descenso en el caso de *E. coli*, del 20,7% en 2013-2017 al 15,4% en 2017-2021[225]. De forma muy similar, en nuestro estudio centrado en la epidemiología de los hemocultivos en pacientes ingresados en unidades de alta complejidad, vemos un incremento importante en la prevalencia de resistencia a cefalosporinas de espectro extendido en *Klebsiella* spp. del 9,2% en 2013-2017 al 23,3% en 2017-2021, manteniéndose estable en el caso de *E. coli* (12,8-14%) y de *P. aeruginosa* (24,5-27,9%) [225].

En conjunto, los datos previos descritos por nuestro grupo, así como por otros grupos en diferentes zonas geográficas, demuestran que en la actualidad *K. pneumoniae* es el patógeno más relevante en pediatría, igual que en adultos, a nivel de resistencia a antibióticos, tanto en el caso de resistencia a cefalosporinas como a carbapenemes[228].

1.2. Factores de riesgo de resistencia en bacilos gramnegativos en pediatría

En nuestro estudio realizado en unidades de alta complejidad, la prevalencia de aislamientos de bacilos gramnegativos multirresistentes fue mayor en los niños de mayor edad[225], tal y como se ha demostrado en otros estudios realizados en países de renta alta[12,229,230]. Por el contrario, los aislamientos en hemocultivos de pacientes ingresados en unidades neonatales presentaron menor prevalencia de resistencias. Un estudio reciente que evaluó los episodios de bacteriemia en niños en Japón mostró una prevalencia menor de BMR en bacilos gramnegativos en las unidades neonatales (14,4%) en comparación con otras unidades, como oncohematología (35,1%) o la unidad de cuidados intensivos pediátricos (UCIP, 22,4%) [231]. Siguiendo una distribución similar, en el estudio europeo ARPEC la prevalencia de resistencias en diferentes bacilos gramnegativos fue más baja en niños menores de 1 año (por ejemplo, a las fluoroquinolonas en *E. coli* o a los carbapenemes en *K. pneumoniae*) que en pacientes mayores de 1 año[12].

No obstante, los datos de países de ingresos bajos y medios muestran una prevalencia similar o incluso mayor de BMR en neonatos en comparación con niños mayores[232,233]. Por lo tanto, parecen existir diferencias geográficas relevantes en la prevalencia de BMR en neonatos entre países de renta alta y países de renta media y baja. Así, aunque los regímenes antibióticos de primera línea son efectivos contra la mayoría de los episodios de sepsis neonatal en el Reino Unido, incluidas las sepsis de inicio temprano y tardío[234], los aislamientos en hemocultivos de neonatos en países como India, Bangladesh o Nigeria muestran una elevadísima prevalencia de BMR[232,235].

Al considerar la unidad de ingreso, en nuestro estudio encontramos una mayor prevalencia de BMR en Enterobacterales en los aislamientos procedentes de oncohematología en comparación con los procedentes de la UCIP o de neonatología[225]. Un estudio multicéntrico realizado en EE.UU. que analizó los aislamientos en infecciones relacionadas con la asistencia sanitaria en niños entre 2011 y 2014, describió una distribución similar, con una mayor prevalencia en unidades de oncología pediátrica de

la resistencia antimicrobiana entre Enterobacterales[236]. En ese estudio, los aislamientos de *E. coli* y *Klebsiella* spp. de pacientes ingresados en estas unidades también presentaron una mayor prevalencia de resistencia a la mayoría de los antibióticos en comparación con otras.

En nuestro estudio sobre bacteriemias por *P. aeruginosa* se encontró en el análisis multivariante una asociación significativa entre la presencia de resistencia a carbapenemes con haber recibido tratamiento con estos antimicrobianos durante el mes previo (Odds ratio ajustada [ORa] 11,15) y el antecedente de trasplante de órgano sólido (ORa 7,64), siendo el foco de la infección desconocido un factor protector (ORa 0,33). Estos factores también han sido descritos en otros estudios sobre bacteriemias por *P. aeruginosa*[118,237,238]. Un estudio más reciente evaluando posibles riesgos de presentar una infección por *P. aeruginosa* resistente a carbapenemes en niños, demostró que la exposición previa a carbapenemes y el haber precisado una broncoscopia fueron factores de riesgo, mientras que el uso previo de β-lactámicos combinados con inhibidores de β-lactamasa en los últimos 90 días fue considerado un factor protector frente a esta infección[239]. Por todo ello, la reducción del uso innecesario de antibióticos y el ajuste del espectro, especialmente disminuyendo el consumo de carbapenemes, parecen estrategias importantes para reducir la resistencia a estos antibióticos.

En la revisión realizada sobre infecciones por BGN resistentes a carbapenemes, la cual es una de las pocas realizadas hasta la fecha en pacientes pediátricos, encontramos los siguientes factores de riesgo de presentar una infección o colonización por estos microorganismos: la exposición previa a antibióticos (principalmente de amplio espectro y duración prolongada), el uso de dispositivos médicos (principalmente ventilación mecánica), la estancia en la UCI, cirugía previa y la hospitalización prolongada [240]. Esta revisión fue realizada antes de la publicación del resto de artículos que componen esta tesis, confirmándose varios de estos datos en nuestros estudios.

1.3. Mortalidad en infecciones por bacilos gramnegativos multirresistentes en pediatría

Las infecciones por BGN MDR presentan mayor mortalidad que las debidas a cepas sensibles a los antibióticos de primera línea. Esto podría ser debido a múltiples factores, como la mayor virulencia del agente causal, el retraso en el inicio de un tratamiento antibiótico activo o a la mayor comorbilidad de los individuos que desarrollan una infección por estos microorganismos.

La mayoría de los estudios que han comparado la mortalidad entre BGN sensibles y multirresistentes, con diferentes perfiles de resistencia, han demostrado una mayor mortalidad en el segundo grupo en el análisis univariante. Sin embargo, en los análisis multivariantes existen resultados dispares.

La tasa de mortalidad en niños con infecciones por BGN resistentes a carbapenemes oscila entre el 8% y el 52%, variando según el foco de la infección, la enfermedad de base y la edad del paciente[240]. Dos estudios han demostrado un incremento de la mortalidad de 6 a 11 veces en pacientes pediátricos con infecciones por BGN resistentes en comparación con las infecciones por BGN sensibles a carbapenemes[241,242].

Nuestro estudio sobre bacteriemias por *P. aeruginosa* en niños mostró una elevada mortalidad en el conjunto de la población analizada (23,2%), similar a estudios previos que han objetivado tasas de mortalidad del 15%-52% en episodios de bacteriemias por este microorganismo[113–115,117,118]. Al comparar la mortalidad a los 30 días en las infecciones producidas por aislamientos sensibles con la ocurrida en los resistentes a carbapenemes, encontramos una mortalidad superior en el segundo grupo (16,0% vs 40,0%, p=0,001). Sin embargo, la resistencia a carbapenemes no se mantuvo significativamente asociada a la mortalidad a los 30 días al ajustarse en un análisis multivariante. El modelo final se objetivó una asociación estadísticamente significativa con la ventilación mecánica (ORa 4,24), la sepsis (ORa 5,72), la antibioterapia empírica inadecuada (ORa 5,86) como factores de riesgo, siendo el control de la infección un factor protector (ORa 0,16).

Esta disparidad podría explicarse por el hecho de que los aislamientos resistentes a carbapenemes no sean más virulentos, y que sus mayores tasas de mortalidad puedan atribuirse a un retraso en recibir el tratamiento antibiótico adecuado. Lodise et al. evaluaron el impacto sobre la mortalidad de distintas variables entre pacientes con infecciones graves por Enterobacterales, demostrando que un retraso en la terapia adecuada resultaba ser un predictor más importante en comparación con la resistencia a carbapenemes. Estos autores llegaron a la conclusión de que no era la resistencia a los antibióticos *per se* lo que afectaba los resultados clínicos, sino la administración más precoz de una terapia antibiótica adecuada[31]. De esta manera, aunque estas cepas no presenten más virulencia que las cepas sensibles, parece claro que el retraso en el inicio de tratamiento antibiótico efectivo, debido al perfil de resistencias que inactivan los antibióticos empíricos recomendados en las guías de práctica clínica habituales, podría ser la causa de la mayor mortalidad. Varios estudios han demostrado una mayor frecuencia del tratamiento empírico inadecuado en las infecciones por BMR. Un estudio multicéntrico realizado en EE.UU que incluyó 21.608 episodios de bacteriemia demostró que las infecciones por BMR se asociaron con un tratamiento empírico inadecuado (ORa 9,09, intervalo de confianza [IC] 95%: 7,68-10,76, p<0,001)[243]. De forma similar, un estudio centrado en los episodios de bacteriemia en pacientes con neutropenia febril mostró una mayor frecuencia de tratamiento empírico inapropiado en las producidas por BGN MDR (39% vs 7%, p<0,001), con una mortalidad mayor en los episodios con tratamiento empírico inadecuado (36% vs 24%, p=0,004)[244]. Esta mayor mortalidad se hizo aún más notable en el caso de que estos episodios se presentaran como shock séptico (76% vs 51%, P=0,002)[245].

En nuestro estudio sobre bacteriemias por *P. aeruginosa*, los episodios ocurridos por cepas resistentes a carbapenemes recibieron con mayor frecuencia un tratamiento empírico inadecuado (5,7% vs 53,3%, p<0.001), siendo éste un factor de riesgo con una mayor mortalidad a los 30 días (ORa 5,86, IC 95% 1,89-18,16).

Para hacer frente a esta problemática y reducir el riesgo de administrar un tratamiento empírico inadecuado, de especial importancia en las infecciones graves, sin que suponga un consumo desmesurado de antibióticos de espectro excesivo, se han propuestos diferentes estrategias, que se podrían resumir en dos grandes grupos: a)

modelos que sean capaces de predecir el riesgo de presentar una infección por una BMR; y b) nuevas técnicas diagnósticas capaces de reducir los tiempos de identificación y determinación de la sensibilidad a los antibióticos.

En cuanto al primer planteamiento, diferentes modelos han tratado de predecir el riesgo de infecciones por BMR, existiendo modelos centrados en diferentes tipos de fenotipos de resistencia. Sick-Samuels AC et al propusieron un árbol de decisión en bacteriemias por BGN en niños, en el que el tratamiento previo con carbapenemes, el cultivo previo con un organismo resistente a piperacilina-tazobactam, el trasplante intestinal, la edad ≥3 años y ≥7 episodios de bacteriemias por BGNs se asociaron con un mayor riesgo de una infección por un BGN resistente a los antibióticos de amplio espectro habituales [246].

Otros modelos han centrado la predicción de infecciones por BMR en la colonización previa por BGN MDR. Varios estudios han demostrado un mayor riesgo de infección por diferentes tipos de BGN MDR, como BLEEs o resistentes a carbapenemes, en individuos colonizados previamente por estos microorganismos[247,248]. Un estudio poblacional realizado en Suecia evaluó la incidencia acumulada a los 6 años de episodios de bacteriemia por Enterobacterales productores de BLEEs en individuos colonizados por estos microorganismos, mostrando una incidencia superior (3,8% y 1,6% en los que se detectó la colonización en orina y heces, respectivamente) que en los no colonizados previamente (0,02%)[249].

En nuestro estudio sobre bacteriemias por *P. aeruginosa*, en el 8,9% de los pacientes con una bacteriemia por una cepa de *P. aeruginosa* resistente a carbapenemes se había identificado previamente una colonización por una cepa similar en los 6 meses anteriores, mientras que no se observaron casos de colonización previa en los 106 pacientes con aislamientos sensibles a carbapenemes (p=0,002). Además, factores como el foco de la infección o el mecanismo de resistencia han demostrado influir en el riesgo de infección por el microorganismo colonizante[250,251]. Giannella M et al diseñaron un score predictivo de bacteriemia por *K. pneumoniae* resistente a carbapenemes en adultos colonizados por este tipo de cepas[111]. El score final incluyó el ingreso en UCI, el antecedente de cirugía abdominal, el tratamiento quimioterápico o

radioterápico, y la cantidad de sitios de colonización adicionales, como factores asociados a la infección en los sujetos colonizados. Este mismo score ha sido posteriormente evaluado en población pediátrica, mostrando una capacidad predictiva aceptable[112]. Sin embargo, la amplia variedad en el perfil de pacientes y la notable diversidad epidemiológica entre centros y regiones hace que estos modelos precisen de una validación antes de implementarse en la práctica clínica de cada centro.

Por otro lado, modelos como el INCREMENT score, han evaluado la necesidad de tratamiento antibiótico combinado en bacteriemias por Enterobacterales resistentes a carbapenemes, estableciendo grupos de riesgo de mortalidad en los que la combinación podría presentar un beneficio[252,253]. Resulta importante considerar que estos modelos se evaluaron antes de la aprobación de las nuevas combinaciones de β-lactámicos. Estudios con estos antibióticos han demostrado que la combinación podría no aportar ningún beneficio en infecciones por microorganismos sensibles a estos nuevos antibióticos[254].

Otra cuestión importante en el tratamiento antibiótico es la optimización del diagnóstico microbiológico, de tal forma que permita adelantar la identificación y el antibiograma de los microorganismos aislados[255,256]. Esto redunda en un menor tiempo hasta la instauración de un tratamiento antibiótico adecuado, en el caso de no serlo el tratamiento empírico iniciado[257].

En nuestro centro hemos realizado recientemente un estudio en el que hemos evaluado el impacto de la incorporación de un paquete de técnicas microbiológicas en hemocultivos en pacientes con bacteriemia por Enterobacterales resistentes a carbapenemes [258]. En el periodo tras la implementación de las técnicas, el tiempo hasta obtener el resultado microbiológico fue menor que en el periodo previo (superior a 30 horas en el 70,2% de los casos del primer periodo frente al 45,2% en el segundo). Además, en el análisis multivariante, se asoció a un peor pronóstico (mortalidad a los 30 días y/o bacteriemia persistente y/o recurrente) un tiempo mayor de 30 horas hasta el resultado. Esto demuestra la importancia de establecer un diálogo estrecho entre clínicos y microbiólogos, y de optimizar las técnicas microbiológicas con el objetivo de reducir el tiempo hasta establecer un tratamiento antibiótico adecuado.

2. Resistencia a antibióticos en cocos grampositivos en pediatría

2.1. Epidemiología de las resistencias en cocos grampositivos en pediatría

Dentro de las infecciones por cocos grampositivos en pediatría, la principal preocupación radica en la resistencia a meticilina en *S. aureus.* Además, dentro de estas infecciones, la resistencia a distintos antibióticos, como clindamicina, levofloxacino o vancomicina, dificulta aún más su tratamiento[259,260].

A nivel global, se estima que en 2019 se produjeron más de 100.000 muertes atribuidas a infecciones por SARM[99]. La resistencia a meticilina en *S. aureus* adquirido en la comunidad en niños empezó a describirse en España en el año 2006[171].

En nuestro estudio sobre bacteriemias en pacientes pediátricos hospitalizados entre los años 2013 y 2021, la prevalencia de SARM entre los aislados de *S. aureus* fue del 11,0 % (n=15/136) [225]. Al comparar los dos periodos del estudio, se evidenció un incremento no significativo en su prevalencia (del 8,3% en 2013-2017 al 13,2% en 2017-2021, p=0,249). Este dato difiere de lo descrito en varios estudios realizados en distintos países europeos y de América, en los que se ha objetivado un descenso significativo en la incidencia de infecciones por SARM en niños y adultos [261–264], si bien es cierto que en España la prevalencia de SARM no ha llegado a ser excesivamente elevada.

Por otro lado, en el estudio realizado por nuestro grupo sobre NAC por *S. aureus,* objetivamos la alarmante prevalencia del 26,5% (9/34), cifra muy superior a la descrita en estudios centrados en otros síndromes clínicos en niños en España: 4,4% en exudados nasales de niños atendidos de forma ambulatoria en atención primaria [172], 8,8% y 16,2% en infecciones de cualquier localización [173,174], 7,8% en bacteriemias por *S. aureus*, 12% en infecciones de piel y partes blandas[177] y 10,3% en infecciones osteoarticulares[178]. Igualmente, según los datos del ECDC, en aislamientos en muestras invasivas (sangre y líquido cefalorraquídeo), la prevalencia de SARM en menores de 18 años se sitúa en torno al 12-18% del total de aislamientos de *S. aureus* durante los últimos años[97]. Esta disparidad plantea múltiples hipótesis que podrían justificarla, como la existencia de

cierto tropismo de los clones circulantes en nuestro medio de SARM por el tejido pulmonar, lo que podría aumentar su prevalencia en las NAC comparado con otras infecciones, o una diferencia geográfica que suponga una mayor prevalencia en la Comunidad de Madrid, que es donde se ha realizado el estudio de neumonías; aunque esto último parece menos probable, pues nuestro estudio realizado en bacteriemias en niños hospitalizados demostró una prevalencia muy inferior. De forma similar a nuestro trabajo, un estudio realizado en adultos con NAC en España demostró también una proporción de SARM en los casos por *S. aureus* inusualmente superior (40%) a la descrita en otras infecciones[265]. Además, en un estudio europeo en infecciones graves por *S. aureus* en niños, la proporción de neumonías fue mayor en el grupo de SARM que en el de SASM (46,2% vs 14,5%, p=0,004) [266].

Al comparar la prevalencia de SARM entre los niños con NAC en nuestro estudio con otros estudios, objetivamos que fue similar a la observada en varios países europeos[267–269], pero menor que la descrita en otros estudios realizados en países con una mayor carga de MRSA [182–184,186].

Otro hallazgo relevante de nuestro estudio sobre neumonías fue la prevalencia de resistencia a clindamicina en SARM (22,2%), muy superior a la presente en los aislamientos sensibles a meticilina (8,7%). Esta diferencia también se ha descrito en aislamientos de niños colonizados por *S. aureus* en España (26% vs. 16,9%)[172]. Por otro lado, un estudio realizado en nuestro centro que incluyó aislamientos de *S. aureus* en diferentes muestras clínicas entre 2017 y 2021, demostró una prevalencia de SARM del 19,3%, con una prevalencia de resistencia a clindamicina del 24,8% en SARM (estudio no publicado todavía).

Una prevalencia de resistencia a clindamicina tan elevada cuestiona la idoneidad de este antibiótico como tratamiento empírico de niños con sospecha de infecciones por SARM en nuestro entorno, tal y como recomiendan varias guías [270–272]. Algunas alternativas de forma empírica podrían ser vancomicina, linezolid, cotrimoxazol, ceftarolina o daptomicina, según el foco y gravedad de la infección.

Aunque de menor envergadura en la actualidad que las infecciones producidas por SARM, la resistencia a vancomicina u otros antibióticos en *Enterococcus* spp. puede suponer un motivo de preocupación futuro. En nuestro estudio sobre bacteriemias en pacientes hospitalizados, la prevalencia de resistencia a vancomicina en *Enterococcus* spp. fue del 1,4% (4/287; 0% en *Enterococcus faecalis* y 8,6% en *Enterococcus faecium*)[225]. Otros antibióticos como linezolid o daptomicina no fueron analizados, pero la resistencia a estos antibióticos en la actualidad en nuestro medio es anecdótica.

Según los datos reportados por el ECDC, en los últimos años la resistencia a vancomicina en España en muestras invasivas procedentes de todos los grupos etarios ha sido del 0,1-0,3% para *E. faecalis* y del 1,8-2,5% para *E. faecium*, presentando una tendencia estable[97]. Además, según estos mismos datos, al comparar la resistencia a vancomicina en *E. faecium* en España entre los distintos grupos de edad, vemos que la mayor prevalencia se sitúa en los adultos.

Un estudio que evaluó la prevalencia de resistencias en aislamientos procedentes de hemocultivos en pacientes menores de 18 años entre 2011-2012 en 12 países europeos, mostró una prevalencia de resistencia a vancomicina del 8,3% de *E. faecium* [12], similar a la objetivada en nuestro estudio. Otro estudio realizado en EE.UU. que evaluó los aislamientos pediátricos de *Enterococcus* spp. entre los años 2013 y 2018 mostró una prevalencia de resistencia a vancomicina de *E. faecium* del 18%[214], muy superior a la registrada en la actualidad en España. De la misma forma, otro estudio también realizado en EE.UU objetivó una tendencia creciente en las hospitalizaciones por *Enterococcus* spp. resistente a vancomicina, de 53 hospitalizaciones por 1.000.000 hospitalizaciones en 1997 a 120 en 2012 ($p<0,001$)[273].

2.2. Factores de riesgo de resistencia en cocos grampositivos en pediatría

Establecer factores de riesgo de infecciones por SARM puede ser de gran utilidad para poder seleccionar empíricamente el antibiótico más adecuado. En países con baja prevalencia de resistencia a meticilina, como es España, su cobertura empírica no es

habitual, salvo en pacientes graves e inestables clínicamente, con factores de riesgo de SARM.

En nuestro estudio sobre bacteriemias en pacientes hospitalizados, la prevalencia de SARM fue superior de forma no significativa en el grupo de pacientes mayores de 1 mes que en los menores de 1 mes (13,6% vs 7,6%, p=0,249)[225]. Igualmente, hubo una tendencia a una mayor prevalencia de resistencia a meticilina en las infecciones ocurridas en pacientes ingresados en oncohematología (20,8%) comparado con aquéllos ingresados en UCIP (12,1%) y neonatología (7,6%).

En nuestro estudio sobre neumonías por *S. aureus*, hubo diferencias significativas en la distribución por sexos en el grupo de SARM frente al de SASM, habiendo un mayor porcentaje de varones en el de SARM (88,9% vs 24,0%, p=0,033). Tal y como cabría esperar, el antecedente de patología médica crónica fue superior en los pacientes con NAC por SARM (66,7% vs 20,0%, p=0,010). Sin embargo, no se encontró asociación de la resistencia a meticilina con otros factores descritos previamente. Entre estos factores de riesgo de infección por SARM reportados en niños, se encuentran: la presencia de enfermedades crónicas, igual que hemos evidenciado en nuestro estudio[274]; la menor edad, siendo las neumonías por SARM más frecuentes en menores de 2 años [183,274,275]; y el antecedente reciente de antibioterapia y de infecciones de piel y partes blandas[276,277]. En el estudio COSACO, realizado en nuestro medio, la residencia rural fue el único factor asociado con la colonización nasal por MRSA (OR 3,62; IC 95%: 1,57-8,36)[172].

En países de baja prevalencia de SARM, como es España, también se ha establecido una asociación con la procedencia geográfica, siendo mayor en sujetos procedentes de zonas con una mayor prevalencia de SARM, como Latinoamérica[278]. Un estudio reciente realizado en varias urgencias pediátricas españolas demostró una mayor prevalencia de SARM en niños no nacidos en España y en aquéllos con una infección previa por SARM[279]. En cuanto a la edad, en las infecciones respiratorias por *S. aureus*, en nuestro estudio comparamos las NAC por *S. aureus* con un grupo control de NAC por *S. pneumoniae*, evidenciando una menor edad en el caso de las NAC por *S. aureus* (8 meses vs 3 años, p<0,001).

Las infecciones respiratorias por el virus influenza también han demostrado incrementar el riesgo de infecciones por SARM, lo cual se ha descrito principalmente en EE.UU.[275,280]. Esta asociación posiblemente sea extrapolable a otras infecciones respiratorias de etiología bacteriana, como hemos visto recientemente en Europa con el incremento de casos invasivos por *Streptococcus pyogenes*, en aparente asociación, entre otros factores, con el incremento de infecciones respiratorias de etiología viral, y que hemos podido describir desde nuestro grupo[281].

Un factor ampliamente analizado y de gran utilidad clínica es el análisis del estado de colonización nasal por SARM. Numerosos estudios han demostrado un elevado valor predictivo negativo de infección por SARM en aquellos sujetos no colonizados por dicho microorganismo, especialmente en las infecciones respiratorias[282,283]. Un estudio reciente realizado en pacientes pediátricos en EE.UU. demostró un valor predictivo negativo de presentar una infección por SARM en distintos síndromes clínicos del 99,4% en niños en los que no se aisló SARM en un exudado nasal[284].

Los factores de riesgo de resistencia a vancomicina en *Enterococcus* spp. en niños están menos descritos en la actualidad. Un estudio norteamericano evaluó los factores de riesgo de presentar una infección por *Enterococcus* spp resistente a vancomicina en niños hospitalizados, mostrando una asociación con la infección por *Clostridioides difficile*, la inmunosupresión y la exposición reciente a antibióticos y al sistema sanitario[273].

2.3. Mortalidad en infecciones por cocos grampositivos en pediatría

El análisis de morbimortalidad asociado a SARM en comparación con las infecciones producidas por SASM es uno de los temas más ampliamente estudiados en infectología. Este temor probablemente viene fundamentado por la elevada mortalidad descrita en las bacteriemias por *S. aureus* en adultos (10-20%)[285], siendo aún mayor en el caso de las producidas por SARM[286].

Es importante comenzar destacando que, aunque las infecciones graves por *S. aureus* en niños en países de renta alta pueden presentar una elevada morbilidad, con ingresos prolongados, la mortalidad asociada es muy inferior a la descrita en adultos[190]. Un estudio sobre bacteriemias por *S. aureus* en pacientes pediátricos realizado en EE.UU. objetivó una mortalidad del 2% (8/394), siendo 5 (62,5%) de los casos en pacientes con neumonía.

En cuanto a la diferente gravedad en infecciones por SARM en pediatría respecto a las producidas por SASM, existen resultados discordantes en la literatura. En nuestro estudio sobre NAC por *S. aureus*, ningún paciente incluido murió. Sin embargo, durante el periodo del estudio, una adolescente falleció de forma extrahospitalaria en nuestra región, revelando la autopsia que la muerte había estado relacionada con una neumonía por SARM[287]. Por tanto, de haber sido hospitalizada e incluida en nuestro estudio, la tasa de mortalidad por NAC por *S. aureus* habría sido del 2,9%. Otros estudios que han evaluado la mortalidad asociada a NAC por *S. aureus* en pediatría han descrito una mortalidad del 0,9-4,9%[184,274,288,289].

Considerando otros datos de gravedad, como el ingreso en UCIP o la necesidad de soporte respiratorio o hemodinámico, o la presencia de complicaciones pulmonares (absceso, derrame pleural o necrosis), en nuestro estudio no se objetivaron diferencias entre las NAC por SARM y las producidas por SASM, a pesar de un mayor porcentaje de tratamiento empírico inadecuado y de retraso de tratamiento antibiótico activo frente al agente causal en el grupo de SARM.

Un estudio que incluyó 394 episodios de bacteriemia por *S. aureus* en niños mostró que la resistencia a meticilina se asoció con un mayor riesgo de complicaciones[185]. Sin embargo, en otro estudio que incluyó a 152 niños con infecciones invasivas por *S. aureus* adquiridas en la comunidad, no se objetivó un peor pronóstico en las producidas por SARM[266]. Además, otros estudios centrados en NAC en niños por *S. aureus* no mostraron una mayor morbimortalidad en aquéllos con infecciones por SARM[184,187,274]. Un estudio prospectivo reciente que incluyó a 552 niños con bacteriemia por *S. aureus* mostró que, si bien el desarrollo de neumonía necrotizante aumentaba la mortalidad, el aislamiento de SARM no presentó esta asociación[288]. Por otro lado, en un

estudio europeo que evaluó las infecciones comunitarias invasivas por *S. aureus* en niños, los factores que se asociaron a una mayor gravedad fueron la producción de leucocidina de Panton-Valentine y las neumonías, siendo ambos factores más frecuentes en el grupo de infecciones por SARM [266]. Sin embargo, la resistencia a meticilina no se asoció de forma independiente a una mayor gravedad.

Una de las cuestiones planteadas respecto a la mayor morbimortalidad objetivada de forma casi constante en las infecciones graves en adultos por SARM en comparación por las producidas por SASM[286,290], es el mayor porcentaje de tratamiento empírico inadecuado[291]. En nuestro estudio de NAC, aunque coincidió la asociación de SARM con un mayor porcentaje de tratamiento empírico inadecuado, este retraso no acabó condicionando un peor pronóstico.

Se plantea que la mayor morbimortalidad en las infecciones graves por SARM, además de por el retraso en el inicio de antibioterapia activa, podría tener que ver con el uso frecuente de vancomicina frente a este patógeno, considerado de elección en las guías publicadas hasta la fecha[33,194,271]. Este antibiótico presenta claras desventajas respecto a otras alternativas, como un peor perfil de seguridad, con riesgo de nefrotoxicidad, y un retraso frecuente en la obtención de concentraciones plasmáticas terapéuticas, lo cual redunda en peores resultados clínicos[292,293]. Un estudio que analizó las coinfecciones respiratorias por gripe y SARM en pacientes pediátricos ingresados en UCIP mostró que, de 29 niños que recibieron vancomicina dentro de las primeras 24 horas de hospitalización, la mortalidad fue del 12,5% si el tratamiento también incluía un segundo antibiótico frente a SARM en comparación con el 69,2% que recibieron monoterapia con vancomicina[182]. Este estudio, por tanto, cuestiona la eficacia de vancomicina en las infecciones respiratorias graves por SARM.

En cuanto a las infecciones por *Enterococcus* spp. y el análisis del impacto en la gravedad de las infecciones producidas por cepas resistentes a vancomicina, un estudio analizó las infecciones por *Enterococcus* spp. en pacientes pediátricos hospitalizados, mostrando una mayor estancia hospitalaria y un aumento en los costes económicos, sin presentar una asociación significativa con la mortalidad [273].

3. Consumo de antibióticos durante los primeros meses de la pandemia de SARS-CoV-2 como determinante del desarrollo de resistencias a antimicrobianos

Uno de los determinantes del desarrollo de resistencias a antibióticos es el consumo de antimicrobianos. La presión selectiva ejercida por el tratamiento antibiótico es capaz de seleccionar cepas resistentes[39]. A nivel internacional, se observan notables disparidades en la cantidad de antibióticos consumidos según el país, y España destaca como uno de los países con mayor consumo comunitario[40].

Es importante resaltar que los niños menores de 3 años son el grupo con la mayor probabilidad acumulada de recibir tratamiento antibiótico a lo largo del tiempo, superando a otros grupos etarios de adultos[42]. Además, estudios recientes llevados a cabo, tanto en Europa como en EE.UU, han revelado que hasta un tercio de las prescripciones de antibióticos en niños fueron consideradas inapropiadas[43,44].

La pandemia por SARS-CoV-2 supuso un escenario ideal para evaluar el consumo de antibióticos por la posibilidad de establecer cierta homogeneidad en el perfil de pacientes, al analizar los casos atendidos por la infección producida por este virus. Además, eran pacientes que, en su mayoría, no presentaban coinfecciones o sobreinfecciones bacterianas[51–53], por lo que, *a priori*, la prescripción de antibióticos era inadecuada en la mayoría de los casos. La profundización en el conocimiento de los patrones de prescripción de antibióticos en poblaciones específicas, como la población pediátrica con COVID-19, permite ayudar a detectar una posible intervención de tipo PROA dirigida a mejorar la prescripción de los antibióticos.

En nuestro estudio realizado durante los primeros meses de la pandemia por SARS-CoV-2, entre marzo de 2020 y marzo de 2021, se detectó alguna coinfección o sobreinfección bacteriana en el 7,0% de los niños infectados por SARS-CoV-2, más frecuentemente (p=0,020) en los casos con diagnóstico de COVID-19 (8,2%) que en pacientes con MIS-C (2,2%)[294]. Este dato es similar al descrito en otros estudios, que estiman una incidencia de coinfecciones o sobreinfecciones bacterianas del 7-8%[51–53].

En nuestro estudio, las ITUs fueron las infecciones bacterianas más frecuentes (40,0%) principalmente por *E. coli*, seguidas de las bacteriemias (31,1%).

Se evidenció un consumo muy elevado de antibióticos en nuestro estudio. Así, el 54,2% de los pacientes recibieron uno o más antibióticos sistémicos, con una duración de 38,7 días/100 pacientes-día y una mediana de duración de 4,5 días. La prescripción de antibióticos fue más común (p<0,001) entre los pacientes con MIS-C (88,9%) que en aquellos con COVID-19 (45,0%). El antibiótico prescrito con mayor frecuencia fue cefotaxima/ceftriaxona (53,9%), seguido de azitromicina (26,5%) y amoxicilina-clavulánico (18,4%).

Durante el periodo de nuestro estudio se objetivó una disminución en la prescripción de antibióticos en los pacientes con COVID-19 (cambio porcentual mensual: -5,5% [IC 95%: -9,7, -1,0], p=0,021). Este hecho podría estar en relación con la evidencia creciente en ese momento sobre la baja incidencia de coinfecciones y sobreinfecciones bacterianas en los pacientes con COVID-19, y en la evidencia en contra del uso de azitromicina en las infecciones por SARS-CoV-2 que refutó las hipótesis previas[295].

Yock-Corrales et al[296] observaron una tasa más baja de prescripción de antibióticos (24,5%) en niños con COVID-19 o MIS-C en América Latina, pero la población analizada incluyó tanto niños ambulatorios como hospitalizados. Sin embargo, nuestra tasa es inferior al 69% descrito por Swann et al[297] en niños hospitalizados en el Reino Unido, tal vez porque nuestro estudio se prolongó por más tiempo (hasta marzo de 2021 frente a julio de 2020), con una evidencia creciente de la baja prevalencia de coinfecciones y sobreinfecciones bacterianas en COVID-19. Otros estudios realizados en Serbia y Pakistán en pacientes pediátricos hospitalizados con COVID-19 durante los primeros meses de la pandemia también mostraron un consumo de antibióticos muy elevado, del 47,2% y 85,5%, respectivamente[298,299]. Hay que destacar, además, que el 80,4% de los antibióticos prescritos en el estudio realizado en Pakistán formaban parte del grupo *Watch* de la clasificación AWaRe de la OMS[50].

Por otro lado, se ha descrito una tasa mayor de consumo de antibióticos en adultos (55-85%)[300,301], probablemente justificada por la mayor gravedad de las infecciones por SARS-CoV-2 en esta población en comparación con los niños.

Varios estudios han evaluado el consumo de antibióticos en niños durante la pandemia de SARS-CoV-2. Más allá del elevado consumo de antibióticos en pacientes pediátricos con COVID-19, la pandemia de SARS-CoV-2 ha tenido un impacto positivo en el consumo de antibióticos de forma ambulatoria, con una disminución notable demostrada en varios estudios[302,303]. Este hecho probablemente tenga que ver con la disminución evidenciada de las infecciones respiratorias en niños durante los primeros meses de la pandemia, posiblemente en relación con la implementación de medidas no farmacológicas para evitar la transmisión del virus SARS-CoV-2, que tuvieron un impacto también en otras infecciones con una vía de transmisión similar[281,304].

A nivel hospitalario, el estudio realizado por Velasco-Arnaiz E et al. en Cataluña evaluó la calidad de las prescripciones de antimicrobianos en pacientes pediátricos hospitalizados en un hospital terciario durante los primeros meses de la pandemia en comparación con un periodo similar del año previo, sin objetivar cambios significativos en la calidad de las prescripciones de forma global[305].

V. Conclusiones

Conclusiones

1. Actualmente, la incidencia global de infecciones por bacilos gramnegativos resistentes a carbapenemes en pediatría es baja, con la excepción de los brotes descritos en distintas instituciones sanitarias, y con una mayor incidencia en regiones consideradas de alta prevalencia de este tipo de infecciones.

2. La distribución de carbapenemasas varía según el país, con diferencias descritas a nivel local entre adultos y niños. Estas infecciones presentan mayor mortalidad que las producidas por cepas sensibles a carbapenemes.

3. Las NAC por *S. aureus* en niños en la Comunidad de Madrid presentan una elevada prevalencia de resistencia a meticilina, con una tendencia estable a lo largo de los últimos años.

4. Los aislamientos de SARM en NAC en niños presentan resistencia a clindamicina en un número notable de casos, cuestionando la utilidad de su uso empírico en la actualidad.

5. Las NAC por SARM no demostraron presentar mayor riesgo de mortalidad ni de complicaciones que las producidas por SASM, ni tampoco en comparación con las producidas por *S. pneumoniae*.

6. Durante los primeros meses de la pandemia de SARS-CoV-2, en niños hospitalizados en España con COVID-19 o MIS-C encontramos una prevalencia muy baja de coinfecciones o sobreinfecciones bacterianas. Sin embargo, más de la mitad de los pacientes recibieron algún antibiótico durante el ingreso.

7. Con el paso de los meses, se evidencia una tendencia decreciente en la prescripción de antibióticos en niños hospitalizados con COVID-19, en probable relación con la evidencia creciente en contra de su prescripción de forma sistemática.

8. En bacteriemias en pacientes pediátricos ingresados en unidades de alta complejidad (UCIP, neonatología u oncohematología) se evidencia una elevada prevalencia de resistencia a antibióticos. De particular preocupación es la tendencia creciente durante los últimos años en la prevalencia de resistencia a carbapenemes, cefalosporinas de espectro extendido y fluoroquinolonas en Enterobacterales.

9. Se evidencia un mayor riesgo de presentar un aislamiento resistente a diferentes antibióticos en bacteriemias ocurridas en niños mayores de 1 mes y en aquellos ingresados en unidades no neonatales.

10. Casi un tercio de las bacteriemias por *P. aeruginosa* en niños fueron resistentes a carbapenemes, asociadas con el consumo reciente de carbapenemes y el trasplante de órganos sólidos. Esta prevalencia se mantuvo estable a lo largo del estudio.

11. Los episodios de bacteriemia por *P. aeruginosa* presentaron una elevada mortalidad a los 30 días, estando asociada con el tratamiento empírico inadecuado, la neutropenia y la sepsis al diagnóstico, siendo el control óptimo del foco un factor protector.

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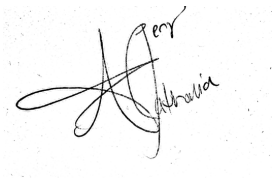
Anexos

A quien corresponda,

Como co-primera autora junto a David Aguilera Alonso del artículo “Pseudomonas aeruginosa bloodstream infections in children and adolescents: risk factors associated with carbapenem resistance and mortality”, actualmente en fase de revisión, manifiesto que David Aguilera Alonso y yo compartimos primera autoría del artículo y que no voy a utilizar dicho artículo para una tesis doctoral.

Fdo.



Nathalia E. Gerig Rodríguez

Hospital General Universitario Gregorio Marañón

DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS

Don Roberto Collado Borrell, Secretario Técnico del **COMITÉ de ÉTICA DE LA INVESTIGACIÓN con MEDICAMENTOS HOSPITAL GENERAL UNIVERSITARIO GREGORIO MARAÑÓN**,

CERTIFICA

Que este Comité ha evaluado la propuesta del Promotor **Coordinador Nacional**, para que se realice el estudio observacional con medicamentos:
Código: ARBCAM
Título: "Antibiotic Resistance in Bloodstream Isolates from High-Complexity Pediatric Units in Madrid, Spain (ARBCAM)"
Investigador coordinador: Dr. David Aguilera Alonso - Hospital General Universitario Gregorio Marañón

Protocolo versión 1.1 – 6/5/2023
Se acepta la realización del estudio sin CI

y consideró que:

- EL ESTUDIO CUMPLE CON LA DEFINICIÓN DE INVESTIGACION SIN INTERÉS COMERCIAL según lo establecido en el párrafo e) del artículo 2.2 del RD 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamento, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos.

- El proyecto se plantea siguiendo los requisitos del Real Decreto 957/2020, de 3 de noviembre, por el que se regulan los estudios observacionales con medicamentos de uso humano y su realización es pertinente.
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto, teniendo en cuenta los beneficios esperados.
- El proceso de selección de los sujetos participantes es apropiado.
- Se considera adecuado el procedimiento previsto para información y obtención del consentimiento informado o, alternativamente, se acepta la exención de consentimiento propuesta para este estudio.
- Se han evaluado las compensaciones económicas previstas (cuando las haya) y su posible interferencia con el respeto a los postulados éticos y se consideran adecuadas.

Por lo que este CEIm emite un **DICTAMEN FAVORABLE**

Y HACE CONSTAR QUE:

1° En la reunión celebrada el día **11 de abril de 2023** ACTA **07/2023** se decidió emitir el informe correspondiente al estudio de referencia.
2° En dicha reunión se cumplieron los requisitos establecidos en la legislación vigente y las normas de funcionamiento interno del comité para que la decisión del citado CEIm sea válida.
3° El CEIm, tanto en su composición, como en los PNT cumple con las normas de BPC (CPMP/ ICH/ E6 R2)
4° La composición actual del CEIm es la siguiente:

D. ANDRÉS JESÚS MUÑOZ MARTÍN (Oncología Médica - Presidente)
Dª. MARÍA LUISA NAVARRO GÓMEZ (Pediatría - Vicepresidenta)
D. ROBERTO COLLADO BORRELL (Farmacia Hospitalaria – Secretario Técnico)

D. JUAN ANTONIO ANDUEZA LILLO (Medicina Interna)
Dª. MARÍA LUISA BAEZA OCHOA DE OCÁRIZ (Alergología)
Dª. PILAR AITANA CALVO FERRÁNDIZ (Farmacología Clínica)
Dª. ISABEL CASTREJÓN FERNÁNDEZ (Reumatología)
Dª MARÍA DEL CARMEN DE LA CRUZ ARGUEDAS (Unidad de Apoyo a la Investigación)
D. VICENTE DE LAS PEÑAS GIL (Psicología Representante Paciente)
D. JAVIER DE MIGUEL DÍEZ (Neumología)
Dª. PATRICIA FONT LÓPEZ (Hematología y Hemoterapia)
Dª. ISABEL GÓMEZ VALBUENA (Farmacia de Atención Primaria)
D. PABLO GONZÁLEZ NAVARRO (Bioestadística)
Dª. MARÍA DEL CARMEN HERAS ESCOBAR (Enfermería)
D. LUIS IBÁÑEZ SAMANIEGO (Digestivo)
Dª. ANA MARÍA IGLESIAS MOHEDANO (Neurología)
D. LUIS ANDRÉS LÓPEZ FERNÁNDEZ (Biología)
Dª. ANA ESTHER LÓPEZ PÉREZ (Anestesiología y Reanimación)
D. ANTONIO MUIÑO MIGUEZ (Medicina Interna)
Dª. SARA PÉREZ RAMÍREZ (Oncología Médica)
D. JOSÉ LUIS REVUELTA HERRERO (Farmacia Hospitalaria)
D. CARLOS ROJAS-MARCOS ASENSI (Licenciado en Derecho)
D. EDUARDO ZATARAÍN NICOLÁS (Cardiología)

Se recuerda al investigador el requisito de solicitar a la AEMPS la publicación en el **Registro Español de estudios clínicos** al inicio de los estudios de seguimiento prospectivo y se recomienda para el resto de estudios observacionales con medicamentos.
Además, se recuerda que se deberá actualizar la información de seguimiento en dicha plataforma y enviar las **notificaciones e informes correspondientes al CEIm**.

Para que conste donde proceda, y a petición del promotor,

firmado en Madrid, a 08 de mayo de 2023

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Fdo.: Dr. Roberto Collado Borrell

Nº CEIm: 20/101

DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS (CEIM)

Dña. María Ugalde Díez, Secretaria del Comité de Ética de la Investigación con medicamentos (CEIm) del **HOSPITAL UNIVERSITARIO 12 DE OCTUBRE.**

CERTIFICA

Que este Comité, ha evaluado la propuesta presentada del promotor, de la modificación ***6*** correspondiente al Proyecto de Investigación:

Título: "Estudio epidemiológico de las infecciones respiratorias por el nuevo Coronavirus (SARS-CoV.2) en población pediátrica (EPICO)"
Subestudio sobre efectos a largo plazo post-COVID-19 en población pediátrica de EPICO-AEP (EPICO-LONG)
Subestudio sobre respuesta inmunológica a la vacuna frente a SARS-CoV-2 en población pediátrica (EPICO-VAC).

El CEIm del Hospital Universitario 12 de Octubre, en su reunión del ***08/02/2022,*** tras la evaluación de los siguientes documentos modificados:

- **Protocolo v. 8 - 14 enero 2022**
- **HIP y CI padres/tutores grupo control v.8 - 14 enero 2022 (EPICO-LONG)**
- **HIP y CI padres - tutores pacientes v.8 - 14 enero 2022 (EPICO-VAC).**
- **HIP y CI participantes 12-18 años v.8. - 14 enero 2022 (EPICO-LONG)**
- **HIP y CI participantes 12-18 años (EPICO-VAC)**

Considera que:

Se han ponderado los aspectos metodológicos, éticos y legales y se recogerá la decisión adoptada en el acta correspondiente.

Que este Comité ha realizado la evaluación de la modificación, de acuerdo con lo previsto en las normas de funcionamiento interno del comité y emite un **DICTAMEN FAVORABLE**

Que el CEIm Hospital Universitario 12 de Octubre, tanto en su composición como en sus procedimientos, cumple con las normas de BPC (CPMP/ICH/135/95) y con la legislación vigente que regula su funcionamiento, y que la composición del CEIm Hospital Universitario 12 de Octubre es la indicada en el anexo I, teniendo en cuenta que en el caso de que algún miembro participe en el estudio o declare algún conflicto de interés no habrá participado en la evaluación del estudio.

Lo que firmo en Madrid, a 8 de febrero de 2022

UGALDE DIEZ DULCE MARIA - 05242157C

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Secretaria del CEIm Hospital Universitario 12 de Octubre

ANEXO I: COMPOSICIÓN DEL CEIm

Nº CEIm: 20/101

CODIGO: EPICO
TITULO: "Estudio epidemiológico de las infecciones respiratorias por el nuevo Coronavirus (SARS-CoV.2) en población pediátrica (EPICO)"
Subestudio sobre efectos a largo plazo post-COVID-19 en población pediátrica de EPICO-AEP (EPICO-LONG)
Subestudio sobre respuesta inmunológica a la vacuna frente a SARS-CoV-2 en población pediátrica (EPICO-VAC).

Dña**. MARÍA UGALDE DÍEZ,** Secretaria del Comité de Ética de Investigación Clínica del **HOSPITAL UNIVERSITARIO 12 DE OCTUBRE.**

HACE CONSTAR QUE:

1. En la reunión ordinaria celebrada el día ***08/02/2022,*** se decidió emitir el informe correspondiente al estudio de referencia.
2. El CEIm del Hospital Universitario 12 de Octubre, tanto en su composición como en sus PNTs, cumple con las normas de BPC (CPMP/ICH/135/95)
3. La composición del CEIm del Hospital Universitario 12 de Octubre en la citada fecha, era la siguiente:

PRESIDENTE	Dra. Mª del Puy Goyache Goñi	Farmacéutico Adjunto de Farmacia Hospitalaria
SECRETARIA	Dra. María Ugalde Díez	Dra. en Ciencias Biológicas
VICEPRESIDENTE	Dra. Sarahí Elizabeth Valdez Acosta	Farmacóloga Clínica
VOCALES:	Dra. Elena Puerto García Martín	Médico Cardiología
	Dr. Tycho Baumann	Médico Hematología
	Dr. Luis Manso Sánchez	Médico Oncología
	Dª Cristina Martín-Arriscado Arroba	Licenciada Estadística
	Dª Mª Luisa Albelda de la Haza	Licenciada Derecho
	Dª. Montserrat Pilas Pérez	Diplomado Universitario en Enfermería
	Dª Candelas López López	Diplomado Universitario en Enfermería
	Dr. Gonzalo Carreño Gómez Tarragona	Medico Hematología
	Dr. Jorge Adeva Alfonso	Médico Oncología
	Dr. Rafael San Juan Garrido	Médico Microbiología
	Dr. Roberto Rodríguez Jiménez	Médico Psiquiatría
	Dra. Ana Jiménez Ubieto	Médico Hematología
	Dra. Gema Ruiz Hurtado	Comisión de Investigación
	Dra. Mar Espino Hernández	Pediatra de Atención Primaria
	Dra. María del Carmen Riesco Martínez	Médico Oncología
	Dra. Mercedes Catalán González	Médico Intensivista
	Dra. Raquel Siguín Gómez	Farmacéutica Atención Primaria
	Dra. Laura Lema Roso	Médico Oncología
	Dra. Yolanda Rodríguez Gil	Médico Anatomía Patológica
	Sr. Francisco Javier Mazuecos Gómez	Trabajador Social Ayuntamiento Madrid
	Sra. Sagrario Alegre Alonso	Coordinadora AECC
	Sra. Mª Pilar Hernández Suarez	Diplomado Universitario en Enfermería
	Dra. Raquel Sopeña Sutil	Medico Urología
	Dr. David Sanchez Guzmán	Médico Atención Primaria
	Sra. Maria Teresa Garcia Morales	Ingeniero de Telecomunicaciones (Delegado Protección Datos).

Hospital Universitario La Paz
SaludMadrid
Hospital Carlos III
Hospital Cantoblanco

CONFORMIDAD DE LA DIRECCI□ N DEL CENTRO

Don José María Muñoz y Ramón, Director Médico del Hospital Universitario La Paz y vista la aprobación del Comité de Ética de la Investigación con medicamentos del Hospital Universitario La Paz

C E R T I F I C A

QUE CONOCE la propuesta presentada por el investigador Fernando Baquero Artigao del Servicio de Pediatría General del Hospital Infantil del Hospital Universitario "La Paz" para que se realice en este Centro el estudio EPA-OD titulado □**ESTUDIO DE NEUMON□AS COMUNITARIAS EN EDAD PEDI□TRICA POR STAPHYLOCOCCUS AUREUS EN ESPAÑA**□, código de protocolo: **DAA-VAN-2018-01** Versiones de Protocolo y Hojas de Información/CI aprobadas por el CEIm correspondiente, código HULP: **PI-3352**

por el investigador Fernando Baquero Artigao del Servicio de Pediatría General del Hospital Infantil del Hospital Universitario "La Paz", como investigador principal.

QUE ACEPTA la realización de dicho estudio en el Hospital Universitario La Paz.

Lo que firmo en Madrid a 6 de septiembre de 2018

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Dr. D José María Muñoz y Ramón

Hospital Universitario La Paz
SaludMadrid
Hospital Carlos III
Hospital Cantoblanco

DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS

Dª Emma Fernández de Uzquiano, Secretaria técnica del COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS del Hospital Universitario La Paz

C E R T I F I C A

Que este Comité ha evaluado la propuesta del estudio titulado: **"BACTERIEMIA POR PSEUDOMONAS AERUGINOSA RESISTENTE A CARBAPENÉMICOS EN NIÑOS: FACTORES DE RIESGO ASOCIADOS A MORTALIDAD Y PERFIL CLuNICO",** Versión 1, julio 2021, código HULP: **PI-4949.**

y considera que:

- El estudio se plantea siguiendo los requisitos legalmente establecidos, se ajusta a las normas éticas esenciales y su realización es pertinente.
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- La capacidad del investigador y sus colaboradores, y las instalaciones y medios disponibles, tal y como ha sido informado, son apropiados para llevar a cabo el estudio.

Que este Comité decidió emitir **DICTAMEN FAVORABLE** el día **07/10/2021 (acta n° 18/2021)** y acepta que dicho estudio sea realizado por la Dra. Nathalia Esther Gerig Rodríguez, del Servicio de Pediatría, del Hospital Universitario La Paz, como investigadora principal.

Que en dicha reunión se cumplieron los requisitos establecidos en la legislación vigente – Real Decreto 1090/2015 – para que la decisión del citado CEIm sea válida.

Que el CEIm del Hospital Universitario La Paz tanto en su composición como en sus procedimientos, cumple con las normas de BPC (CPMP/ICH/135/95) y con la legislación vigente que regula su funcionamiento, y que la composición del CEIm del Hospital Universitario La Paz es la indicada en el anexo I, teniendo en cuenta que en el caso de que algún miembro participe en el estudio o declare algún conflicto de interés no habrá participado en la evaluación ni en el dictamen de la solicitud de autorización del estudio.

Lo que firmo en Madrid a 07 de octubre de 2021

Firmado: Dª Emma Fernández de Uzquiano
Secretaria técnica del CEIm

Firmado digitalmente por: FERNANDEZ DE UZQUIANO MARIA EMMA
Fecha: 2021.10.08 14:09

Hospital Universitario La Paz
Hospital Carlos III
Hospital Cantoblanco

Anexo I

COMPOSICION DEL CEIm

Presidente **Cardiología**	**Dra. Almudena Castro Conde**
Vicepresidente **Farmacología Clínica** **Representante de la Comisi□n de Investigaci□n**	**Dr. Jes□s Frías Iniesta**
Secretaria Técnica	**Dra. Emma Fernández de Uzquiano**
Vocales	
Medicina Intensiva	**Dr. José Manuel A□□n Elizalde**
Medicina Interna	**Dr. José Ignacio Bernardino**
Laboratorio Hematología-IdiPAZ	**Dra. Nora Butta Coll**
Pediatría y Neonatología	**Dr. Fernando Caba□as González**
Servicio de Asesoría Jurídica **PDP. Miembro no sanitario/licenciado en Derecho**	**Dr. Filiberto Chulia Fernández**
Analista de Datos- Bioestadística	**Dra. Mariana Díaz Almir□n**
Ginecología Y Obstetricia	**Dra. M□Dolores Diestro Tejeda**
Neumología	**Dr. Jaime Fernández-Bujarrabal Villoslada**
Urología **Representante del Comité de Ética Asistencial**	**Dra. M□Justa García-Matres**
Hematología	**Dra. Mercedes Gasior Kabat**
Dermatología	**Dr. Pedro Herranz Pinto**
Medicina Interna	**Dr. Carlos Lahoz Rallo**
Representante de los intereses de los pacientes y miembro no sanitario y ajeno a la instituci□n.	**D. Evaristo Moliné Jorques**
Farmacéutica Especialista en Análisis Clínicos	**Dra. Paloma Oliver Sáez**
Farmacéutica de Atenci□n Primaria	**Dra. Eva Prieto Utiel**
Oncología Médica	**Dra. Nuria Rodríguez Salas**
Aparato Digestivo	**Dra. Miriam Romero Portales**
Nefrología **Diplomada en Enfermería**	**D□. Filomena Trocoli González**
Cirugía Pediátrica	**Dra. Alejandra Vilanova Sánchez**
Farmacia Hospitalaria	**Dra. Elena Villama□an Bueno**
Psiquiatría	**Dra. Rosa Villanueva Pe□a**

DAVID AGUILERA ALONSO

Madrid, 2024