Temocillin versus carbapenems for bacteraemia due to third-generation cephalosporin-resistant Enterobacterales in Spain (ASTARTÉ): a multicentre, phase 3, open-label, non-inferiority, randomised clinical trial

*Francesco Cogliati Dezza, Lydia Barrera Pulido, Irene Borreguero Borreguero, Fernando Docobo Pérez, Virginia Palomo Jiménez, Sandra de la Rosa Riestra, José María Bravo-Ferrer, Zaira Raquel Palacios-Baena, Miguel Ángel López Zuñiga, Fernando Cobo, Joan Gómez-Junyent, Juan P Horcajada, Esperanza Merino, Mónica Parra, Joaquín López-Contreras, Alba Rivera, Dolores Sousa Regueiro, Martín Pampín Garcia, Salvador López Cardenas, María Carmen Gómez Sánchez, Inés Pérez Camacho, Sergio Manuel Martín Ramos, Eva León Jiménez, Ana Isabel Aller García, M Teresa Pérez-Rodríguez, Adrián Sousa, Maria Siller Ruiz, Francisco Arnaiz de las Revillas Almajano, Laura Gisbert Pérez, Josune Goikoetxea Agirre, Ángela Cano, Francisco Javier Martínez-Marcos, María José García País, Rosa Escudero Sánchez, Sofía de la Villa, José Ramón Yuste Ara, María Ángeles Esteban-Moreno, Andrés Ruiz-Sancho, Marc Pedrosa Aragón, Jorge Alba Fernández, Ana María Barrios Blandino, Helem Haydeé Vilchez-Rueda, Rocío Álvarez-Marín, Alberto Romero Palacios, Elisa García Vázquez, Enrique Nuño Álvarez, Clara Rosso-Fernández, Belén Gutiérrez-Gutiérrez, Álvaro Pascual, Lorena López-Cerero, Jesús Rodríguez-Baño, for the ASTARTÉ-GEIRAS study group**

Summary

Background Alternatives to carbapenems for the treatment of third-generation cephalosporin-resistant Enterobacterales (3GCR-E) are urgently needed to reduce the selection pressure posed by these drugs. Temocillin is a neglected narrow-spectrum β-lactam. The aim of the trial was to investigate if temocillin is non-inferior to carbapenems for the targeted treatment of bacteraemia due to 3GCR-E.

Methods This multicentre, phase 3, open-label, non-inferiority, randomised, pragmatic, investigator-initiated clinical trial was conducted in 29 Spanish hospitals. We randomly assigned patients with bacteraemia caused by 3GCR-E to receive intravenous temocillin (2 g every 8 h) or meropenem (1 g every 8 h; or ertapenem [1 g per day] if appropriate). Patients aged 18 years or older were eligible if they had monomicrobial bacteraemia due to any 3GCR-E that was susceptible to meropenem and temocillin and treatment for at least 4 days with an active intravenous drug was considered necessary. Randomisation (1:1) was stratified according to previous active drug and to source of infection; no blocks were used. The primary endpoint was clinical success (clinical cure, no need to stop or change the study drug because of adverse event or clinical failure, absence of recurrence, and survival by day 28) in all randomly assigned patients who received at least one dose of a study drug (modified intention-to-treat population [mITT]). Adverse events were assessed in the mITT population. No missing data were reported. A 10% non-inferiority margin was established. The trial was registered in ClinicalTrials.gov (NCT04478721) and is complete and closed to new participants.

Findings 334 eligible patients were enrolled between Dec 15, 2020, and Nov 29, 2024, of whom 328 were included in the mITT population (163 assigned temocillin and 165 assigned carbapenems). In 328 participants, the median age was 72 years (IQR 65–80), 106 (32%) were female, 222 (68%) were male, and the median Charlson Comorbidity Index was 2 (IQR 0–4). In the mITT population, clinical success occurred in 120 (74%) of 163 patients assigned temocillin and 121 (73%) of 165 patients assigned carbapenems (difference 0·3% [95% CI −7·7 to ∞]; non-inferiority p=0·017). Serious adverse events were reported in 31 (19%) of 163 patients assigned temocillin and 35 (24%) of 165 patients assigned carbapenems.

Interpretation In patients with bacteraemia caused by 3GCR-E, temocillin was non-inferior to carbapenems as targeted treatment. These findings support the use of temocillin as an effective and safe alternative to carbapenems in this setting.

Funding Instituto de Salud Carlos III.

Published **Online** July 9, 2026 https://doi.org/10.1016/S0140-6736(26)00760-9

See **Online/Comment** https://doi.org/10.1016/S0140-6736(26)01334-6

*Members of the ASTARTÉ–GEIRAS study group are listed at the end of the Article

Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena and Departamento de Medicina, Universidad de Sevilla, Instituto de Biomedicina de Sevilla(IBiS)/CSIC, Seville, Spain (F Cogliati Dezza MD, L Barrera Pulido PhD, V Palomo Jiménez CNA, S de la Rosa Riestra PhD, J M Bravo-Ferrer MD, Z R Palacios-Baena PhD, B Gutiérrez-Gutiérrez PhD, Prof J Rodríguez-Baño PhD); **Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy** (F Cogliati Dezza); **CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain** (F Cogliati Dezza, L Barrera Pulido, F Docobo Pérez PhD, V Palomo Jiménez, S de la Rosa Riestra, J M Bravo-Ferrer, Z R Palacios-Baena, J P Horcajada PhD, M Siller Ruiz MD, F Arnaiz de las Revillas Almajano PhD, Á Cano PhD, R Escudero Sánchez MD,

Introduction

The rise of multidrug-resistant bacteria has become a primary threat to global health. Third-generation cephalosporin-resistant Enterobacterales (3GCR-E) are a leading cause of mortality attributable to and associated with antimicrobial-resistant microorganisms,[1] and are

R Álvarez-Marín PhD, B Gutiérrez-Gutiérrez, Prof Á Pascual PhD, L López-Cerero PhD, Prof J Rodríguez-Baño); **Unidad de Investigación Clínica y Apoyo a Ensayos Clínicos (UICEC-HUVR), Clinical Trial Unit (CTU-HUVR), Hospitales Universitarios Virgen Macarena y Virgen del Rocío, Seville, Spain** (I Borreguero Borreguero MScP, C Rosso-Fernández PhD); **Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena, Departamento de Microbiología, Facultad de Medicina, Universidad de Sevilla, Instituto de Biomedicina de Sevilla/CSIC, Seville, Spain** (F Docobo Pérez, Prof Á Pascual, L López-Cerero); **Infectious Diseases Unit, Hospital Universitario Virgen de las Nieves, Granada, Spain** (M Á López Zuñiga PhD); **Servicio de Microbiología, Hospital Universitario Virgen de las Nieves, Granada, Spain** (F Cobo PhD); **Department of Infectious Diseases, Hospital del Mar, Hospital del Mar Research Institute, Universitat Pompeu Fabra (UPF), Barcelona, Spain** (J Gómez-Junyent PhD, J P Horcajada); **Unit of Infectious Diseases, Dr Balmis University General Hospital, Alicante, Spain** (E Merino PhD, M Parra MD); **Institute for Health and Biomedical Research (ISABIAL), Alicante, Spain** (E Merino); **Microbiology Service, Dr Balmis University General Hospital, Alicante, Spain** (M Parra); **Infectious Diseases Division, Hospital de la Santa Creu i Sant Pau, Institut Recerca Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain** (J López-Contreras PhD); **Microbiology Department, Hospital de la Santa Creu i Sant Pau, Institut Recerca Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain** (A Rivera PhD); **Infectious Diseases Division, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain** (D S Regueiro PhD, M Pampín Garcia PharmD); **Unidad Clínica de Enfermedades Infecciosas y Microbiología Clínica, Hospital**

Research in context

Evidence before this study

Global spread of third-generation cephalosporin-resistant Enterobacterales (3GCR-E) has led to a substantial increase in carbapenem consumption, as they are considered the drugs of choice, which is fuelling the spread of carbapenem-resistant organisms. We searched PubMed from Jan 1, 1980, to July 31, 2025, for studies estimating temocillin efficacy in infections caused by 3GCR-E in humans. The search terms used were temocillin AND (ESBL OR cephalosporin-resistant OR AmpC OR cefotaxime-resistant OR ceftriaxone-resistant OR ceftazidime-resistant) AND (outcome OR cure OR failure OR mortality). No language limits were applied. We identified several observational studies evaluating temocillin efficacy in different types of infections caused by 3GCR-E, but no randomised controlled trial for these pathogens. Two previous trials have investigated potential alternatives to carbapenems in invasive infections caused by 3GCR-E, including piperacillin–tazobactam and fosfomycin; both did not show non-inferiority compared with meropenem. Therefore, high-level evidence supporting appropriate carbapenem-sparing alternatives for bacteraemia due to 3GCR-E are needed. Temocillin, due to its in vitro activity against these bacteria, is a potential candidate.

Added value of this study

This study is the first randomised controlled trial investigating the efficacy and safety of temocillin compared with carbapenems in bacteraemic infections caused by 3GCR-E. Temocillin was shown to be non-inferior in efficacy to carbapenems. No differences were observed in the rate of severe adverse events between the two treatment groups. Therefore, an alternative antibiotic to carbapenems has been shown for the first time in these infections.

Implications of all the available evidence

These results support the use of temocillin as an effective and safe alternative to carbapenems in bacteraemic infections caused by 3GCR-E. As temocillin is a narrow-spectrum agent, its use in these infections instead of carbapenems might contribute to reduce the spread of resistance to carbapenems.

considered of critical priority for drugs research by WHO.[2] Carbapenems are recommended as the drugs of choice for the treatment of invasive infections caused by 3GCR-E,[3,4] and, therefore, their consumption has increased, fuelling the spread of carbapenem-resistant organisms worldwide. Alternatives to carbapenems for 3GCR-E are urgently needed to spare their use, but no drug has been shown to be non-inferior to carbapenems so far. As such, there is an increasing interest in old agents active against 3GCR-E.[5,6]

Temocillin is a semi-synthetic β-lactam antibiotic derivative of ticarcillin,[7] which is only approved in a few countries. Temocillin is resistant to hydrolysis by different β-lactamases, and specifically by extended-spectrum β-lactamases (ESBLs) and AmpC enzymes;[8] it might retain some activity against class A carbapenemases (eg, *Klebsiella pneumoniae* carbapenemases), but it is generally inactive against class D and class B enzymes.[6] No activity against Gram-positive bacteria, anaerobes, or non-fermenting Gram-negative bacteria has been reported (except *Burkholderia cepacia* complex). Therefore, temocillin could be an attractive potential carbapenem-sparing alternative for 3GCR-E.[5,6] However, no randomised trial has been performed for these infections. We conducted the ASTARTÉ trial to test the hypothesis that temocillin has non-inferior efficacy to carbapenems as targeted treatment for patients with bloodstream infection due to 3GCR-E.

Methods

Study design

ASTARTÉ is a multicentre, phase 3, open-label, non-inferiority, randomised, pragmatic, investigator-initiated clinical trial in patients with bloodstream infection caused by 3GCR-E. The trial was performed in 29 Spanish hospitals. The study was approved by the Seville province Ethic Committee on Clinical Research (reference 10/2020). The trial was registered in ClinicalTrials.gov (NCT04478721) and is complete and closed to new participants. Patients were not involved in the design, conduct, or reporting of the study. The study protocol was published previously,[9] and is available together with the statistical analysis plan in appendix 1. Appendix 2 contains the summary study scheme (p 5). The results are reported in accordance with the updated CONSORT statement (appendix 2 pp 23–24).[10]

Participants

Adult patients aged 18 years or older with monomicrobial bloodstream infection due to any Enterobacterales were eligible for enrolment if they fulfilled all the following criteria: the isolate was resistant to cefotaxime (minimum inhibitory concentration [MIC] >2 mg/L), ceftriaxone (MIC >2 mg/L), or ceftazidime (MIC >4 mg/L) and susceptible to meropenem (MIC ≤2 mg/L) and temocillin (MIC ≤8mg/L or MIC ≤16mg/L in case of bloodstream infection from urinary source); and treatment for at least 4 days with an active intravenous drug was considered necessary. Exclusion criteria included: pregnancy or breastfeeding, patients under palliative care or life expectancy less than 30 days, allergy to β-lactam drugs, polymicrobial bloodstream infection, recruitment delayed for more than 48 h after susceptibility data were available, administration of in vitro active drugs for 96 h or more before randomisation, infections typically needing more than 14 days of therapy (eg, endocarditis), meningitis, and patients receiving peritoneal dialysis or continuous haemofiltration (appendix 2 p 2). Eligible participants were detected by daily review of blood

cultures results at the microbiology laboratory at each site. Written informed consent was obtained from all participants. Sex (male or female) and ethnicity data were reported by the local investigators by asking the patients.

Randomisation and masking

Recruited patients were randomly assigned 1:1 to receive temocillin or a carbapenem (meropenem or ertapenem if appropriate). Randomisation was stratified according to previous receipt of in vitro active drug and to source of bloodstream infection (urinary or other); no blocks were used. Randomisation was performed centrally by a web-based automated system integrated in the electronic case report form, which was activated by the local investigator once participant eligibility was confirmed and informed consent obtained. The randomisation sequence was generated by an independent statistician who had no further involvement in the trial and was not accessible to investigators. Endpoints were checked by two investigators (FCD and LBP) who were masked to allocation; otherwise, there was no masking.

Procedures

Patients in the experimental group received 2 g of temocillin intravenously every 8 h in a 30–40 min infusion, and patients in the control group received 1 g of meropenem intravenously every 8 h in a 15–30 min infusion delivered by the hospital pharmacy at each hospital. Ertapenem 1 g per day could be used instead of meropenem if deemed appropriate by the local investigator. Dosing was adjusted in patients with renal insufficiency according to drugs labels (appendix 2 p 3). Following usual clinical practice, switch to an in vitro active oral drug was allowed after 4 days of intravenous therapy from randomisation with one of the following regimens: ciprofloxacin, 500 mg every 12 h; trimethoprim–sulfamethoxazole, 160/800 mg every 12 h; amoxicillin–clavulanic acid, 875/125 mg every 8 h; and, in case of bloodstream infection from a urinary source, fosfomycin trometamol 3 g every 24 h the first 3 days, then 3 g every 48 h.[11] Suggested duration of total active therapy was 7–14 days, with a strong recommendation for 7 days in case of early clinical response and source control if needed. Outpatient parenteral antimicrobial therapy was allowed. Metronidazole, vancomycin, or linezolid could be added if deemed necessary for monomicrobial bacteraemia with a potentially polymicrobial source (eg, intra-abdominal infection). Patients were followed up for 28 days after randomisation; visits were performed on days 0 (randomisation), 1, 3, end of treatment, test of cure, and day 28). Full details of the assessments done during follow-up are in appendix 1 (pp 32–34).

Blood cultures at baseline were processed at local laboratories using standard microbiological procedures. Bacteria identified as Enterobacterales were subcultured on CHROMagar ESBL (BioMerieux, Marcy l'Étoile, France) for rapid phenotypic detection of resistance to third-generation cephalosporins. Isolates growing in this media were tested for temocillin susceptibility by gradient strip assay (E-test, BioMérieux, Marcy l'Étoile, France). Isolates with MIC value over 8 mg/L were considered resistant based on the breakpoint recommended by the British Society of Antimicrobial Chemotherapy (BSAC),[12] the only one available when the study protocol was written; for a urinary tract source of infection, resistance was afterwards defined as MIC over 16 mg/L based on the updated breakpoint established by European Committee on Antimicrobial Susceptibility Testing (EUCAST) for urinary tract infection (UTI) sources.[13] The breakpoints for cephalosporin and carbapenems in the eligibility criteria were defined based on those established by EUCAST.[13] Isolates from recruited patients were preserved and sent to Hospital Universitario Virgen Macarena, where identification was checked using matrix-assisted laser desorption ionisation time of flight and antimicrobial susceptibility testing by Microscan NMRD2 (Beckman Coulter, Barcelona, Spain), except for temocillin, which was studied by broth microdilution assay. All isolates were sequenced using an Illumina MiSeq platform (Illumina, Madrid, Spain) and a Nextera Flex DNA sample preparation kit (Illumina, Madrid, Spain).

Outcomes

The primary endpoint was clinical success, defined as all of the following: clinical cure (resolution of all new signs and symptoms related to infection at the test of cure [TOC]); no need to stop or change the study drug because of adverse event or clinical failure (not reaching clinical cure); no recurrence until day 28 (bacteraemia due to same organism with similar susceptibility profile); and survival at day 28. TOC was performed 7–10 days after the last day of antibiotic therapy. Classification of patients as clinically cured or not was checked in all patients by two masked investigators (FCD and LBP) against the individual assessment of disappearance of all specific new signs and symptoms present at baseline.

Secondary endpoints were individual components of the primary endpoint, reinfections until day 28 (ie, bacteraemia caused by a different bacteria), microbiological cure, length of hospital stay, change in Sequential Organ Failure Assessment score (SOFA) score from baseline to TOC, and adverse events at day 28. Change in Barthel scale was also measured in patients older than 70 years (results not provided here). Investigators were instructed to report all adverse events according to standard criteria using a dedicated form in the electronic case report form. The potential relationship between adverse events and study drugs, as assessed by the investigators, was recorded, and their severity was classified as mild, moderate, or severe. Adverse events were considered serious if life-threatening, causing death or new hospitalisation, or lengthening hospital stay.

Universitario de Jerez, Departamento de Medicina y Cirugía, Universidad de Cádiz, Instituto de Investigación e Innovación Biomédica de Cádiz (INiBICA), Cádiz, Spain (S López Cardenas PhD); **Unidad Clínica de Enfermedades Infecciosas y Microbiología Clínica, Hospital Universitario de Jerez, Instituto de Investigación e Innovación Biomédica de Cádiz (INiBICA), Cádiz, Spain** (M C Gómez Sánchez MD); **Servicio de Enfermedades Infecciosas, Hospital Regional Universitario de Málaga, IBIMA, Málaga, Spain** (I Pérez Camacho MD); **Servicio de Microbiología, Hospital Regional Universitario de Málaga, Málaga, Spain** (S M Martín Ramos MD); **Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario de Valme, Seville, Spain** (E León Jiménez PhD, A I A García PhD); **Unidad de Infecciosas, Hospital Álvaro Cunqueiro, Galicia Sur Health Research Institute, Vigo, Spain** (M T Pérez-Rodríguez PhD, A Sousa MD); **Servicio de Microbiologia, Hospital Universitario Marqués de Valdecilla-IDIVAL, Universidad de Cantabria, Cantabria, Spain** (M Siller Ruiz, F A de las Revillas Almajano); **Infectious Diseases Department, Hospital Universitari Mútua de Terrassa, Barcelona, Spain** (L Gisbert Pérez MD); **Servicio de Enfermedades Infecciosas Hospital Universitario de Cruces, Bizkaia, Spain** (J Goikoetxea Agirre PhD); **Servicio de Enfermedades Infecciosas, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Hospital Universitario Reina Sofía-Universidad de Córdoba, Córdoba, Spain** (Á Cano); **Unidad Clínica de Enfermedades Infecciosas Hospital Universitario Juan Ramón Jiménez, Huelva, Spain** (F J Martínez-Marcos PhD); **Unidad infecciosas Hospital Universitario de Lugo, Lugo, Spain** (M J García País PhD); **Servicio de Enfermedades Infecciosas, Hospital Ramón y Cajal, Instituto Ramón y Cajal de investigación sanitaria IRYCIS, Madrid, Spain** (R Escudero Sánchez); **Clinical**

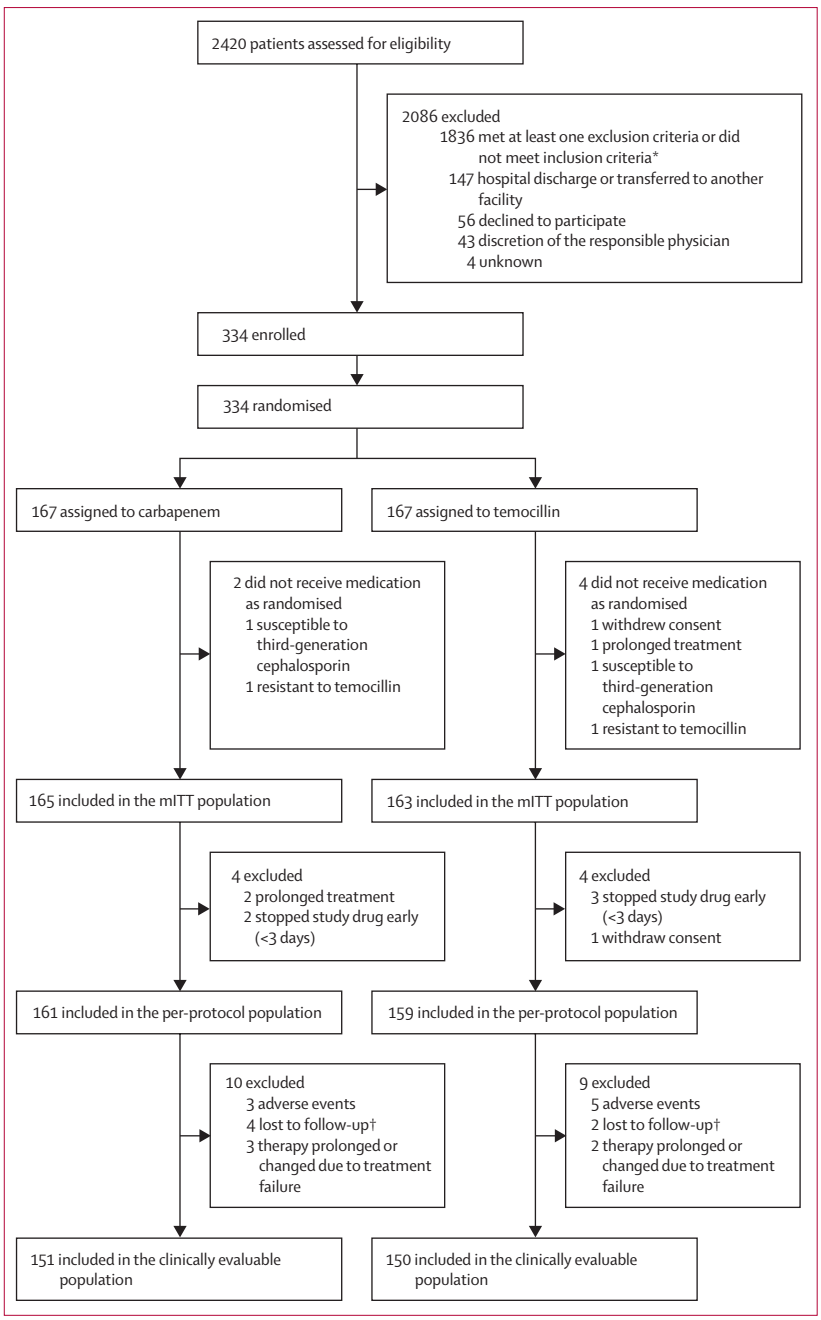

Figure 1: **Profile of the ASTARTÉ trial**
*More detailed data on exclusion criteria are in appendix 2 (p 2). †All were alive at day 28 but were lost to follow-up because they did not attend at least two consecutive visits for any reason. mITT=modified intention-to-treat.

Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain (S de la Villa MD)**; Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain** (S de la Villa)**; Division of**

Statistical analysis

Based on previous trials providing data for clinical success and mortality in Enterobacterales bacteraemia,[14,15] we estimated an 85% success rate in both groups. Overall, 334 patients (167 per group) were needed to reject non-inferiority of temocillin with 10% non-inferiority margin, 80% power, 5% one-sided significance level, and 5% of missing patients. The 10% non-inferiority margin was chosen following previous trials in Gram-negative bacteraemia using composite outcomes,[16] and is also recommended by the European Medicines Agency for the most common sources of bloodstream infection with similar endpoints.[17]

Differences in proportions were calculated with one-sided 95% CIs for the primary and secondary categorical endpoints using the Miettinen–Nurminen method; the Mann–Whitney *U* test was used for continuous variables. No missing data were reported for primary or secondary outcomes in patients who attended scheduled visits according to the protocol. As per intention-to-treat principles, patients not evaluated for whatever reason were classified as having a negative outcome.

The primary endpoint was analysed in the modified intention-to-treat population (mITT), formed of randomly assigned patients who received at least one dose of a study drug. It was also examined in the per-protocol population (patients who received at least 3 days of study drugs), clinically evaluable population (patients evaluated at TOC), and pre-determined specific subgroups, including bloodstream infection source, age groups, micro-organisms, temocillin MIC, appropriate empirical therapy, sepsis, immunosuppressive therapy, and use of sequential oral therapy. Adverse events and secondary outcomes were assessed in the mITT population.

Additionally, multivariate analysis for the primary outcome was performed to control for residual confounding using logistic regression; the model was based on a previously published direct acyclic graph.[18] Also, a generalised linear mixed model was performed including sites as random effect to account for potential centre effect (appendix 2 p 4). Finally, we also performed a desirability of outcome ranking (DOOR) in the mITT population; patients' outcomes were classified according to six mutually exclusive hierarchical levels in descending order of desirability (appendix 2 p 4). The ranks were derived from an appraisal of published literature followed by consensus among the ASTARTÉ coordination group during the protocol design phase. The probability of patients in the temocillin group having a better DOOR score than those in the control group was calculated (appendix 2 p 4). Data were analysed using SPSS Statistics version 29. All patients' data collected were monitored and verified against the original data sources. An external independent data safety monitoring board reviewed three interim analyses, recommending continuing with recruitment in all of them (appendix 2 p 4).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Temocillin (n=163)	Carbapenem* (n=165)
Demographics		
Age, years	74 (65–82)	71 (66–77)
Sex		
Female	59 (36%)	47 (28%)
Male	104 (64%)	118 (72%)
Ethnicity		
Western Europe	146 (90%)	144 (87%)
Latino	15 (9%)	17 (10%)
Other	2 (1%)	4 (2%)
Underlying conditions		
Charlson Comorbidity Index	2 (1–4)	2 (0–3)
Type 1 or type 2 diabetes	55 (34%)	35 (21%)
Chronic heart failure	28 (17%)	30 (18%)
Chronic pulmonary disease	20 (12%)	21 (13%)
Solid cancer	34 (21%)	30 (18%)
Haematological cancer	6 (4%)	6 (4%)
Chronic renal disease, moderate–severe	30 (18%)	27 (16%)
Chronic liver disease, mild–severe	12 (7%)	11 (7%)
Immunosuppressive therapy	40 (25%)	37 (22%)
Fully or partial dependent for basic activities	59 (36%)	51 (31%)
Barthel score (only participants aged 70 years or older)†	65 (30–95)	90 (48–100)
Surgery in past month	26 (16%)	24 (15%)
Invasive procedure in past week	74 (45%)	80 (48%)
Dialysis	2 (1%)	9 (5%)
Infection features		
Nosocomial acquisition	28 (17%)	38 (23%)
Health care-associated acquisition	72 (44%)	68 (41%)
Community acquisition	63 (39%)	59 (36%)
Source of bacteraemia		
Urinary tract	123 (75%)	123 (75%)
Biliary tract	17 (10%)	15 (9%)
Intra-abdominal, no biliary	8 (5%)	9 (5%)
Catheter-related	8 (5%)	6 (4%)
Respiratory tract	2 (1%)	3 (2%)
Unknown	4 (2%)	5 (3%)
Other	1 (1%)	4 (2%)
Pitt score on day of blood culture	1 (0–2)	1 (0–2)
SOFA score on day of blood culture	2 (1–3)	2 (1–3)
Days from blood culture to randomisation‡	3 (2–3)	3 (2–3)
(Continued from previous column)		
Cause of infection		
Escherichia coli	118 (72%)	109 (66%)
Klebsiella pneumoniae	33 (20%)	42 (25%)
Other Enterobacterales	12 (7%)	14 (8%)
ESBL-producing bacteria§	148/158 (94%)	145/158 (92%)
AmpC-producing bacteria§	4/158 (3%)	6/158 (4%)
Treatment variables		
First drug administered	103 (63%)	103 (62%)
Carbapenem as first drug administered	61 (37%)	60 (36%)
Any drug administered before randomisation¶	154 (94%)	153 (93%)
Carbapenem, at least one dose	137 (84%)	133 (81%)
Duration of therapy before randomisation, days	2 (1–3)	2 (1–3)
Duration of intravenous treatment with study drug, days	6 (4–8)	6 (4–8)
Duration of oral therapy in patients receiving oral drugs, days	4 (2–6)	4 (2–6)
Total therapy from randomisation, days	8 (6–10)	7 (6–11)
Switched to oral treatment	60 (37%)	64 (39%)
Ciprofloxacin	16 (10%)	17 (10%)
Cotrimoxazole	19 (12%)	22 (13%)
Amoxicillin–clavulanic acid	14 (9%)	22 (13%)
Fosfomycin	11 (7%)	3 (2%)

Data are median (IQR), n (%), or n/N (%). SOFA=Sequential Organ Failure Assessment score. ESBL=extended-spectrum β-lactamase. *99 patients received meropenem and 66 patients received ertapenem. †The limit for recruitment was 2 days after susceptibility results were available; susceptibility results were typically available 1–2 days after blood cultures were drawn. ‡Subset of patients aged 70 years or older: temocillin n=92 and carbapenems n=103. §Five isolates were not available for the characterisation of the resistance mechanisms in the temocillin group and seven isolates were not available in the carbapenem group. ¶Due to use of rapid phenotypic detection of cephalosporin resistance.

Table 1: **Baseline and general characteristics in the modified intention-to-treat population**

Results

Overall, 2420 patients with Enterobacterales bacteraemia were screened at participating sites, between Dec 15, 2020, and Nov 29, 2024, of whom 334 were eligible and randomly assigned (167 in each group). Among screened patients, 464 were excluded because of having a temocillin-resistant isolate. Six (2%) randomly assigned patients were not included in the mITT population: five because of wrong inclusion (two had a cephalosporins-susceptible Enterobacterales, two had a temocillin-resistant isolate, and one had an infection requiring prolonged treatment) and one who withdrew consent immediately after randomisation. Therefore, the mITT population included 163 patients in the temocillin group and 165 in the carbapenem group, of whom 99 received meropenem and 66 received ertapenem (figure 1 and appendix 2 p 10).

Baseline characteristics of the patients were balanced between the two groups (table 1). In 328 participants, the median age was 72 years (IQR 65–80), 106 (32%) were female, 222 (68%) were male, and the median Charlson Comorbidity Index was 2 (IQR 0–4). The most frequent comorbidities were type 1 or type 2 diabetes (90 patients [27%]) and solid cancer (64 patients [20%]); 77 (23%) patients were receiving immunosuppressive therapy. Barthel score, measured in patients older than

Infectious Diseases, Clínica Universidad de Navarra, Pamplona, Spain (J R Yuste Ara PhD); **Unidad de Enfermedades Infecciosas, Hospital Universitario Torrecárdenas, Almería, Spain** (M Á Esteban-Moreno MD); **Servicio de Enfermedades Infecciosas, Hospital Universitario Clínico San Cecilio, Granada, Spain** (A Ruiz-Sancho PhD); **Consorcio Sanitari Parc Taulí, Barcelona, Spain** (M P Aragón MD); **Departamento de Enfermedades Infecciosas, Hospital San Pedro, Logroño, Spain** (J A Fernández PhD); **Sección de Enfermedades Infecciosas, Hospital Universitario de La Princesa, Madrid, Spain** (A M Barrios Blandino MD); **Infectious Diseases Unit, Internal Medicine Department, Hospital Universitari Son Espases, Fundació Institut d'Investigació Sanitària Illes Balears (IdISBa), Palma De Mallorca, Spain** (H H Vilchez-Rueda MD); **Clinical Unit of Infectious Diseases, Microbiology and Parasitology, Instituto de Biomedicina de Seville (IBiS), Virgen del Rocío University Hospital/CSIC/University of Seville, Seville, Spain** (R Álvarez-Marín); **Unidad de Enfermedades Infecciosas, Hospital Universitario Puerto Real, Instituto de investigación biomédica e innovación de Cádiz (INIBICA), Cádiz, Spain** (A Romero Palacios PhD); **Unidad de Enfermedades Infecciosas, Hospital Clínico Universitario Virgen de la Arrixaca, IMIB, Facultad Medicina, Universidad Murcia, Murcia, Spain** (E García Vázquez PhD); **Unidad de Enfermedades Infecciosas Hospital Universitario Virgen de la Victoria, Málaga, Spain** (E Nuño Álvarez MD)

Correspondence to:
Prof Jesús Rodríguez Baño, Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena and Departamento de Medicina, Universidad de Sevilla, Instituto de Biomedicina de Sevilla(IBiS)/CSIC, Seville 41071, Spain
jesusrb@us.es

See **Online** for appendices 1 and 2

	Temocillin (n=163)	Carbapenem (n=165)	Difference (one-sided 95% CI)	One-sided p value*
Primary outcome				
Clinical success	120 (74%)	121 (73%)	0·3 (–7·7 to ∞)	0·017
Components of the primary outcome and secondary outcomes				
Clinical cure	130 (80%)	135 (82%)	–2·0 (–9·2 to ∞)	0·032
Stop or change study drug for any reason	10 (6%)	8 (5%)	1·3 (–∞ to 5·4)	0·0016
Recurrence until day 28	6 (4%)	10 (6%)	–2·4 (–∞ to 1·5)	<0·0001
Death, any cause at day 28	4 (2%)	6 (4%)	–1·2 (–∞ to 1·9)	<0·0001
Other outcomes				
Microbiological cure (only urinary tract infection) at TOC	37/82 (45%)	35/81 (43%)	1·9 (–10·9 to ∞)	0·063
Changes in SOFA score†	–1·4 (–1·7)	–1·2 (–1·5)	0·2 (–9·1 to ∞)	<0·0001
Reinfection until day 28	2 (1%)	2 (1%)	0·0 (–∞ to 2·0)	<0·0001
Length of hospital stay‡, days	8·9 (8·5)	9·7 (10·6)	–0·8 (–∞ to 9·5)	<0·0001

Data are n (%) or mean (SD), unless otherwise stated. TOC=test of cure. SOFA=Sequential Organ Failure Assessment score. *Non-inferiority p value. †Difference between SOFA score at blood culture day and SOFA score on TOC, data available for 146 patients receiving temocillin and 148 patients receiving carbapenem. ‡Time from inclusion to discharge, data available for 136 patients receiving temocillin and 132 patients receiving carbapenem.

Table 2: **Primary and secondary outcomes in the modified intention-to-treat population**

70 years, was lower in the temocillin group than the carbapenem group (median 65 [IQR 30–95] *vs* 90 [48–100]). The most frequent source of bloodstream infection in 328 total participants was urinary tract (226 patients [69%]), followed by biliary tract (32 patients [10%]). The most common Enterobacterales were *Escherichia coli* (227 patients [69%]) and *K pneumoniae* (75 patients [23%]); in total, 294 (90%) patients had infections caused by ESBL-producing bacteria (appendix 2 p 8). The first antibiotic treatment administered empirically was active against 3GCR-E in 206 patients (63%), but an additional 101 patients (31%) received an active drug later based on rapid microbiological results. Overall, the first empirical drug was active against the 3CGR-E in 103 (63·2%) of 163 participants in the temocillin group and 103 (62%) of 165 participants in the carbapenems group. 154 (94%) of 163 participants in the temocillin group and 153 (93%) of 165 participants in the carbapenems group received at least one dose of an active drug following the results of rapid tests, before randomisation. Median duration of targeted treatment was 7 days (IQR 6–10), and 124 (38%) of 328 patients underwent sequential oral therapy.

In the mITT population, clinical success occurred in 120 (74%) of 163 participants in the temocillin group and 121 (73%) of 165 participants in the carbapenem group (absolute difference 0·3 percentage points [one-sided 95% CI –7·7 to ∞], non-inferiority p=0·017; table 2, figure 2), demonstrating the non-inferiority of temocillin. The reasons for not reaching clinical success in both groups are listed in appendix 2 (p 9). No differences in terms of clinical success were observed between patients receiving meropenem and ertapenem in the carbapenem group (appendix 2 p 10). The results were similar in the per-protocol population (difference 1·0 [95% CI –7·0 to ∞], non-inferiority p=0·012) and in the clinically evaluable population (difference 0·5 [95% CI –8·5 to ∞], non-inferiority p=0·012; figure 2 and appendix 2 p 11).

The mortality rate at day 28 was 2% (four of 163 patients) in the temocillin group and 4% (six of 165 patients) in the carbapenems group (difference –1·2 [95% CI –∞ to 1·9]; table 2). The clinical cure rate was 80% (130 of 163 patients) with temocillin and 82% (135 of 165 patients) with carbapenems (difference –2·0 [95% CI –9·2 to ∞]). Recurrence at day 28 occurred in six (4%) of 163 patients assigned temocillin and ten (6%) of 165 patients assigned carbapenems (difference –2·4 [95% CI –∞ to 1·5]). The study drug had to be stopped or changed for any reason in ten (6%) of 163 patients assigned temocillin and eight (5%) of 165 patients assigned carbapenems (difference 1·3 [95% CI –∞ to 5·4]). No significant differences were found in microbiological cure in patients with urinary tract bloodstream infection (difference 1·9 [95% CI –10·9 to ∞]), change in SOFA score from baseline to TOC (mean difference 0·2 [95% CI –9·1 to ∞]), and reinfection rates (difference 0·0 [95% CI –∞ to 2·0]). Mean hospital stay was 8·9 (SD 8·5) in patients receiving temocillin and 9·7 (10·6) in patients receiving carbapenems (mean difference –0·8 [95% CI –∞ to 9·5]; table 2). Analysis of the secondary outcomes in the per-protocol and clinically evaluable populations was consistent with these results (appendix 2 p 11).

Results in prespecified subgroups were mostly consistent with those obtained in the whole mITT population (figure 2 and appendix 2 p 12). Multivariate analysis showed an adjusted odds ratio (OR) for clinical success in the temocillin group of 1·03 (95% CI 0·62–1·72, p=0·186; appendix 2 p 13). A similar result was obtained with the mixed effects model analysis considering sites (adjusted OR 1·02 [95% CI 0·61–1·71], p=0·943; appendix 2 p 13). Kaplan–Meier curves for mortality are shown in appendix 2 (p 6); Cox regression analysis was not performed due to low number of events.

The definition of DOOR ranks is shown in appendix 2 (p 4). The probability that patients in the temocillin group had a better DOOR than those in the carbapenem group was 50·4% (95% CI 45·0–55·8; appendix 2 p 7). Individual components of the DOOR were similar between the two groups (appendix 2 p 14).

Overall, adverse events were reported in 83 (60%) of 163 patients receiving temocillin and 68 (41%) of 165 patients receiving carbapenems (p=0·078; table 3 and appendix 2 pp 15–16). *Clostridioides difficile* infection occurred in 10 (6%) of 163 patients assigned temocillin and four (2%) of 165 patients assigned carbapenems (p=0·10). Serious adverse events occurred in 31 (19%) of 163 patients assigned temocillin and 35 (24%) of 165 patients assigned carbapenems (p=0·62; table 3 and appendix 2 pp 17–18). Among serious adverse events, only five events were considered related to study drugs: four events in the temocillin group (two *C difficile* infection, one diffuse

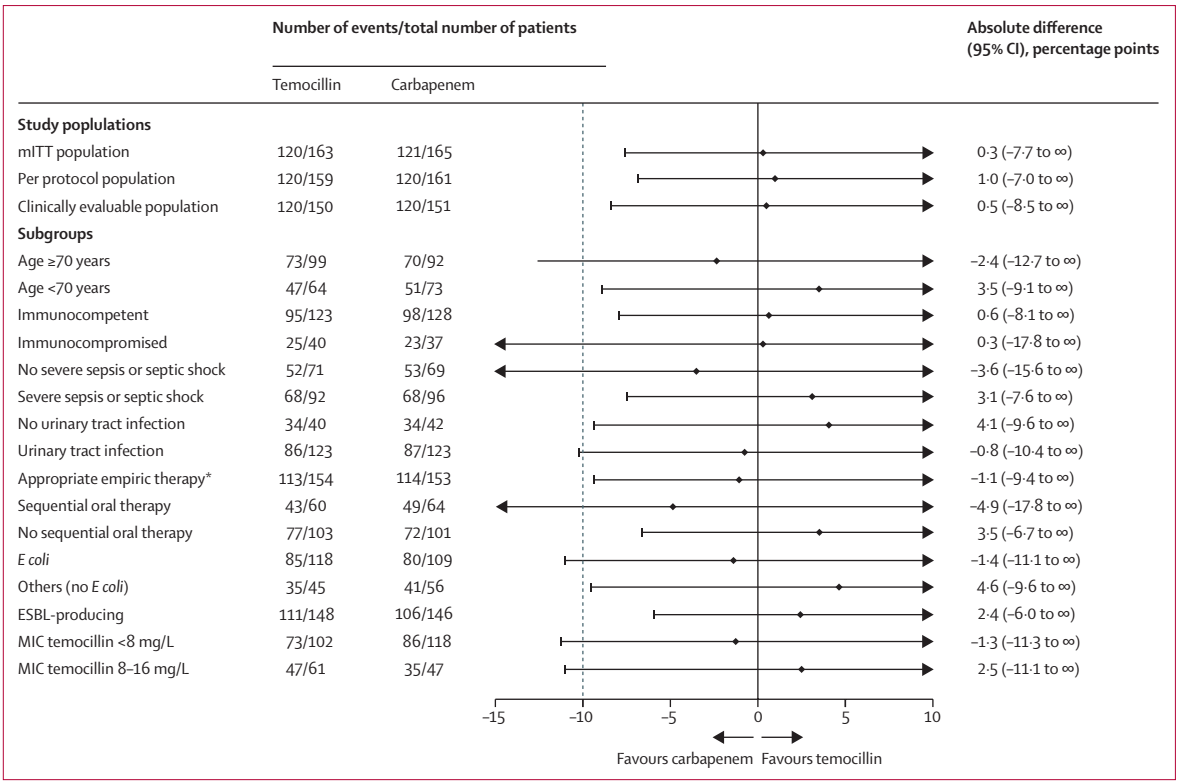

Figure 2: **Forest plot of study populations and subgroups for clinical success**
Oral therapy subgroups were not pre-planned and were added in the review process. More detailed data is in appendix 2 (p 12). *E coli*=*Escherichia coli*. ESBL=extended-spectrum β-lactamase. mITT=modified intention-to-treat. MIC=minimum inhibitory concentration. *Data on inappropriate empirical therapy is not reported due to the low number of this subgroup; full data are shown in appendix 2 (p 12).

itching, and one hypertransaminasaemia) and one event in the carbapenem group (*C difficile* infection; appendix 2 p 18). Adverse events of specific interest are shown in table 3. Non-serious adverse events considered related to the study drug are shown in appendix 2 (p 19).

	Temocillin (n=163)	Carbapenem (n=165)
Patients with at least one adverse event	83 (51%)	68 (41%)
Patients with at least one serious adverse event	31 (19%)	35 (21%)
Patients with a treatment-related serious adverse event	4 (2%)	1 (1%)
Patients with adverse events of special interest*		
Clostridioides difficile infection	10 (6%)	4 (2%)
Diarrhoea	12 (7%)	9 (5%)
Aspartate aminotransferase or alanine aminotransferase elevation	1 (1%)	1 (1%)
Leukopenia	1 (1%)	0
Vaginal candidiasis	0	1 (1%)
Nausea or vomiting	3 (2%)	2 (1%)
Acute renal failure	2 (1%)	1 (1%)
Rash or pruritus	4 (2%)	2 (1%)

*Individual patients who had at least one occurrence of the event.

Table 3: **Adverse events occurring until day 28 of follow-up (modified intention-to-treat population)**

Discussion

In this study, temocillin was non-inferior to carbapenems as targeted treatment in patients with bacteraemia due to 3GCR-E. The results were consistent in the per-protocol and clinically evaluable populations, secondary endpoints, subgroups, and DOOR analyses.

Overall, there is a scarcity of trials of temocillin. A Swedish randomised trial on the empirical treatment of patients with febrile UTI compared temocillin with cefotaxime.[19] Because of the comparator, patients with cephalosporin-resistant bacteria were not investigated. In that trial, temocillin was non-inferior in secondary endpoints, including clinical and bacteriological efficacy. Notably in the primary outcome, temocillin showed less gut microbiota disturbance. Previous uncontrolled case series and cohort studies in different types of infections caused by ESBL or AmpC-producing Enterobacterales showed cure rates between 72% and 94% with temocillin.[20–24] A retrospective matched cohort study of treatments of UTI caused by ESBL producers found clinical cure rates of 94% in those who received temocillin versus 99% in those who received carbapenems.[22]

We found no previous randomised trials of temocillin for 3GCR-E infections. Two previous trials studied potential alternatives to carbapenems in invasive infections caused by 3GCR-E. In the MERINO trial, piperacillin–tazobactam was not non-inferior to meropenem, which could have been partly due to the inclusion of patients with isolates with false susceptibility to piperacillin–tazobactam.[25,26] The FOREST trial compared fosfomycin with ceftriaxone or meropenem for multidrug-resistant *E coli* causing UTI bacteraemia; overall and in the subgroup of ceftriaxone-resistant cases, fosfomycin was not non-inferior despite being highly efficacious, mostly due to patients who were withdrawn because of adverse events.[15] Therefore, our results provide the first high-level evidence for a suitable alternative to carbapenems as targeted treatment in these infections, which would contribute to reducing the large worldwide overuse of carbapenems, eventually helping to limit the dramatic spread of carbapenem-resistant Gram-negatives.

In our study, we used a composite primary endpoint to increase sensitivity in detecting any sign of temocillin inferiority than if only mortality or cure were considered. The MERINO trial used 30-day mortality as the primary endpoint, which was a secondary endpoint in ASTARTÉ; the 95% CI for the difference in mortality in our study was also within the 5% non-inferiority margin established in MERINO. Interestingly, 28-day mortality in our study (3·0%) was low, but similar to the 30-day mortality rate with meropenem in MERINO (3·7%) and identical to the FOREST trial (3·0%).[15,25] The low mortality in these trials is explained by some of the exclusion criteria (ie, palliative care, life expectancy less than 30 days, polymicrobial bloodstream infection, endocarditis, meningitis, peritoneal dialysis, and continuous haemofiltration).

Of note, approximately 20% of screened patients were excluded due to having a temocillin-resistant isolate, and, therefore, checking susceptibility to temocillin (as also happens with carbapenems) is vital when considering therapy. Dosing and susceptibility breakpoint are important considerations for the use of temocillin. When the study protocol was developed, there was no breakpoint established by EUCAST; later, the committee recommended a breakpoint but only for UTIs (susceptible with increased exposure ≤16 mg/L).[13] In our protocol, we considered isolates with MIC of 8 mg/L or lower as susceptible based on the breakpoint established by the BSAC,[12] and 16 mg/L or lower for bloodstream infection originating from the urinary tract. We decided to use 2 g every 8 h based on pharmacokinetic studies,[27] which is also the EUCAST high dosage recommendation for a MIC of 16 mg/L or lower in temocillin.[13] The results of this study support these susceptibility breakpoints.

The overall median duration of active therapy in our trial was 9 days (6 days of intravenous therapy with study drugs), which is reasonable considering that this trial was performed before the BALANCE trial results and that some of our patients would have been excluded from BALANCE due to exclusion criteria (eg, patients who are neutropenic, receiving immunosuppresive therapy after transplantation, or have a prosthetic valve or synthetic endovascular graft**)**. The BALANCE trial showed that 7 days of antibiotic therapy was non-inferior to 14 days in bloodstream infection caused by different bacteria, including Enterobacterales.[28] This finding means that temocillin might save an average of 5–6 days of carbapenem exposure per patient. Because ASTARTÉ was a pragmatic trial, switching to oral therapy was permitted after 4 days of active intravenous treatment. However, the availability of effective oral agents for 3GCR-E is limited, which explains why only about a third of patients were transitioned to oral therapy. The results of the subgroup analysis, together with the fact that only a third of patients transitioned to oral therapy, suggest that the oral switch did not have a significant effect on the outcomes.

The number of adverse events reported was higher for patients assigned to temocillin than for patients assigned carbapenems, without significant differences in serious adverse events or in study drug-related adverse events between the groups. Also, there were more *C difficile* infections in patients assigned to temocillin than those assigned to carbapenems. *C difficile* infections being more frequent in the temocillin group is contradictory with previous reports including the results of the Swedish trial, in which none of the 77 patients assigned temocillin developed *C difficile* infection.[19] Low *C difficile* infection rates or absence of such episodes were reported in previous case series and cohort studies.[20–24,29]

Despite empirical therapy being appropriate only in 63% of patients, most could have received at least one dose of an active drug (mostly carbapenems) before randomisation due to the use of a rapid test for the detection of cephalosporin resistance, which is now standard practice in Spanish hospitals. In any case, median duration of active therapy until randomisation was only 2 days. Randomisation was stratified by appropriateness of empirical therapy and, therefore, this was balanced between groups. Although most patients receiving at least one dose of an active drug before randomisation could have also contributed to the overall low mortality rate, our pragmatic trial answers the question of whether temocillin can be used as target therapy instead of a carbapenem once a temocillin-susceptible 3GCR-E is isolated from blood cultures. In any case, the results in the subgroup of patients receiving inappropriate empirical therapy, although limited by low numbers, do not suggest a differential effect.

This study has several limitations. We could not perform a masked trial because the control groups included two optional drugs with different dosing schemes. To mitigate the potential effect of an open design in evaluation of clinical cure, individual signs and symptoms included in this endpoint were double-checked by masked

investigators. Although we cannot report the number of patients admitted to intensive care unit as we did not collect that information, median SOFA score was 2, indicating that no less than 50% of patients had sepsis (according to SEPSIS-3 criteria);[30] therefore, we think the results would be applicable to critically ill patients. The overall median duration of therapy was slightly longer than is recommended by the most recent evidence in the management of bacteraemia. The most frequent bacteria in our study were ESBL-producing *E coli* and *K pneumoniae,* and, therefore, our results mostly apply to them; however, there is no reason to suspect that AmpC-producing Enterobacterales would respond differently if they are susceptible to temocillin. Also, UTIs were predominant. Although subgroup analyses did not suggest different outcomes for other infection sources, the evidence is less strong. Finally, the study was performed in only one country, and the majority of patients were of western Europe ethnicity, but management of patients was according to standard protocols. Some strengths include its randomised, multicentre, and pragmatic design; the inclusion of patients who are immunocompromised or have cancer; the use of a comprehensive composite endpoint and DOOR analysis; high adherence to study protocol; and high consistency of results in all populations and subgroup analyses.

In conclusion, we found that temocillin is non-inferior to carbapenems as targeted therapy for hospitalised patients with bloodstream infection caused by 3GCR-E. These findings support the use of temocillin as an effective, suitable, and safe alternative to carbapenems in this setting.

ASTARTÉ-GEIRAS study group members

Pilar Retamar-Gentil, Luis Eduardo López-Cortés, María Macías Barrera, Aurora Alemán Rodríguez, Lola Cubero-Aranda, Blanca Fombuena Rubio, Vicente Merino Bohórquez, José Manuel Carretero, and Inés Portillo (Hospital Universitario Virgen Macarena, Sevilla, Spain); Sergio Sequera-Arquelladas, Svetlana Sadyrbaeva-Dolgova, Ramiro Cañaveral Vaccari, and Miguel Ángel López Ruz (Hospital Universitario Virgen de las Nieves, Granada, Spain); Silvia Castañeda, Elena Sendra, Sandra Esteban-Cucó, and Ana Siverio (Hospital del Mar, Barcelona, Spain); Livia Giner, PIlar González-de-la-Aleja, Héctor Pinargote, and Juan Carlos Rodríguez (Dr Balmis University General Hospital, Alicante, Spain); Álvaro Izquierdo-Cardenas, Celso Soares Batista, Virginia Pomar, and Iris Artesero (Hospital de la Santa Creu i Sant Pau, Barcelona, Spain); Brais Castelo López, María Rodríguez Mayo, and Alicia Alonso (Complejo Hospitalario Universitario A Coruña, A Coruña, Spain); Rubén Lobato Cano, Juan Manuel Sánchez Calvo, and Antonio Jesús Hidalgo Castellón (Hospital Universitario de Jerez, Cádiz, Spain); Ignacio Márquez Gómez, Luis Francisco Caballero Martínez, and Carmen Pérez López (Hospital Regional Universitario Málaga, Málaga, Spain); Nicolás Merchante Gutiérrez, Reinaldo Espíndola Gómez, and Antonio Fernández Pevida (Hospital Universitario de Valme, Sevilla, Spain); Franciso José Vasallo, Antonio Pérez-Landeiro, and Olalla Lima (Hospital Álvaro Cunqueiro, Vigo, Spain); M Carmen Fariñas, Paula Runza Buznego, and Noelia Ruiz Alonso (Hospital Universitario Marqués de Valdecilla, Santander, Spain); Esther Calbo and Beatriz Dietl Gómez-Luengo (Hospital Universitari Mútua de Terrassa, Barcelona, Spain); Maria Jose Blanco Vidal and Javier Nieto Arana (Hospital Universitario de Cruces, Barakaldo, Spain); Julián Torre-Cisneros and Isabel Machuca (Hospital Universitario Reina Sofía, Córdoba, Spain); Alicia Hidalgo-Jiménez and Francisco Franco Álvarez de Luna (Hospital Universitario Juan Ramón Jiménez, Huelva, Spain); Eva María Romay Lema and Patricia Capón González (Hospital Universitario de Lugo, Lugo, Spain); Ana Verónica Halperin and Francesca Gioia (Hospital Universitario Ramón y Cajal, Madrid, Spain); Emilia Cercenado and Sara Rodríguez (Hospital General Universitario Gregorio Marañón, Madrid, Spain); Amaya C Oteiza and Idoia Bilbao (Clinica Universidad de Navarra, Pamplona, Spain); Waldo Sánchez-Yebra Romera and Alexandra María Aceituno-Caño (Hospital Universitario Torrecárdenas, Almería, Spain); Natalia Chueca and David Vinuesa García (Hospital Universitario Clínico San Cecilio de Granada, Granada, Spain); Oriol Gasch Blasi and Elisa Nuez Zaragoza (Hospital Universitari Parc Taulí, Sabadell, Spain); Lara García-Álvarez and Carla Andrea Alonso Arribas (Hospital Universitario San Pedro, Logroño, Spain); Maria Auxiliadora Semiglia Chong and Marianela Ciudad Sañudo (Hospital Universitario de La Princesa, Madrid, Spain); María Peñaranda Vera and Xavier Mulet Aguilo (Hospital Universitari Son Espases, Palma de Mallorca, Spain); Adelina Gimeno-Gascón and María Paniagua Garcia (Hospital Universitario Virgen del Rocío, Sevilla, Spain); Blanca Anaya Baz and María Luisa Fernández Ávila (Hospital Universitario Puerto Real, Puerto Real, Spain); Genoveva Yagüe and Aychel Elena Roura Piloto (Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain); and María Victoria García López and Marina Villalobos Hernández (Hospital Universitario Virgen de la Victoria, Málaga, Spain).

Contributors

Concept and design: LL-C, FDP, and JR-B. Obtained funding: LBP, IBB, VPJ, and JR-B. Study coordination: FCD, LBP, IBB, VPJ, LL-C, FDP, and JR-B. Recruitment of patients, follow-up, and collection of patients' data: all authors. Directly accessed and verified the underlying data in the study: FCD and LBP. Statistical analysis: FCD and JR-B. Drafting of the manuscript: FCD and JR-B. All authors were involved in revising the work for intellectual content and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JG-J has received honoraria for educational lectures from MSD and support for attending scientific meetings from Angelini, Pfizer, and Menarini. CR-F has received honoraria for participation on a data safety monitoring board or advisory board from Aelis Farma and RemAb Therapeutics. JGA has received honoraria from Angelini Pharma España as support for meeting and travel costs for ECCMID Global 2024. MÁLZ has received payment or honoraria for presentations from Tillotts. JPH has received payment or honoraria for presentations and consulting fees from Pfizer, MSD, Menarini, Advanz, GSK, and Allifax and support for attending meetings and travel from Pfizer, MSD, and Shionogi. JL-C has received grants or contracts from the AstraZeneca Supernova clinical trial, Pfizer C3601002 REVISIT trial, GSK Eagle clinical trial, and Pfizer C4617035 clinical trial on COVID-19; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Pfizer, AstraZeneca, and Advanz; and support for attending meetings and travel from Pfizer, MSD, Menarini, AstraZeneca, and Advanz. LGP has received payment or honoraria for presentations from Perlas Clínicas and support for attending meetings from Pfizer and Janssen. FAdlRA has received payment or honoraria for lectures and presentations from ViiV Healthcare, Pfizer, Johnson and Johnson, and GILEAD. ZRP-B obtained a postdoctoral contract through a competitive call from the Andalusian Regional Government and obtained a grant for a research project on Strategic Health Action 2023 from the Instituto de Salud Carlos III; receives overarching funding for research from CIBERINFEC; and served as scientific advisor for Tillotts. RES has received a Juan Rodes contract from Instituto de Salud Carlos III and support for attending meetings and travel from Menarini and Mundipharma. ARP has received competitive research grants from Gilead and ViiV-GSK to conduct independent projects; payment for educational events from Gilead and ViiV-GSK; payment for participation on advisory boards from Johnson & Johnson; and support from Gilead and Johnson & Johnson to attend national and international conferences. All other authors declare no competing interests.

Data sharing

De-identified participant data will be available following publication on request to the corresponding author's institution; requests should include the purpose for using the data and an adequate justification of the scientific interest of the proposal. A contract with the author's institution for the use of data should be signed.

Acknowledgments

This study was funded by Instituto de Salud Carlos III through the project ICI19/00093 (co-funded by European Regional Development Fund and European Social Fund). Temocillin was provided by Eumedica Pharmaceuticals (Switzerland), through partner company Belpharma (Luxembourg). We thank all participants and all contributing clinicians, microbiologists, nurses, and investigators from the participating centres. Spanish Clinical Research Network funded by the Spanish Ministry of Health, Instituto de Salud Carlos III has acted with local support for the study start-up and monitoring activities coordinated and directed from Clinical Trials Unit, Hospital Universitario Virgen del Rocío (PT20/00123-PT23/00135).

References

1 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022; **399:** 629–55.

2 Sati H, Carrara E, Savoldi A, et al, and the WHO Bacterial Priority Pathogens List Advisory Group. The WHO Bacterial Priority Pathogens List 2024: a prioritisation study to guide research, development, and public health strategies against antimicrobial resistance. *Lancet Infect Dis* 2025; **25:** 1033–43.

3 Paul M, Carrara E, Retamar P, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European Society of Intensive Care Medicine). *Clin Microbiol Infect* 2022; **28:** 521–47.

4 Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections. *Clin Infect Dis* 2024; published online Aug 7. https://doi.org/10.1093/cid/ciae403.

5 Gutiérrez-Gutiérrez B, Rodríguez-Baño J. Current options for the treatment of infections due to extended-spectrum beta-lactamase-producing Enterobacteriaceae in different groups of patients. *Clin Microbiol Infect* 2019; **25:** 932–42.

6 Cosimi L, Zerbato V, Grasselli Kmet N, et al. Temocillin: a narrative review of its clinical reappraisal. *Antibiotics (Basel)* 2025; **14:** 859.

7 Alexandre K, Fantin B. Pharmacokinetics and pharmacodynamics of temocillin. *Clin Pharmacokinet* 2018; **57:** 287–96.

8 Stewart AG, Henderson A, Bauer MJ, Paterson DL, Harris PNA. Activity of temocillin against third-generation cephalosporin-resistant *Escherichia coli* and *Klebsiella pneumoniae* bloodstream isolates from a clinical trial. *JAC Antimicrob Resist* 2021; **4:** dlab192.

9 Marín-Candón A, Rosso-Fernández CM, Bustos de Godoy N, et al, and the ASTARTÉ Study Group. Temocillin versus meropenem for the targeted treatment of bacteraemia due to third-generation cephalosporin-resistant *Enterobacterales* (ASTARTÉ): protocol for a randomised, pragmatic trial. *BMJ Open* 2021; **11:** e049481.

10 Hopewell S, Chan A-W, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. *BMJ* 2025; **389:** e081123.

11 Sojo-Dorado J, López-Hernández I, Hernández-Torres A, et al. Effectiveness of fosfomycin trometamol as oral step-down therapy for bacteraemic urinary tract infections due to MDR *Escherichia coli*: a post hoc analysis of the FOREST randomized trial. *J Antimicrob Chemother* 2023; **78:** 1658–66.

12 British Society for Antimicrobial Chemotherapy. BSAC methods for antimicrobial susceptibility testing. 2015. https://bsac.org.uk/wp-content/uploads/2012/02/BSAC-disc-susceptibility-testing-method-Jan-2015.pdf (accessed Sept 21, 2025).

13 European Committee on Antimicrobial Susceptibility Testing. Clinical breakpoint tables. https://www.eucast.org/clinical_breakpoints (accessed July 16, 2025).

14 López-Cortés LE, Delgado-Valverde M, Moreno-Mellado E, et al, and the SIMPLIFY study group. Efficacy and safety of a structured de-escalation from antipseudomonal β-lactams in bloodstream infections due to Enterobacterales (SIMPLIFY): an open-label, multicentre, randomised trial. *Lancet Infect Dis* 2024; **24:** 375–85.

15 Sojo-Dorado J, López-Hernández I, Rosso-Fernandez C, et al, and the REIPI-GEIRAS-FOREST group. Effectiveness of fosfomycin for the treatment of multidrug-resistant *Escherichia coli* bacteremic urinary tract infections: a randomized clinical trial. *JAMA Netw Open* 2022; **5:** e2137277.

16 von Dach E, Albrich WC, Brunel A-S, et al. Effect of C-reactive protein-guided antibiotic treatment duration, 7-day treatment, or 14-day treatment on 30-day clinical failure rate in patients with uncomplicated Gram-negative bacteremia: a randomized clinical trial. *JAMA* 2020; **323:** 2160–69.

17 European Medicines Agency. Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections: revision 3. May 24, 2022. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-revision-3_en.pdf (accessed Sept 21, 2025).

18 Varon B, Palacios-Baena ZR, de Kraker MEA, et al, and the UNIFORM research group. Universal risk factors for mortality in bloodstream infections (UNIFORM): a systematic review and Delphi survey. *Clin Microbiol Infect* 2024; **30:** 453–61.

19 Edlund C, Ternhag A, Skoog Ståhlgren G, et al, and the Temocillin Study Group. The clinical and microbiological efficacy of temocillin versus cefotaxime in adults with febrile urinary tract infection, and its effects on the intestinal microbiota: a randomised multicentre clinical trial in Sweden. *Lancet Infect Dis* 2022; **22:** 390–400.

20 Mamona Kilu C, Menvielle C, Cataldi A, et al, and the Paris Temocillin Study Group. Effectiveness of temocillin in treatment of non-urinary tract infections caused by ESBL-producing Enterobacterales and risk factors for failure. *JAC Antimicrob Resist* 2024; **6:** dlae164.

21 Dinh A, Duran C, Singh S, et al, and the Temocillin Greater Paris Study Group. Real-life temocillin use in greater Paris area, effectiveness and risk factors for failure in infections caused by ESBL-producing Enterobacterales: a multicentre retrospective study. *JAC Antimicrob Resist* 2022; **5:** dlac132.

22 Delory T, Gravier S, Le Pluart D, et al. Temocillin versus carbapenems for urinary tract infection due to ESBL-producing Enterobacteriaceae: a multicenter matched case-control study. *Int J Antimicrob Agents* 2021; **58:** 106361.

23 Brousse X, Andry F, Lahouati M, et al. Temocillin efficacy against AmpC β-lactamase-producing Enterobacterales: a relevant alternative to cefepime? *J Antimicrob Chemother* 2025; **80:** 576–82.

24 Oosterbos J, Schalkwijk M, Thiessen S, et al. Clinical and microbiological evaluation of temocillin for bloodstream infections with Enterobacterales: a Belgian single-centre retrospective study. *JAC Antimicrob Resist* 2022; **4:** dlac086.

25 Harris PNA, Tambyah PA, Lye DC, et al, and the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN). Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. *JAMA* 2018; **320:** 984–94.

26 Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Kahlmeter G. Antibiotics for ceftriaxone-resistant gram-negative bacterial bloodstream infections. *JAMA* 2019; **321:** 612–13.

27 Laterre PF, Wittebole X, Van de Velde S, et al. Temocillin (6 g daily) in critically ill patients: continuous infusion versus three times daily administration. *J Antimicrob Chemother* 2015; **70:** 891–98.

28 Daneman N, Rishu A, Pinto R, et al. Antibiotic treatment for 7 versus 14 days in patients with bloodstream infections. *N Engl J Med* 2025; **392:** 1065–78.

29 Habayeb H, Sajin B, Patel K, Grundy C, Al-Dujaili A, Van de Velde S. Amoxicillin plus temocillin as an alternative empiric therapy for the treatment of severe hospital-acquired pneumonia: results from a retrospective audit. *Eur J Clin Microbiol Infect Dis* 2015; **34:** 1693–99.

30 Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; **315:** 801–10.