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

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Summary

Background De-escalation from broad-spectrum to narrow-spectrum antibiotics is considered an important measure to reduce the selective pressure of antibiotics, but a scarcity of adequate evidence is a barrier to its implementation. We aimed to determine whether de-escalation from an antipseudomonal β-lactam to a narrower-spectrum drug was non-inferior to continuing the antipseudomonal drug in patients with Enterobacterales bacteraemia.

Methods An open-label, pragmatic, randomised trial was performed in 21 Spanish hospitals. Patients with bacteraemia caused by Enterobacterales susceptible to one of the de-escalation options and treated empirically with an antipseudomonal β-lactam were eligible. Patients were randomly assigned (1:1; stratified by urinary source) to de-escalate to ampicillin, trimethoprim–sulfamethoxazole (urinary tract infections only), cefuroxime, cefotaxime or ceftriaxone, amoxicillin–clavulanic acid, ciprofloxacin, or ertapenem in that order according to susceptibility (de-escalation group), or to continue with the empiric antipseudomonal β-lactam (control group). Oral switching was allowed in both groups. The primary outcome was clinical cure 3–5 days after end of treatment in the modified intention-to-treat (mITT) population, formed of patients who received at least one dose of study drug. Safety was assessed in all participants. Non-inferiority was declared when the lower bound of the 95% CI of the absolute difference in cure rate was above the –10% non-inferiority margin. This trial is registered with EudraCT (2015-004219-19) and ClinicalTrials.gov (NCT02795949) and is complete.

Findings 2030 patients were screened between Oct 5, 2016, and Jan 23, 2020, of whom 171 were randomly assigned to the de-escalation group and 173 to the control group. 164 (50%) patients in the de-escalation group and 167 (50%) in the control group were included in the mITT population. 148 (90%) patients in the de-escalation group and 148 (89%) in the control group had clinical cure (risk difference 1·6 percentage points, 95% CI –5·0 to 8·2). The number of adverse events reported was 219 in the de-escalation group and 175 in the control group, of these, 53 (24%) in the de-escalation group and 56 (32%) in the control group were considered severe. Seven (5%) of 164 patients in the de-escalation group and nine (6%) of 167 patients in the control group died during the 60-day follow-up. There were no treatment-related deaths.

Interpretation De-escalation from an antipseudomonal β-lactam in Enterobacterales bacteraemia following a predefined rule was non-inferior to continuing the empiric antipseudomonal drug. These results support de-escalation in this setting.

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Introduction

Inappropriate antimicrobial treatment of patients with invasive infections is associated with increased mortality;[1] therefore, empiric treatment with broad-spectrum antibiotics is recommended in severe infections to ensure appropriate coverage of the causative microorganism.[2]

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Research in context

Evidence before this study

De-escalation is an antimicrobial stewardship strategy in which empiric antimicrobials are either replaced by narrow-spectrum agents or discontinued if used in unneeded combination, with the aim to reduce selection pressure on microorganisms to contribute to the control of antimicrobial resistance. Despite being considered as standard practice by many infectious diseases specialists, there is a scarcity of high-level evidence for the effectiveness of de-escalation. A systematic review including studies published in MEDLINE via PubMed from inception until Jan 1, 2020 found low-level evidence for recommending de-escalation in short-term treatments. To update this review, we performed a literature search in MEDLINE via PubMed from inception to Aug 21, 2023, restricted to English and Spanish, including the terms "de-escalation" OR "streamlining", AND "antimicrobial therapy" OR "antibiotics", but could not find any randomised trial published thereafter. As de-escalation is a broad concept, randomised trials in specific clinical situations using structured de-escalation protocols are needed.

Added value of this study

We investigated de-escalation in a specific clinical situation (patients with bacteraemia due to Enterobacterales receiving empirical therapy with an antipseudomonal β-lactam), using a pragmatic, predefined rule to select a narrower-spectrum drug. We found de-escalation to be non-inferior in clinical efficacy to continuing the initial antipseudomonal drug, and there was no difference in the number of severe adverse events between groups.

Implications of all the available evidence

Beyond other considerations, an important barrier to de-escalate antimicrobial therapy is the scarcity of adequate evidence for its efficacy and safety in specific clinical situations. To our knowledge, this is the first randomised trial investigating the efficacy of antibiotic de-escalation in a specific clinical situation. These results should facilitate the implementation of de-escalation in general clinical practice, which might help reduce the ecological impact of antipseudomonal β-lactams.

However, these drugs also exert a significant selection pressure that contributes to the spread of multidrug-resistant bacteria.[3] This is particularly important in the case of antipseudomonal β-lactams, which in addition to selection pressure, can also induce the expression of resistance mechanisms in *Pseudomonas aeruginosa*[4,5] and are associated with an increased risk of infections caused by *Clostridioides difficile*[6] and carbapenem-resistant Enterobacterales.[7] Unfortunately, exposure to anti-pseudomonal drugs is very common in hospitalised patients.

De-escalation to a narrow-spectrum drug in patients initially treated with broad-spectrum antibiotics, once the cause of an infection is known, is advocated as a key measure to reduce exposure to broad-spectrum antibiotics. Although considered standard of care by most infectious diseases specialists, the frequency with which de-escalation is performed could be improved.[6,8–10] An important barrier to de-escalation for many physicians is the scarcity of adequate evidence on its efficacy and safety, particularly when early improvement with empirical therapy is not evident. In fact, a Cochrane review found insufficient evidence to recommend for or against de-escalation in adults with sepsis,[11] and a recent systematic review of studies published up to Jan 1, 2020, found low-level evidence for recommending de-escalation in short-term treatments.[12] Therefore, randomised trials are needed. Because de-escalation is a broad concept, trials should include specific clinical situations and structured de-escalation protocols to be applicable in clinical practice.

Antipseudomonal agents are frequently recommended as empirical drugs in patients with severe health care-associated or nosocomial infections; if the infection is shown to be caused by an Enterobacterales, the question of whether de-escalation to a non-antipseudomonal agent with in-vitro activity against the infecting microorganism should be done is then typically raised. We aimed to determine whether de-escalation to an active non-antipseudomonal drug in patients with bacteraemia caused by an Enterobacterales, using a predefined rule, would be non-inferior to continuing with the empirical drug.

Methods

Study design

The SIMPLIFY trial was an investigator-driven, pragmatic, multicentre, open-label, randomised, controlled trial in patients with bacteraemia caused by Enterobacterales who received empirical treatment with an antipseudomonal β-lactam. The trial was conducted in 21 Spanish public tertiary hospitals, with the support of the Spanish Network for Research in Infectious Diseases and the Spanish Clinical Research Network (SCReN).

The Hospital Universitario Virgen Macarena Ethics Committee approved the study. The study protocol was published[13] and is available in appendix 1. The results are reported in accordance with the CONSORT statement extension (appendix 2 pp 49–50) for non-inferiority and equivalence trials.[14]

Participants

Hospitalised patients aged 18 years or older with monomicrobial Enterobacterales bacteraemia were eligible for enrolment if they fulfilled all the following inclusion criteria: receipt of empiric monotherapy (started

<24 h after blood cultures were taken) with an antipseudomonal β-lactam with in-vitro activity against the causative bacterium, including meropenem, imipenem, piperacillin–tazobactam, cefepime, ceftazidime, or aztreonam; the causative organism was susceptible in vitro to at least one of the antibiotics prespecified for de-escalation; and intravenous antimicrobial treatment was planned for at least 5 days from receipt of the first active drug. A negative pregnancy test was required for women of childbearing age. Exclusion criteria were: life expectancy less than 30 days; pregnancy or breastfeeding; isolation of carbapenemase-producing Enterobacterales; recruitment more than 48 h after the antimicrobial susceptibility report was available; neutropenia less than 500 cells per µL at randomisation; and a planned duration of treatment of more than 28 days (eg, osteomyelitis or infectious endocarditis). Written informed consent for participation was obtained from all patients.

Randomisation and masking

In the first 48 h after the antimicrobial susceptibility report was available, patients were randomly assigned (1:1) to continue with the same empiric intravenous antipseudomonal drug (control group) or to switch to the first drug showing in-vitro activity from a predefined de-escalation list (de-escalation group), both in monotherapy. Assignment to treatment group was performed centrally by a web-based automated system integrated with the electronic case report form. Simple randomisation was performed, stratified only by source of bacteraemia (urinary tract infection or other). Source was defined according to organ-related signs and symptoms and, when appropriate, isolation of the bacterium from an appropriate sample from the infection site. Blinding was not possible due to multiple options in both groups.

Procedures

Baseline patient characteristics were collected on the day of randomisation, except for clinical severity variables, which were collected retrospectively for the day the first blood cultures were drawn. Blood isolates were frozen at –80°C and sent to the reference laboratory (Hospital Universitario Virgen Macarena, Seville, Spain), where identification was confirmed using MALDI-TOF (Bruker, Billerica, MA, USA), and antimicrobial susceptibility testing was performed by manual broth microdilution, interpreted according to European Committee on Antimicrobial Susceptibility Testing guidelines.[15,16]

The order of the de-escalation list was as follows: ampicillin, trimethoprim–sulfamethoxazole (urinary tract infections only), cefuroxime, cefotaxime or ceftriaxone, amoxicillin–clavulanic acid, ciprofloxacin, and ertapenem. Amoxicillin–clavulanic acid was placed after the cephalosporins because of its anti-anaerobic activity. Ciprofloxacin, despite being potentially active against *Pseudomonas aeruginosa*, was included as per standard de-escalation practice. As an exception to the rule, the options for AmpC β-lactamase or extended-spectrum β-lactamase (ESBL) producers were restricted to meropenem or imipenem in the control group, and trimethoprim–sulfamethoxazole, ciprofloxacin, or ertapenem in the de-escalation group, regardless of susceptibility to other drugs. Standard doses of all drugs for invasive infections were used in both groups (in appendix 1 p 22). The recommended duration of treatment was 7–14 days. Switching to oral therapy was allowed after 5 days of active intravenous therapy in stable patients showing clinical improvement with adequate source control if it was necessary, and if the patient was tolerant of oral intake. Permitted oral drugs were chosen following standard practice and are listed in appendix 1 (p 22).

For patients participating in a colonisation substudy, rectal swabs were taken at randomisation, end of treatment, and test of cure. The microorganisms investigated were Enterobacterales producing ESBLs, carbapenemases or plasmid-mediated AmpC (pAmpC) or hyperproducing chromosomal AmpC (cAmpC), carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *P aeruginosa,* and *Stenotrophomonas maltophilia*. Rectal swabs were cultured in MacConkey agar with 2 mg/L cefotaxime. ESBL, cAmpC, pAmpC, and carbapenemase production were determined by standard phenotypic methods.[17] PCR assays were used to characterise β-lactamase genes. In *P aeruginosa*, disk diffusion was used to detect carbapenem resistance.

Patients were followed up for 60 days; 30-day and 60-day visits could be performed by telephone. SCReN monitors verified electronic case report form data against original data sources.

Outcomes

The primary endpoint was clinical cure, assessed 3–5 days after completion of antibiotic treatment (test of cure). Secondary endpoints were microbiological cure at test of cure, recurrence, *C difficile* infection, adverse events, clinical cure, and mortality at day 60.

Clinical cure was defined as resolution of all symptoms and signs of infection and no need for treatment modification due to an unfavourable clinical response or adverse events. Patients who died were considered not to have reached clinical cure. Microbiological cure was defined as negative follow-up blood cultures and, when applicable, negative follow-up cultures from the site of infection. Recurrence was defined as a new bacteraemia episode caused by the same bacterial species as the initial episode within 60 days of randomisation. Adverse events were defined as any incident detrimental to health in a randomised patient, regardless of the potential causal relationship with the treatment assigned. Adverse events were considered severe if life-threatening or causing death, relevant disability, lengthening of hospital stay, or new hospitalisation.

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See **Online** for appendices 1 and 2

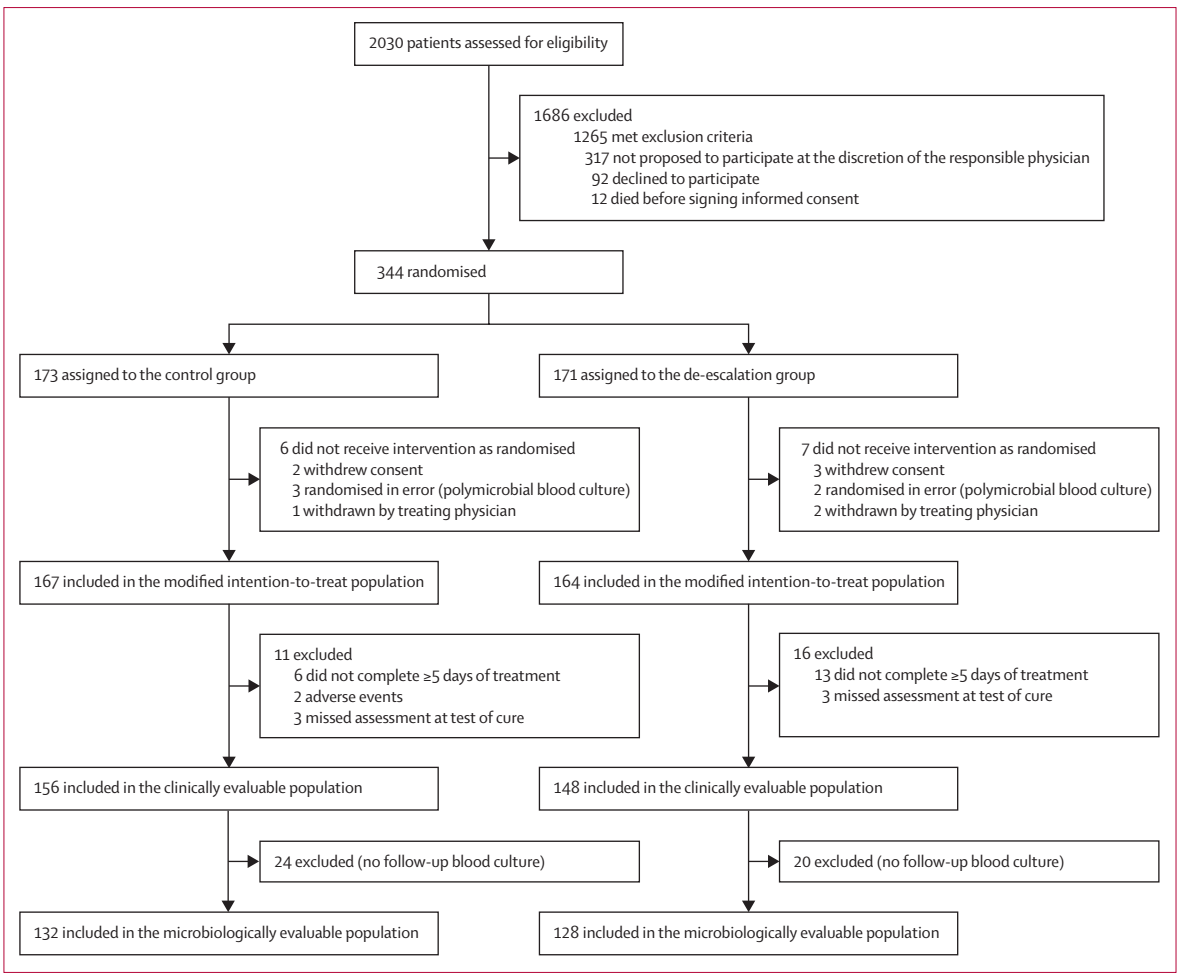

Figure 1: **Study profile**
The microbiologically evaluable population included patients in the clinically evaluable population who had at least one follow-up blood culture taken 48 h or more after randomisation.

In addition, all patients recruited from eight sites were proposed as participants in an exploratory substudy of rectal colonisation with multidrug-resistant Gram-negative bacteria.

Statistical analysis

Assuming an 85% cure rate in both groups based on previous observational data,[10] 344 patients (172 per group) were needed to reject the inferiority of de-escalation, considering a 10% margin, 80% power, a two-sided alpha of 5%, and a 5% dropout rate. The –10% non-inferiority margin followed recent trials of complicated urinary tract infections and intra-abdominal infections.[18,19] Non-inferiority was declared when the lower bound of the 95% CI of the absolute difference in cure rate between the two groups was above the –10% non-inferiority margin.

Differences in proportions were calculated with two-sided 95% CIs for the endpoints, using the control group as the reference. The primary analysis was done in the modified intention-to-treat (mITT) population, which included all correctly randomised patients who received at least one dose of intravenous antibiotics after randomisation. For this analysis, patients not reaching clinical cure or who missed the test-of-cure visit were considered as not cured. Multivariable analysis using logistic regression was performed to control for the effect of potential residual confounders on the primary outcome.

As a secondary analysis we assessed clinical cure in the clinically evaluable population, which included all patients evaluated at test of cure who had completed at least 5 days of intravenous therapy (or who died earlier having received at least one dose of intravenous antibiotic) and a total treatment duration of at least 7 days. Microbiological cure was assessed in the microbiologically evaluable population, which included those in the clinically evaluable population with at least one follow-up blood culture taken 48 h or more after randomisation.

	De-escalation group (n=164)	Control group (n=167)
Age in years, mean (SD)	69·5 (12·8)	71·9 (12·2)
Sex		
Female	64 (39%)	71 (43%)
Male	100 (61%)	96 (57%)
Charlson comorbidity index, median (IQR)	2·5 (1–4)	3 (1–5)
Comorbidities		
Congestive heart failure	19 (12%)	21 (13%)
Chronic pulmonary disease	21 (13%)	29 (17%)
Solid-organ cancer	55 (34%)	54 (32%)
Haematological cancer	3 (2%)	2 (1%)
Diabetes	56 (34%)	64 (38%)
Chronic kidney disease	37 (23%)	39 (23%)
Obstructive uropathy	18 (11%)	15 (9%)
Chronic liver disease	18 (11%)	19 (11%)
Obstructive biliary tract disease	29 (18%)	38 (23%)
Inflammatory intestinal disease	4 (2%)	6 (4%)
Immunosuppressive drug use	30 (18%)	17 (10%)
Fully dependent for basic activities	13 (8%)	19 (11%)
Acquisition type		
Community-acquired	89 (54%)	79 (47%)
Community-onset, health care-associated	48 (29%)	44 (26%)
Nosocomial	27 (17%)	44 (26%)
Severity of infection at presentation		
Severe sepsis	31 (19%)	28 (17%)
Septic sock	17 (10%)	7 (4%)
Source of bacteraemia		
Biliary tract	62 (38%)	67 (40%)
Urinary tract	61 (37%)	65 (39%)
Abdominal (other than biliary tract)	16 (10%)	14 (8%)
Vascular catheter	7 (4%)	12 (7%)
Skin and skin structure	4 (2%)	0
Respiratory tract	2 (1%)	2 (1%)
Other	2 (1%)	1 (1%)
Unknown	10 (6%)	6 (4%)
Cause of bacteraemia		
Escherichia coli	103 (63%)	112 (67%)
Klebsiella pneumoniae	30 (18%)	24 (14%)
Klebsiella oxytoca	9 (6%)	7 (4%)
Enterobacter cloacae	3 (2%)	11 (7%)
Proteus mirabilis	6 (4%)	7 (4%)
Other	13 (8%)	6 (4%)
(Continued from previous column)		
Pitt score, median (IQR)	0 (0–2)	0 (0–1)
Days from blood culture to administration of empirical therapy, median (IQR)	0 (0–0)	0 (0–0)
Days from blood culture to randomisation, median (IQR)*	2 (2–3)	2 (2–3)
Days of intravenous therapy, median (IQR)	7 (6–10)	7 (6–9)
Days of oral therapy, median (IQR)	3 (0–6)	3 (0–6)
Total days of therapy, median (IQR)	11 (9–14)	11 (9–14)
Source control within 72 h		
Not required	98 (60%)	106 (64%)
Required and performed	54 (33%)	57 (34%)
Required and not performed	12 (7%)	4 (2%)
Empirical drugs used		
Imipenem or meropenem	45 (27%)	47 (28%)
Piperacillin–tazobactam	104 (63%)	107 (64%)
Cefepime or ceftazidime	14 (9%)	11 (7%)
Aztreonam	1 (1%)	2 (1%)
De-escalation intravenous drug		
Ampicillin	23 (14%)	NA
Trimethoprim–sulfamethoxazole	6 (4%)	NA
Cefuroxime	23 (14%)	NA
Cefotaxime or ceftriaxone	52 (32%)	NA
Amoxicillin–clavulanic acid	24 (15%)	NA
Ciprofloxacin	18 (11%)	NA
Ertapenem	18 (11%)	NA
Switched to oral drugs	96 (59%)	118 (71%)
Ciprofloxacin	21 (20%)	97 (78%)
Cefuroxime	26 (25%)	17 (14%)
Amoxicillin	19 (18%)	1 (1%)
Amoxicillin–clavulanic acid	17 (17%)	4 (3%)
Cefixime	14 (14%)	1 (1%)
Trimethoprim–sulfamethoxazole	6 (6%)	2 (2%)
Ertapenem	0	2 (2%)

Data are for the modified intention-to-treat population and are number of patients (%), except where otherwise specified. NA=not applicable. *Equals the time to de-escalation in the de-escalation group.

Table 1: **Baseline characteristics**

We did a prespecified subgroup analysis of the primary endpoint according to source of infection. In addition, we did post-hoc subgroup analyses according to age, acquisition type (defined according to Friedman's criteria[20]), severe sepsis or shock, and microorganism. We also did a prespecified desirability of outcome ranking (DOOR) analysis in the clinically evaluable population.[19] Patient outcomes evaluated at 60 days were classified according to an ordinal scale with five mutually exclusive hierarchical levels in descending order of desirability (the lower the DOOR rank, the more desirable the outcome: 1=cured without events, 2=cured with non-severe events, 3=cured with severe events, 4=not cured, and 5=death). We calculated, with 95% CI, the probability of patients in the de-escalation group having better DOOR scores than those in the control group. In addition, we did a prespecified superiority analysis by adding a response adjusted for duration of antibiotic risk (RADAR), in which the duration of exposure to anti-pseudomonal β-lactams was added as a tie-breaking

	De-escalation group	Control group	Difference in percentage points (two-sided 95% CI)
Primary analysis (modified intention-to-treat population)			
Clinical cure at test of cure	148/164 (90%)	148/167 (89%)	1·6 (–5·0 to 8·2)
Reasons for not reaching clinical cure at test of cure			
Clinical failure	7/164 (4%)	12/167 (7%)	–2·9 (–7·9 to 2·1)
Missed assessment	6/164 (4%)	5/167 (3%)	0·7 (–3·2 to 4·6)
Withdrawn due to adverse events	3/164 (2%)	2/167 (1%)	0·6 (–2·0 to 3·2)
Secondary analysis			
Clinical cure at test of cure (clinically evaluable population)	143/148* (97%)	144/156† (92%)	4·3 (–0·9 to 9·5)
Microbiological cure at test of cure (microbiologically evaluable population)	124/128 (97%)	125/132 (95%)	2·2 (–2·7 to 7·1)
Clinical cure at day 60	142/153‡ (93%)	144/160§ (90%)	2·8 (–3·4 to 9·0)
Recurrence until day 60	9/153‡ (6%)	18/160§ (11%)	–5·5 (–11·6 to 0·8)
Death at day 60	7/153‡ (5%)	9/160§ (6%)	–1·0 (–5·9 to 3·9)
Clostridioides difficile infection until day 60	1/153‡ (1%)	1/160§ (1%)	0·10 (–1·7 to 1·9)

Data are n (%).*16 patients were excluded from the modified intention-to-treat population for not completing 5 days of treatment (n=13) or for missing the assessment at test of cure (n=3). †11 patients were excluded from the modified intention-to-treat population due to not completing 5 days of treatment (n=6), being withdrawn due to adverse events (n=2), or missing the assessment at test of cure (n=3). ‡11 patients excluded from the modified intention-to-treat population due to missed assessment at day 60. §Seven patients excluded from the modified intention-to-treat population due to missed assessment at day 60.

Table 2: **Primary and secondary endpoint analyses**

variable for the DOOR rank.[21] Data were analysed using SPSS Statistics 26 (IBM Corp). This trial is registered with EudraCT (2015-004219-19) and ClinicalTrials.gov (NCT02795949).

Role of the funding source

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Results

2030 patients were evaluated for inclusion between Oct 5, 2016, and Jan 23, 2020; of the 765 who had no exclusion criteria, 344 were randomly assigned (figure 1). 13 (4%) randomised patients were not included in the mITT population, including five patients who withdrew their consent, five randomised in error due to having polymicrobial bacteraemia, and three who were withdrawn by the physician in charge. Therefore, the mITT population included 331 patients: 164 in the de-escalation group and 167 in the control group (non-de-escalation).

Patient characteristics in the two study groups are summarised in table 1. The median age of patients was 72 (IQR 64–80) years; 196 (59%) were male, and the median Charlson Comorbidity index was 3 (IQR 1–5); the most frequent comorbidities were diabetes (120 patients [36%]) and solid-organ cancer (109 [33%]); 168 patients (51%) had a community-acquired infection. The biliary and urinary tracts (129 [39%] and 126 [38%], respectively) were the most frequent sources of bacteraemia. *Escherichia coli* (215 [65%]) and *Klebsiella pneumoniae* (54 [16%]) were the most frequent pathogens.

More patients in the control group versus the de-escalation group had chronic pulmonary disease (29 [17%] *vs* 21 [13%]) and diabetes (64 [38%] *vs* 56 [34%]), but the opposite was true for use of immunosuppressive drugs (17 [10%] *vs* 30 [18%]). More patients in the de-escalation group had nosocomial infection (44 [26%] *vs* 27 [17%]), but fewer presented with severe sepsis or septic shock (35 [21%] *vs* 48 [29%]). The median time on antipseudomonal drugs was 2 days (IQR 2–3) in the de-escalation group and 7 days (6–9) in the control group.

The most frequent empirical antipseudomonal drug used in both groups was piperacillin–tazobactam (104 [63%] of 164 in the de-escalation group and 107 [64%] of 167 in the control group; table 1). The drugs to which patients were de-escalated in the de-escalation group are shown in table 1. 96 (59%) of 164 patients in the de-escalation group and 118 (71%) of 167 in the control group were later switched to oral drugs (table 1).

Clinical cure rates at test of cure were 148 (90%) of 164 patients in the de-escalation group and 148 (89%) of 167 patients in the control group (risk difference 1·6 percentage points; 95% CI –5·0 to 8·2; table 2); thus, de-escalation met the prespecified non-inferiority criterion. The reasons for not reaching clinical cure were similar in both groups (table 2). In multivariable analysis, the adjusted odds ratio (OR) for reaching clinical cure at test of cure in the de-escalation group versus the control group (controlling for chronic pulmonary disease, diabetes, immunosuppressants, acquisition type, and severe sepsis or shock) was 0·56 (95% CI 0·16–2·02; p=0·38).

No significant differences were found for secondary endpoints. Clinical cure at test of cure in the clinically evaluable population (per protocol analysis) was reached

by 143 (97%) of 148 patients in the de-escalation group and 144 (92%) of 156 in the control group (risk difference 4·3 percentage points, 95% CI –0·9 to 9·5). Microbiological cure in the microbiologically evaluable population at test of cure occurred in 124 (97%) of 128 patients in the de-escalation group and 125 (95%) of 132 patients in the control group (risk difference 2·2, 95% CI –2·7 to 7·1; table 2). 60-day mortality was 5% (seven of 153) in the de-escalation group versus 6% (nine of 160) in the control group. At day 60, relapse occurred in nine (6%) of 153 patients in the de-escalation group and 18 (11%) of 160 patients in the control group; only one case of *C difficile* infection was diagnosed in each group.

Subgroup analyses were performed on the mITT population (table 3). Overall, the results were consistent with the primary analysis. Clinical cure rates at test of cure in patients presenting with severe sepsis or septic shock at randomisation were similar in the de-escalation group and control group (44/47 [94%] *vs* 31/34 [91%], risk difference 2·4% [–9·1 to 14·0]). Among patients with urinary tract infection, clinical cure was reached in 59 (98%) of 60 patients in the de-escalation group and 55 (87%) of 63 patients in the control group (risk difference 11·0 [1·8–20·2]). Interactions between the subgroups and treatment group were analysed; none were significant (data not shown).

A DOOR analysis was performed on 146 patients in the de-escalation group and 155 patients in the control group for whom an assessment of all variables at 60 days was available. In the de-escalation group, 55 (38%) patients were cured without events, 53 (36%) were cured with non-severe events, 27 (19%) were cured with one or more severe events, four (3%) were not cured, and seven died (5%; figure 2; appendix 2 p 3). In the control group, 59 (38%) patients were cured without events, 57 (37%) were cured with non-severe events, 26 (17%) were cured with one or more severe events, six (4%) were not cured, and seven (5%) died (figure 2; appendix 2 p 3). The probability of patients in the de-escalation group having a better DOOR score than patients in the control group was 0·50 (95% CI 0·44–0·56). When duration of exposure to antipseudomonal β-lactams was used to break ties (RADAR analysis), the probability of a better DOOR score in patients in the de-escalated group than in patients in the control group was 0·68 (95% CI 0·63–0·73).

99 (60%) of 164 patients in the de-escalation group and 94 (56%) of 167 patients in the control group were reported to have had at least one adverse event (risk difference 4·0 percentage points, 95% CI –6·6 to 14·6; p=0·23). The total number of reported adverse events was 219 in the de-escalation group versus 175 in the control group, and 53 (24%) of 219 events versus 56 (32%) of 175 events were considered severe. Five patients were withdrawn due to adverse events: three in the de-escalation group (persistent fever, development of septic shock, and hepatic abscess) and two in the control group (renal and hepatic toxicity and pancreatitis with abdominal abscess). Table 4 and appendix 2 (p 4) list adverse events and serious adverse events, respectively. 204 minor and ten major protocol deviations were documented without associated safety risks after being assessed by the study team and the monitoring group.

Rectal samples were taken at recruitment and test of cure from 46 patients in the de-escalation group and 64 patients in the control group who gave their consent. Of these, seven in the de-escalation group (15%) and 15 in the control group (23%) acquired any multidrug-resistant Gram-negative bacteria (p=0·28). Multidrug-resistant organisms acquired in the de-escalation group were six Enterobacterales (two AmpC-producing and four ESBL-producing) and one *S maltophilia*, and in the

	De-escalation group	Control group	Difference in percentage points (two-sided 95% CI)
Age			
<80 years	117/124 (94%)	112/121 (93%)	1·8 (4·4 to 8·0)
≥80 years	31/32 (97%)	36/40 (90%)	6·9 (–4·9 to 18·7)
Acquisition type			
Community	82/85 (97%)	70/75 (93%)	3·1 (–3·6 to 9·9)
Non-community	66/71 (93%)	78/86 (91%)	2·3 (–6·4 to 10·9)
Severe sepsis or septic shock			
Yes	44/47 (94%)	31/34 (91%)	2·4 (–9·1 to 14·0)
No	104/109 (95%)	117/127 (92%)	3·3 (–3·0 to 9·5)
Source			
Urinary	59/60 (98%)	55/63 (87%)	11·0 (1·8 to 20·2)
Non-urinary	89/96 (93%)	93/98 (95%)	2·2 (–9·0 to 4·6)
Biliary	57/58 (98%)	61/64 (95%)	3·0 (–3·4 to 9·3)
Non-biliary	89/96 (93%)	86/96 (90%)	3·1 (–4·9 to 11·2)
Urinary or biliary	113/118 (96%)	122/126 (97%)	1·1 (–3·7 to 5·8)
Neither urinary or biliary	36/39 (92%)	33/33 (100%)	7·7 (7·7 to 7·7)
Bacteraemia caused by *Escherichia coli*			
Yes	95/100 (95%)	98/106 (93%)	2·5 (–4·1 to 9·2)
No	53/56 (95%)	50/55 (91%)	3·7 (5·9 to 13·4)

Data are shown for the modified intention-to-treat population. Eight patients in the de-escalation group and six in the control group were excluded for missing the assessment at test of cure.

Table 3: **Subgroup analyses for clinical cure at test of cure**

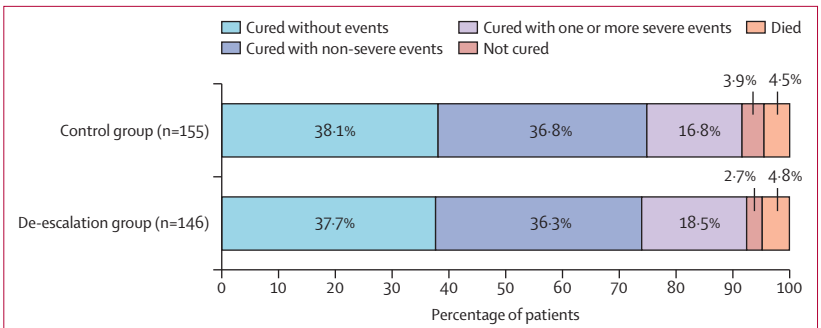

Figure 2: **Desirability of outcome rank scores**

	De-escalation group (n=164)	Control group (n=167)
Gastrointestinal disorders		
Nausea or vomiting	4 (2%)	5 (3%)
Diarrhoea	6 (4%)	11 (7%)
Pancreatitis	0	5 (3%)
Abdominal pain	5 (3%)	5 (3%)
Oral mucosis	3 (2%)	1 (1%)
Constipation	3 (2%)	1 (1%)
Cholangitis	3 (2%)	2 (1%)
Cholecystitis	2 (2%)	2 (1%)
Gastrointestinal bleeding	0	2 (1%)
Liver abscess	1 (1%)	1 (1%)
Cirrhotic decompensation	2 (1%)	3 (2%)
Liver toxicity	0	2 (1%)
Intestinal occlusion	0	1 (1%)
Jaundice	1 (1%)	0
Dehiscence of ileal anastomosis	1 (1%)	0
Infections and infestations		
Respiratory tract	6 (4%)	4 (2%)
Primary bacteraemia or sepsis with unknown source	8 (5%)	2 (1%)
Clostridioides difficile infection	1 (1%)	1 (1%)
Sepsis	3 (2%)	1 (1%)
Urinary tract infection	11 (7%)	6 (4%)
Bacteraemia due to *Escherichia coli*	0	6 (4%)
Otitis	0	1 (1%)
Skin soft tissue	1 (1%)	0
Septic shock	1 (1%)	0
Conjunctivitis	1 (1%)	0
Candidemia	3 (2%)	0
Surgical wound infection	1 (1%)	0
Biliary prosthesis infection	1 (1%)	0
Varicella Zoster virus reactivation	1 (1%)	0
Influenza A infection	1 (1%)	0
General disorders and administration site conditions		
Oedema	1 (1%)	3 (2%)
Phlebitis or extravasation	9 (5%)	1 (1%)
Fever	12 (7%)	8 (4·8)
Multi-organ failure	0	1 (1%)
Fatigue	1 (1%)	0
Exanthema	1 (1%)	0
Abdominal haematoma	1 (1%)	0

(Table 4 continues in next column)

(Continued from previous column)

	De-escalation group (n=164)	Control group (n=167)
Blood and lymphatic system disorders		
Anaemia	2 (1%)	2 (1%)
Thrombocytopenia	2 (1%)	1 (1%)
Leucopoenia	4 (2%)	1 (1%)
Neutropenia	6 (4%)	1 (1%)
Thrombocytosis	1 (1%)	0
Bicytopenia	1 (1%)	0
Investigations		
Hypopotassaemia	0	2 (1%)
Hypophosphatemia	0	1 (1%)
Aspartate transaminase, alanine transaminase elevation	1 (1%)	2 (1%)
Hyperuricemia	0	1 (1%)
Hypernatremia	0	1 (1%)
Hyperbilirubinemia	0	1 (1%)
Creatinine elevation	1 (1%)	0
Hypoalbuminemia	1 (1%)	0
Nervous system disorders		
Acute vestibular neuritis	0	1 (1%)
Epileptic seizures	0	1 (1%)
Syncope	1 (1%)	0
Headache	2 (1%)	0
Asthenia	3 (2%)	2 (1%)
Collection in the anterior epidural space	1 (1%)	0
Respiratory, thoracic, and mediastinal disorders		
Hydropneumothorax	0	1 (1%)
Pleural effusion	0	1 (1%)
Dyspnoea	5 (3%)	3 (2%)
Bronchospasm	0	1 (1%)
Respiratory distress	1 (1%)	1 (1%)
Massive haemoptysis	0	1 (1%)
Cough	2 (1%)	0
Epistaxis	2 (1%)	0

(Table 4 continues in next column)

control group were 13 Enterobacterales (six AmpC-producing, six ESBL-producing, and one carbapenemase-producing) and two *S maltophilia* (appendix 2 p 5).

Discussion

In this pragmatic randomised trial in patients with bacteraemia caused by Enterobacterales, de-escalation following a prespecified rule from an antipseudomonal β-lactam to a narrower-spectrum antibiotic active in vitro against the causative microorganism was non-inferior in efficacy to continuing with the empiric drug. The results of the different outcomes, subgroups, and DOOR analyses were consistent and supported the non-inferiority hypothesis; when time of exposure to antipseudomonal β-lactams was considered, de-escalation was superior. Notably, the 95% CI of the risk difference was greater than 1 for the de-escalation group among patients with urinary tract infection, which is relevant because randomisation was stratified for urinary source.

De-escalation is a broad concept that includes discontinuation of unnecessary drugs or switching to narrower-spectrum antibiotics as targeted therapy, based on microbiological data or clinical re-evaluation.[22] Therefore, it includes heterogeneous drugs (those used initially and for de-escalation) and very diverse clinical

	De-escalation group (n=164)	Control group (n=167)
(Continued from previous column)		
Renal and urinary disorders		
Renal insufficiency	6 (4%)	2 (1%)
Hepatorenal syndrome	1 (1%)	0
Haematuria	3 (2%)	2 (1%)
Dysuria	1 (1%)	1 (1%)
Urinary retention	2 (1%)	1 (1%)
Leukocyturia	0	1 (1%)
Complicated renal cyst	1 (1%)	0
Musculoskeletal and connective tissue disorders		
Chest muscle pain	1 (1%)	1 (1%)
Cardiac disorders		
Heart failure	3 (2%)	2 (1%)
Atrial flutter	0	1 (1%)
Angor	0	1 (1%)
Heart failure	3 (2%)	0
Pericardial effusion	1 (1%)	0
Acute coronary syndrome	1 (1%)	0
Skin and subcutaneous tissue complications		
Rash or urticarial	1 (1%)	2 (1%)
Pruritus	1 (1%)	1 (1%)
Dermatitis	1 (1%)	0
Endocrine disorders		
Gout attack	0	1 (1%)
Hyperglycaemia	1 (1%)	0
Vascular disorders		
Hypotension	3 (2%)	2 (1%)
Ictus	1 (1%)	0
Neoplasms benign, malignant, and unspecified		
Cancer progression	2 (1%)	1 (1%)
Chemotherapy toxicity	1 (1%)	1 (1%)
Myelodysplastic syndrome	1 (1%)	0

Data are number of events (%).

Table 4: **Adverse events**

situations (different infection sources, infection severity, causative pathogens, and patient populations). This heterogeneity poses a challenge for the design of randomised trials with results that can be applied to decisions in individual patients.

We found only three previous randomised trials comparing de-escalation with continuation of initial therapy, all with low statistical power, and none in patients with bacteraemia. Falguera and colleagues evaluated de-escalation based on urine antigens in patients admitted with community-acquired pneumonia in one Spanish hospital;[23] relapse occurred in three (12%) of 25 de-escalated patients after a positive urine antigen result, in one (2%) of 63 patients who were not de-escalated because of a negative urine test, and in two (2%) of 89 not de-escalated because they were assigned to no urine test. Leone and colleagues compared de-escalation (59 patients) and continuation of empiric therapy (57 patients) in patients in the intensive care unit with sepsis of various origins and microorganisms;[24] in that study, de-escalation did not demonstrate non-inferiority for the duration of the intensive care unit stay of the patients, without differences in mortality between groups. The limitations of this study were discussed in detail elsewhere, such as that the enrolled patients were not consecutive and not well balanced, and there was a large variability in the main judgement criteria.[25] Rattanaumpawan and colleagues compared de-escalation with ertapenem (n=32) versus continuing with type-2 carbapenems (n=34) in patients with diverse infections caused by ESBL producers, around 50% of which were bacteraemic.[26] The trial was stopped early because of low recruitment, and no significant differences in outcome were observed in the patients tested. In a meta-analysis of mainly observational studies investigating de-escalation in patients with sepsis or bacteraemia, a possible protective effect of de-escalation on mortality was found, although this effect was no longer significant when only studies providing adjusted estimates were considered.[27] We recently performed an observational study in patients with Enterobacterales bacteraemia initially treated with antipseudomonal agents, in which de-escalation was not associated with worse outcomes in a propensity score-adjusted analysis.[10]

The suggested rank order of drugs used for de-escalation is open to debate because high-level evidence on the differential ecological impact of the drugs is scarce; previously published rankings have been based on expert opinion.[28] Although different antipseudomonals will also have heterogeneous impacts, these drugs have consistently been associated with an increased risk of colonisation and infection with multidrug-resistant *P aeruginosa* and Enterobacterales.[4,5,7] Despite being biologically sound, the possible reduction in risk of acquisition of multidrug-resistant organisms with de-escalation has not been investigated in depth, and the effect might differ depending on the initial and final drugs, the patient's baseline microbiota, and the epidemiological situation. In this study, we performed an exploratory study on the acquisition of multidrug-resistant Gram-negative bacteria in a small subset of patients. The results are encouraging, suggesting that once the efficacy and safety of de-escalation have been demonstrated, these variables could be a primary endpoint in future trials of de-escalation from antipseudomonal drugs. Regarding *C difficile* infection, we could not show any impact because the number of reported cases was very low. A study of an American cohort published in 2019 showed that the use of empirical antipseudomonal β-lactams for more than 48 h was an independent risk factor for *C difficile* infection.[6]

The pragmatic design of this study meant that various antibiotic options could be used in both groups, which raises concerns about potential confounding from

different efficacies of the drugs used by intravenous and oral routes. However, to our knowledge, no significant differences in efficacy have been shown in direct comparisons of the drugs used in randomised trials for susceptible Enterobacterales.[23,24,26] Although more patients in the control group than in the de-escalation group were switched to oral drugs, almost 30% of patients in this group were only treated by the intravenous route, and most patients who were stepped down to an oral drug received ciprofloxacin. A switch to oral fluoroquinolones was much less frequent in the de-escalation group than in the control group as this option was second to last in the list of options for that group, with the intention to avoid it whenever possible because of its antipseudomonal activity. Although the efficacies of all oral drugs used seem similar (at least in bacteraemic urinary tract infection[29,30]), even if fluoroquinolones are considered better the design would have in any case favoured the control group. Overall, we think that the fact that different drugs were used in both groups did not have a relevant impact on the results of the strategies compared.

This study has several limitations. The various antibiotic options in both groups, reflecting actual practice, meant the study could not be blinded. Duration of treatment in most patients was longer than recommended for Enterobacterales bacteraemia based on recent trial results supporting 7 days as an appropriate duration in most patients.[31] The rectal colonisation study was performed on a low number of patients. Some strengths of the study include its randomised pragmatic design and exclusion of stable, low-risk patients who would benefit from very early oral switching. The characteristics of the patients enrolled, including the elderly with comorbidities, are probably representative of the general population in whom de-escalation would be considered.

In conclusion, de-escalation from antipseudomonal β-lactams in patients with bacteraemia caused by Enterobacterales was non-inferior in clinical efficacy to continuing the initial drug, and there was no difference in the number of severe adverse events between groups. The most frequent sources of bacteraemia were the urinary and biliary tracts, so these results apply mostly to these infections. Given the potential ecological benefit, these results provide evidence to implement active actions to promote de-escalation in this clinical setting.

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Contributors
JR-B, LEL-C, and PR-G contributed to the study design and funds proposal; all other authors critically reviewed the study design. LEL-C, JR-B, CR-F, and JMB-F contributed to the study coordination. CR-F and EM-M contributed to the monitoring coordination. MD-V contributed to the microbiological studies; all other authors contributed to the recruitment of patients, follow-up, and collection of patients' data. JR-B and LEL-C contributed to the analyses of data. LEL-C and JR-B drafted the manuscript; all other authors critically reviewed the manuscript. LEL-C and JR-B verified the raw data in the study. 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
LEL-C has served as a scientific adviser for Angelini; a speaker for Angelini, ViiV, Gilead, and Correvio; and a trainer for ViiV, outside the submitted work. LB-P reports fees from Pfizer and Tillotts Pharma Spain, outside the submitted work. PR-G has served as an adviser for Advanz and a speaker for Menarini, Shionogi, and Angelini. All other authors declare no competing interests.

Data sharing
Individual, anonymised data will be shared after a signed agreement with Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla if requested with the objective of performing a meta-analysis with individual patient data. Requests should be submitted to the corresponding author. Interested researchers should obtain the approval of the Ethic Committee CEIM Provincial de Sevilla. A database in SPSS file with the requested data and a dictionary of terms will be provided.

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