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Impact of de-escalation on prognosis of patients with bacteraemia due to Enterobacteriaceae: a post-hoc analysis from a multicenter prospective cohort

--Manuscript Draft--

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Abstract:	Background: More data are needed about the safety of antibiotic de-escalation in specific clinical situations as a strategy to reduce exposure to broad-spectrum antibiotics. The aims of this study were to investigate predictors of de-escalation and its impact on the outcome of patients with bloodstream infection due to Enterobacteriaceae (BSI-E).

	Methods: A post-hoc analysis was performed of a prospective, multicenter cohort of patients with BSI-E initially treated with ertapenem or antipseudomonal β-lactams. Logistic regression was used to analyze factors associated with early de-escalation (EDE) and Cox regression for the impact of EDE and late de-escalation (LDE) on 30-day all-cause mortality. A propensity score (PS) for EDE vs. no de-escalation (NDE) was calculated. Failure at end of treatment and length of hospital stay were also analyzed. Results: Overall, 516 patients were included; EDE was performed in 241 patients (46%), LDE in 95 (18%) and NDE in 180 (35%). Variables independently associated with a lower probability of EDE were multidrug-resistant isolates (OR 0.50, 95% CI 0.30-0.83) and nosocomial infection empirically treated with imipenem or meropenem (OR 0.35, 95% CI 0.14-0.87). After controlling for confounders, EDE was not associated with increased risk of mortality; Hazard ratios (HR) and (95% CI) were: general model, 0.58 (0.25-1.31), model with PS, 0.69 (0.29-1.65), and PS-matched pairs, 0.98 (0.76-1.26). LDE was not associated with mortality. De-escalation was not associated with clinical failure or length of hospital stay. Conclusions: De-escalation in patients with monomicrobial bacteraemia due to Enterobacteriaceae was not associated with a detrimental impact on clinical outcome.
Response to Reviewers:	Sevilla, 18 November 2018 Dear Dr. Paterson, We are submitting the revised version of the manuscript entitled “Impact of de-escalation on prognosis of patients with bacteraemia due to Enterobacteriaceae: a post-hoc analysis from a multicenter prospective cohort” (manuscript ID: CID-91871) according to your and the reviewers’ comments and suggestions. We thank you and the reviewers for their kind and useful comments which have been of help to improve the paper. Please find below our responses to all the comments. Jesús Rodríguez-Baño On behalf of all authors REVIEWER COMMENTS Reviewer #1: This manuscript provides a post-hoc analysis of the effect of de-escalation on the outcome of bacteremic patients who were infected with a single species of Enterobacteriaceae. The conclusion that de-escalation, either early or late, does not affect mortality is important, in that this is the largest study documenting these kinds of data. Although this is a retrospective study and not a randomized, control trial, the data appear to be valid with appropriate statistical analyses. A few minor suggestions have been provided for the consideration of the authors: 1.Line 140. Define BSD: Response: please note that BSD is already defined in line 100 (BSD=broad-spectrum drugs). 2.Lines 140-142. The phrase "or ertapenem" is confusing as it is stands. It appears that this is in the list of antipseudomonal drugs. Perhaps "ertapenem" could be the first drug mentioned followed by the "antipseudomonal beta-lactams such as.." Response: thank you for your comment. We changed this as suggested in line 140, and also in line 285 and in Summary of the main points. 3.Line 180. Please provide further details or a reference for your "phenotypic methods". Response to the reviewer: We used the EUCAST recommendations; we added this information and the appropriate reference. 4.Line 263. The statement that "a urinary or biliary source were protective factors" needs further explanation - they were associated with 40% of the failures. Response to the reviewer: The reviewer is right: 40% of failures occurred in patients with a urinary or biliary tract source (therefore 60% of failures occurred in patients with

	other sources). The protective association of urinary and biliary tract with failure was significant and was confirmed in the multivariate analysis. Please note that the proportion of failures in the whole series was low (6.7%), and in patients with urinary or biliary tract source was 3.7% while for other sources it was 14.3%. If the low rate of failures is not considered, a false impression that failures in such sources was frequent. We added the data for failure rates to avoid such impression. Reviewer #2: In this study, the authors evaluated variables associated with de-escalation, and the impact of de-escalation on prognosis among patients with monomicrobial bacteraemia due to Enterobacterales who received early active empirical monotherapy with antipseudomonal beta-lactams or ertapenem at 13 University hospitals in Spain. They concluded that overall, de-escalation in patients with monomicrobial bacteraemia due to Enterobacteriaceae was not associated with detrimental impact on clinical outcome. Such studies are of clear interest, as they support stewardship activities, which are very important to restrict resistance selection and ultimately the ever increasing incidence of MDR/XDR/PDR infections. There are some limitations, clearly admitted by the authors, but the very large number of cases studied is a strong advantage and the analysis is appropriate, making the manuscript of interest for the literature. I have some suggestions: 1. As the authors performed detailed (phenotypic and molecular) bacteriological analysis of the isolates in a single central laboratory, they could present some data on the resistance patterns (with MICs) and mechanisms of the monomicrobial pathogens of the BSIs, per bacterial species. Response: We added this information in a new supplementary Table (Table S2). 2. The resistance patterns of the community vs hospital Enterobacterales in the study hospitals or, if not available for all hospitals, for Spain overall, would be of interest for the readers. Response: We provide the susceptibility data as requested in a supplementary Table (Table S7). 3. It would be very informative if the authors could also present, further to the existing analysis as a total (to retain the very large number of cases), their results separately for nosocomial/healthcare-associated vs. community BSIs, as nosocomial/healthcare-associated infections are more complicated, as stated also in the text. Response: We performed a stratified analysis for nosocomial and non-nosocomial cases as suggested and provided the results of the estimations of the effect of de-escalation on mortality in the text.

The Editor, *Clinical Infectious Diseases*

Sevilla, Spain, September 18th, 2018

Dear Dr. Schooley,

We are submitting our manuscript entitled: **"Impact of de-escalation on prognosis of patients with bacteraemia due to Enterobacteriaceae: a post-hoc analysis from a multicenter prospective cohort"** to be considered for publication in *Clinical Infectious Diseases*.

This paper is the result of a big multicenter, prospective cohort study investigating the the safety of de-escalation strategy in patients with bacteremia due to Enterobacteriaceae. De-escalation is consider by most infectious diseases specialist as a safe and appropriate strategy for better use of antibiotics; however, it is performed much less that desirable due to different reasons, including scarcity of well-performed studies on its safety. One of the problems of previous studies is the inclusion of different aspects of de-escalation, such as stopping redundant drugs or combination regimens. Our objective was to analyze de-escalation in a specific situation, bacteremia due to Enterobacteriaceae treated empirically with an anti-pseudomonal beta-lactam or ertapenem in monotherapy. We hope our results will reinforce the practice of de-escalation in this situation.

The paper only includes original results, have not been submitted elsewhere and have been seen and approved by all authors.

Sincerely,

Jesús Rodríguez-Baño, on behalf of all authors

Impact of de-escalation on prognosis of patients with bacteraemia due to Enterobacteriaceae: a post-hoc analysis from a multicenter prospective cohort

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Running title: De-escalation in Enterobacteriaceae bacteraemia.

SUMMARY OF THE MAIN POINTS

De-escalation from empirical antipseudomonal β-lactams or ertapenem to lower spectrum antibiotics in patients with bacteremia due to Enterobacteriaceae was not associated with any detrimental impact in terms of mortality, clinical failure or length of hospital stay

ABSTRACT

Background: More data are needed about the safety of antibiotic de-escalation in specific clinical situations as a strategy to reduce exposure to broad-spectrum antibiotics. The aims of this study were to investigate predictors of de-escalation and its impact on the outcome of patients with bloodstream infection due to Enterobacteriaceae (BSI-E).

Methods: A post-hoc analysis was performed of a prospective, multicenter cohort of patients with BSI-E initially treated with ertapenem or antipseudomonal β-lactams. Logistic regression was used to analyze factors associated with early de-escalation (EDE) and Cox regression for the impact of EDE and late de-escalation (LDE) on 30-day all-cause mortality. A propensity score (PS) for EDE vs. no de-escalation (NDE) was calculated. Failure at end of treatment and length of hospital stay were also analyzed.

Results: Overall, 516 patients were included; EDE was performed in 241 patients (46%), LDE in 98 (18%) and NDE in 180 (35%). Variables independently associated with a lower probability of EDE were multidrug-resistant isolates (OR 0.50, 95% CI 0.30-0.83) and nosocomial infection empirically treated with imipenem or meropenem (OR 0.35, 95% CI 0.14-0.87). After controlling for confounders, EDE was not associated with increased risk of mortality; Hazard ratios (HR) and (95% CI) were: general model, 0.58 (0.25-1.31), model with PS, 0.69 (0.29-1.65), and PS-matched pairs, 0.98 (0.76-1.26). LDE was not associated with mortality. De-escalation was not associated with clinical failure or length of hospital stay.

Conclusions: De-escalation in patients with monomicrobial bacteraemia due to Enterobacteriaceae was not associated with a detrimental impact on clinical outcome.

Keywords: De-escalation, streamlining, Enterobacteriaceae, bloodstream infections, mortality.

INTRODUCTION

Patients with sepsis are frequently treated empirically with broad-spectrum drugs (BSD) because the early administration of active drugs has been associated with improved outcome, particularly in the presence of septic shock [1]. This can lead to overuse of these drugs, which is usually considered to be one of the contributing factors for the spread of multidrug-resistant (MDR) bacteria [2]. To minimize this problem, streamlining or de-escalation from broad- to narrower-spectrum drugs is usually advocated once the susceptibility of the causative agent of the infection is known, and antimicrobial stewardship programs frequently include interventions facilitating or recommending this practice [3]. However, de-escalation is performed less frequently than is desirable. Barriers include uncertainty among many prescribers; indeed, although de-escalation is considered standard of care for most infectious diseases specialists, a recent systematic review concluded that there is no adequate evidence as to whether de-escalation of antimicrobial agents is effective and safe for adults with sepsis [4]. Hence, providing more information about the safety of de-escalation would help increase implementation, and knowledge of the variables influencing the performance of de-escalation would lead to better targeting of interventions promoting this practice.

Bloodstream infections (BSI) are an ideal model for de-escalation, since etiology and susceptibility are known, and a more specialized evaluation of patients is possible [5]. A meta-analysis including studies of sepsis, bacteraemia and pneumonia found a trend towards higher mortality with de-escalation in 3 randomized trials, but lower mortality in observational studies [6]. However, the studies were heterogeneous with respect to type of patient and infection, etiology, definitions used and interventions,

which precludes high confidence in the meta-analytic estimates. Studies of specific populations and etiologies are needed therefore. A randomized trial of patients with bacteraemia due to Enterobacteriaceae is now recruiting [7], although the results will not be available for 2 years. The objectives of this study were to evaluate the frequency of variables associated with de-escalation, and the impact of de-escalation on prognosis only among patients with bacteraemia due to Enterobacteriaceae.

METHODS

Study design, sites and study population

This is a post-hoc analysis of the prospective Bactaeremia-MIC cohort, which included BSI episodes due to Enterobacteriaceae at 13 University hospitals in Spain. The methods are detailed in previous reports [8, 9]. Briefly, consecutive adult patients with monomicrobial bacteraemia due to Enterobacteriaceae who received empirical treatment in the first 12 hours after the blood cultures were drawn were included. The original study was conducted between January 2011 and December 2013. Exclusion criteria were polymicrobial bacteraemia, non-hospitalized patients, do-not resuscitate orders, neutropenia (<500/µL) and survival <24 hours after blood cultures were drawn. For this analysis, patients from the Bacteraemia-MIC cohort were selected if: (1) initial treatment was monotherapy with an in vitro active BSD, including antipseudomonal β-lactams such as meropenem, imipenem, doripenem, ceftazidime, cefepime or piperacillin/tazobactam, or ertapenem; and (2) the causative microorganism was susceptible to any of the following narrower-spectrum drugs (NSD): ampicillin, amoxicillin/clavulanic acid, non-antipseudomonal cephalosporins such as cefazolin, cefuroxime, cefotaxime or ceftriaxone, trimethoprim/sulfamethoxazole,

aminoglycosides, fosfomycin and fluoroquinolones. The classification of antibiotics as BSD or NSD was based on a previously published consensus ranking of β-lactams according to spectrum and resistance-promoting potential [10]. Exclusion criteria were treatment change to another broader-spectrum drug between days 2 and 5 (as we were unable to rule out patients having secondary infections that would overestimate the comparative efficacy of NSD), and death before the susceptibility tests were available (since these patients did not have the opportunity to de-escalate). All patients were followed for 30 days.

The Institutional Review Board of the University Hospital Virgen Macarena, Seville, Spain, approved the study and waived the need to obtain informed consent due to the observational nature of the study. This analysis was reported according to STROBE recommendations (Supplementary Table S1) [11].

Variables and definitions

The main outcome variable was 30-day all-cause mortality. Secondary outcomes were: clinical response at day 21, and length of hospital stay among survivors. Clinical response was classified as clinical cure if all signs and symptoms of infection had been completely resolved, and failure if there were any persistent, recurrent or new signs and symptoms related to infection, or if death occurred.

The main exposure of interest was de-escalation, defined as switching from the empirical BSD to any of the NSDs, or from piperacillin-tazobactam, imipenem or meropenem to ertapenem. De-escalation was classified as early de-escalation (EDE) if performed in ≤4 days (the day when blood cultures were drawn was considered day 0), late de-escalation (LDE) it was from day 5 to day 7, or non-de-escalation (NDE) if the empirical drug was continued for at least ≥7 days.

Other exposure variables included demographic data, type of onset of infection (nosocomial, healthcare-associated or community), chronic underlying conditions and severity according to the Charlson index [12], acute severity of underlying condition according to Pitt score [13] measured on day -1, SOFA score measured on day 0 [14], severe sepsis or septic shock at day 0 [15], source of infection using CDC criteria, [16] and microorganism.

All isolates were sent to the Hospital Universitario Virgen Macarena, where identification was confirmed and susceptibility to antimicrobials was studied using microdilution, and interpreted according to EUCAST breakpoints [17]. Extended-spectrum beta-lactamase (ESBL), AmpC and carbapenemase production were studied by phenotypic methods, followed by PCR amplification and molecular sequencing. For the sake of simplicity, isolates producing ESBLs, AmpC or carbapenem resistance were considered as MDR.

Statistical analysis

The chi-square test or Fisher's exact test was used to compare categorical variables. The Mann-Whitney U test was used to compare continuous variables. When appropriate, continuous variables were dichotomized according to their association with death, using Classification and Regression Tree (CART) analysis. Multivariate Cox regression analysis was used to analyze the impact of EDE and LDE on 30-day mortality. Logistic regression and linear regression were used to identify the impact of EDE and LDE on failure and length of hospital stay among survivors, respectively. Variables with a P value of <0.2 in univariate comparisons and those considered of clinical importance were manually entered into the multivariate model. The variables in the models were selected manually using a backward stepwise process. Interactions and

collinearity were evaluated. Sensitivity analyses were performed by reclassifying the main exposure as EDE vs LDE+NDE, and as EDE+LDE vs NDE.

In addition, a propensity score (PS) was calculated for receiving EDE instead of NDE. Its predictive ability was calculated using the area under the receiver operating curve (AUROC) with 95% confidence intervals (CI), and the Hosmer-Lemeshow test was used for goodness of fit. The PS was used in two ways: as a covariate to control for residual confounding in multivariate models after checking for collinearity, and to perform a matched cohort analysis in which patients undergoing EDE and NDE were matched (1:1) according to their propensity scores using calipers of width 0.007. Statistical analysis was carried out using the SPSS program (SPSS 25.0, IBM Corp, Armonk, NY, USA).

RESULTS

The Bacteraemia-MIC cohort included 1058 patients with BSI due to Enterobacteriaceae; of these, 516 (48.7%) patients fulfilled the criteria for the de-escalation analysis (Figure 1). The number of patients per hospital ranged from 8 (1.6%) to 69 (13.4%). Overall, 241 (46.7%) patients received EDE, 95 (18.4%) LDE, and 180 (34.8%) were not de-escalated. The proportion of EDE among hospitals with >20 cases ranged from 13% to 75.4%. The patients' characteristics are shown in Table 1. Compared to patients who underwent EDE, those in the NDE group more frequently had nosocomial infections, had been admitted to the ICU, had respiratory tract infections and received empiric therapy with meropenem. Overall, 70 (13.6%) isolates were ESBL producers, 26 (5.1%) AmpC producers, and 3 (0.6%) were carbapenem-resistant (none were carbapenemase producers). Among patients undergoing de-

escalation, the most frequent empirical drugs were piperacillin-tazobactam, and imipenem or meropenem and the most frequent drugs used for de-escalation were fluoroquinolones (68 patients in EDE and 38 in LDE), cefotaxime or ceftriaxone (92 and 20) and amoxicillin-clavulanic acid (43 and 26) (supplementary Table S2).

Variables associated with EDE

The association of different variables with EDE is shown in Table 2. The variable "center" was dichotomized into low and high proportions of patients with EDE. In multivariate analysis, bacteraemia caused by MDR isolates and nosocomial episodes empirically treated with imipenem or meropenem were associated with a lower probability of receiving EDE. Even after controlling for these variables, patients hospitalized in centers with a high proportion of EDE still had a higher probability of receiving EDE. The AUROC for the model was 0.72 (95% CI 0.66-0.75).

Mortality analysis

Mortality rates were 4.1% (10/241), 6.3% (6/95) and 9.4% (17/180) in patients with EDE, LDE and NDE, respectively (Table 1). The univariate and multivariate analysis of variables associated with 30-day mortality are shown in Table 3. Source of bacteraemia was dichotomized into urinary or biliary tract vs others, according to their association with mortality. Hospitals were also classified into those with lower and higher mortality, and this variable was retained in the models. Multivariate analysis (Table 3) selected Charlson >3, source other than urinary or biliary tract, presentation with severe sepsis or shock, and SOFA >4 as associated with mortality. Among de-escalated patients, no trend toward higher mortality was found, although the model showed poor discrimination (AUROC=0.64; 95% CI: 0.52-0.75). In sensitivity analysis,

the adjusted HR for mortality were: 0.67 (95% CI 0.33-1.36, p=0.27) for EDE or LDE vs. NDE, and 0.60 (95% CI 0.27-1.30, p=0.19) for EDE vs LDE-NDE. No significant interactions were found in either model.

We then investigated the impact of EDE versus NDE including the PS for EDE (LDE patients were excluded from this analysis) (Table 3). No significant collinearity was found between the PS and other variables. Again, EDE did not show an association with higher 30-day mortality (adjusted HR=0.69; 95% CI: 0.29-1.65; p=0.41); the AUROC of this model was higher (0.72; 95% CI: 0.61-0.82). Finally, we matched 137 pairs of patients receiving EDE or NDE according to PS. Matched sub-cohorts had exposure to all other variables (supplementary Table S3). Mortality was 5.4% (n=7) in EDE and 7.7% in NDE (n=10) (HR=0.98; 95% CI: 0.76-1.26; p=0.84).

Clinical cure and length of stay

Overall, 35 patients showed failure at the end of antibiotic treatment (6.7%): 11/2421 (4.6%) with EDE, 6/95 (6.3%) with LDE, and 18/180 (10%) with NDE. The univariate and multivariate analyses of variables associated with failure are shown in Table 4. The multivariate model showed that Charlson index >3, severe sepsis/septic shock at presentation and SOFA score at day 0 were associated with higher treatment failure, while a urinary or biliary source were protective factors. De-escalation was not found to be associated with failure (Table 4).

The median hospital stay after BSI was 14 days (IQR 9-24) and according to group, it was 14 days (9-28) for EDE, 13 (7-20) for LDE and 15 days (IQR 10-25) for NDE. The univariate analysis of variables associated with length of hospital stay is shown at Supplementary Table S4. Linear regression model of variables associated with length of hospital stay showed that nosocomial acquisition, Charlson index >3 and the

253 presence of severe sepsis/septic shock at presentation were associated with more days of
254 hospitalization (p values 0.006, <0.001 and 0.01 respectively). EDE and NDE were not
255 found to be associated with longer hospital stay (p=0.56 and 0.67, respectively)
256 (Supplementary Table S5).
257
258 **DISCUSSION**
259
260 In this cohort, less than half the candidate patients received early de-escalation,
261 and one third of patients were never de-escalated. Patients with MDR isolates or
262 nosocomial infections empirically treated with imipenem or meropenem had a lower
263 probability of de-escalation. Finally, neither EDE nor LDE were shown to be associated
264 with worse outcomes.
265 To our knowledge, this is by far the biggest study of de-escalation among
266 patients with bacteraemia [6]. It is important to note that we only included non-
267 neutropenic, adult patients with monomicrobial bacteraemia due to Enterobacteriaceae
268 who received early active empirical monotherapy with antipseudomonal beta-lactams or
269 ertapenem. We are not therefore addressing the impact of changing from combination
270 therapy to monotherapy, but only of changes in the empirical drug used. This
271 population is somewhat more homogeneous than those considered in most previous
272 studies.
273 The definition of de-escalation used is open to debate [18]. Unfortunately, many
274 previous studies did not provide a specific definition of de-escalation and/or the drugs
275 considered. The objective of de-escalation is to reduce exposure at the individual and
276 group levels to drugs with a high negative ecological impact. However, the ecological
277 impact of the drugs may depend on different variables, including local epidemiology,

the previous colonization status of patients, microbiota composition, and the dosing or duration of antibiotic therapy. In this study we used a classification of beta-lactams developed by consensus [10]; in this consensus, imipenem and meropenem ranked highest in terms of spectrum width and highest resistance selecting potential, followed by ertapenem and piperacillin-tazobactam or antipseudomonal cephalosporins. As drugs for de-escalation, we included the lower-ranked beta-lactams in the consensus, in addition to other drugs suitable for oral use [19] that would allow the earlier discharge of patients, such as fluoroquinolones and trimethoprim-sulfamethoxazole. We also analyzed late de-escalation.

De-escalation is performed less frequently than is desirable [20]. The main barriers identified for de-escalations are uncertainties about etiology, inadequate empirical therapy and isolation of MDR bacteria [19, 20]. In patients with monomicrobial bacteraemia due to Enterobacteriaceae, the only uncertainty about etiology is the possibility of polymicrobial infection in certain types of infection, typically intraabdominal and some skin/skin structure-associated infections. In our study, source of BSI was not associated with higher rates of de-escalation when controlling for confounders, and inadequate empirical therapy was an exclusion criterion. However, MDR bacteria were associated with a lower probability of de-escalation. We also identified nosocomial infection as a predictor for no de-escalation when these patients had been empirically treated with imipenem or meropenem, which may be a marker for more complex clinical situations. We suspect that other factors, such as stewardship interventions, less awareness of susceptibility results at weekends, and the training and opinions of individual prescribers could also play a role in de-escalation practice and merit specific studies.

In crude analysis, de-escalation was associated with lower mortality and failure. This was probably due to confounding by indication as the associations were no longer significant when other mortality predictors were considered in multivariate analysis, which is similar to the results found in the meta-analysis by Paul et al for observational studies of patients with severe sepsis or bacteraemia [6]. The results are reinforced by the fact that all our estimates in different analyses were consistent, and that we included mortality, failure of treatment and length of stay as outcome variables. Interestingly, the estimates provided by multivariate analysis were much less accurate than those provided by the PS-based matched pairs analysis. Our results strongly suggest therefore that de-escalation is safe. In fact, theoretically, it may have some individual beneficial effects if secondary infections caused by MDR bacteria are reduced, although demonstrating such an effect would require specific studies with a very large number of patients. Any analysis of population-level benefits would also require specific studies.

Our study has several limitations. Because it is not a randomized controlled trial, unmeasured confounding variables or residual confounding cannot be ruled out. The data were collected several years ago and changes in antimicrobial resistance may influence the results. Moreover, despite being controlled in the analysis, differences in clinical practice at each center might have influenced the outcomes. Some strengths of the study are its multicenter character, the use of clearly specified definitions, and the use of advance statistical methodologies to control for confounders.

In conclusion, the results of this study reinforce the fact that antibiotic de-escalation in patients with monomicrobial bacteraemia due to Enterobacteriaceae does not have a detrimental impact on outcome, 30-day all-cause mortality, failure, or length of hospital stay when compared with continuation with broad-spectrum antibiotics. These results may be useful for antibiotic stewardship activities.

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Potential Conflicts of Interest

Dr. Zaira Palacios Baena reports personal fees from Gilead, outside the submitted work**.** Dr. Rodríguez-Baño reports personal fees from Merck, personal fees from AstraZeneca for a nondrug related research projects, and grants from Innovative Medicines Initiative (IMI), outside the submitted work. All other authors have no potential conflict of interest to declare.

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Figure 1: Flowchart

TABLES

Table 1. Features of patients with bacteraemia due to Enterobacteriaceae according to de-escalation group.

Variable	Early de-escalation (n=241)	Late de-escalation (n=95)	No de-escalation (n=180)	*P value* early vs no de-escalation	*P value* late vs no de-escalation
High-mortality hospital	81 (33.6)	31(32.6)	69 (38.3)	0.31	0.35
Etiology: *Escherichia coli*	164 (68)	60(63.2)	111 (61.7)	0.17	0.80
ESBL-producing Enterobacteriaceae	26 (10.6)	11 (11.6)	31 (17.2)	0.05	0.21
AmpC-producing Enterobacteriaceae	7 (2.9)	3 (3.2)	16 (8.9)	0.01	0.12
Carbapenem-resistant Enterobacteriaceae	0	2 (2.1)	1 (0.6)	0.88	0.57
Multidrug-resistant Enterobacteriaceae [1]	33 (13.7)	16 (16.8)	48 (26.7)	<0.001	0.06
Male gender	158 (65.6)	64 (67.4)	117 (65)	0.90	0.69
Age >60 years	187 (77.6)	79(83.2)	126 (70)	0.07	0.01
Nosocomial acquisition	57 (23.7)	23 (24.2)	76 (42.2)	<0.001	0.003
Intensive care unit admission	7 (2.9)	1 (1.1)	14 (7.8)	0.02	0.02
Previous surgery	32 (13.3)	14 (14.7)	41 (22.8)	0.01	0.11
Previous antimicrobial therapy	104 (43.2)	33 (34.7)	75 (41.7)	0.76	0.26
Charlson index >3	60 (24.9)	17 (17.9)	42 (23.3)	0.71	0.29
Source					
Urinary tract	104 (43.2)	30 (31.6)	59 (32.8)	0.03	0.94
Biliary tract	86 (35.7)	39 (41.1)	52 (28.9)	0.17	0.39
Other intrabdominal source	18 (7.5)	15 (15.8)	26 (14.4)	0.03	0.90
Skin and skin structures	4 (1.7)	2 (2.1)	8 (4.4)	0.16	0.51
Catheter-related	10 (4.1)	3 (3.2)	9 (5)	0.85	0.68
Respiratory tract	5 (2.1)	2 (2.1)	11 (6.1)	0.05	0.54
Others	2 (0.8)	1 (1.1)	3 (1.7)	0.74	0.68
Unknown source	12 (5)	1 (1.1)	11 (6.1)	0.77	0.10
Pitt score >3	25 (10.4)	3 (3.2)	22 (12.2)	0.55	0.01
Severe sepsis/septic shock	83 (34.4)	24 (25.3)	67 (37.2)	0.55	0.04
SOFA score >4 (day 0)	59 (24.5)	14 (14.7)	45 (25)	0.90	0.04

Empirical therapy					
Piperacillin/tazobactam	124 (51.5)	54 (56.8)	82 (45.6)	0.27	0.09
Ceftazidime	10 (4.1)	1 (1.1)	6 (3.3)	0.86	0.45
Cefepime	5 (2.1)	0	2 (1.1)	0.70	0.77
Ertapenem	37 (15.4)	14 (14.7)	22 (12.2)	0.43	0.68
Imipenem	29 (12)	2 (2.1)	15 (8.3)	0.28	0.07
Meropenem	36 (14.9)	24 (25.3)	53 (29.4)	<0.001	0.55
Mortality at day 30	10 (4.1)	6 (6.3)	17 (9.4)	0.02	0.37
Failure at the end of treatment	11 (4.6)	6 (6.3)	162 (10)	0.02	0.30
Median days of hospital stay (IQR)	14 (9-28)	13 (7-20)	15 (10-25)	0.21	0.003

IQR: interquartile range.
[1]Multidrug-resistant isolates were those producing ESBL or AmpC or carbapenem-resistant.

Table 2. Analysis of the association of different variables with early de-escalation.

Variable	Early de-escalation (n=241)	Late or not de-escalation (n=275)	Crude OR (95% CI)	*P value*	Adjusted OR (95% CI)[1]	*P value*
Hospital with high rate of de-escalation	131 (54.4)	59 (21.5)	4.36 (2.97-6.39)	<0.001	4.34 (2.93-6.45)	<0.001
Etiology: *Escherichia coli*	164 (68)	171 (62.2)	1.29 (0.90-1.86)	0.16		
Multidrug-resistant isolate[2]	33 (13.7)	64 (23.3)	0.52 (0.33-0.83)	0.006	0.50 (0.30-0.83)	0.007
Empirical treatment with piperacillin-tazobactam	124 (51.5)	136 (49.5)	1.08 (0.76-1.53)	0.65		
Empirical treatment with ertapenem	37 (15.4)	36 (13.1)	1.20 (0.73-1.97)	0.46		
Empirical treatment with imipenem or meropenem	65 (27)	94 (34.2)	1.40 (0.96-2.05)	0.07	1.20 (0.73-1.99)	0.46
Male gender	158 (65.7)	181 (65.8)	0.98 (0.68-1.42)	0.95		
Age >60 years	187 (77.6)	205 (74.5)	1.18 (0.78-1.77)	0.41		
Nosocomial infection	57 (23.7)	99 (36)	0.55 (0.37-0.81)	0.002	0.83 (0.50-1.39)	0.49
Intensive care unit admission	7 (2.9)	15 (5.5)	0.51 (0.20-1.29)	0.15		
Previous surgery	32 (13.3)	55 (20)	0.61 (0.38-0.98)	0.04		
Charlson index >3	60 (24.9)	59 (21.5)	1.21 (0.80-1.82)	0.35		
Urinary and biliary tract source	190 (78.8)	180 (65.5)	1.96 (1.32-2.92)	<0.001		
Pitt score >3	25 (10.4)	25 (9.1)	1.15 (0.64-2.07)	0.62		
Severe sepsis/septic shock	83 (34.4)	91 (33.1)	1.06 (0.73-1.53)	0.74		
SOFA score >4 (day 0)	59 (24.5)	59 (21.5)	1.18 (0.78-1.79)	0.41		
Interaction: nosocomial infection and empirical treatment with imipenem or meropenem					0.35 (0.14-0.87)	0.02

[1]Hosmer-Lemeshow test, P value = 0.99; AUROC = 0.71 (0.66-0.75), p<0.001.
[2]Multidrug-resistant isolates were those producing ESBLs or AmpC, or carbapenem-resistant.

Table 3. Univariate and multivariate analyses of risk factors associated with all-cause 30-day mortality using Cox regression.

			Crude analysis		Adjusted analysis[2]		EDE vs NDE, adjusted by PS[3]	
Variable	**No. deceased (%) N= 33**	**No. alive (%) N= 483**	**HR (95 CI%)**	***P value***	**HR (95% CI)**	***P value***	**HR (95% CI)**	***P value***
Hospital with high mortality	19 (57.6)	162 (33.5)	2.56 (1.28-5.12)	0.007	1.68 (0.80-3.53)	0.16	1.91 (0.83-4.36)	0.12
Etiology: *Escherichia coli*	17 (51.5)	318 (65.8)	0.56 (0.281.12)	0.10				
Male gender	22 (66.7)	317 (65.6)	1.05 (0.51-2.17)	0.88				
Age >60 years	27 (81.8)	365 (75.6)	1.45 (0.61-3.52)	0.40				
Nosocomial acquisition	18 (54.5)	138 (28.6)	2.84 (1.43-5.64)	0.003				
Intensive care unit admission	5 (15.2)	17 (3.5)	4.15 (1.60-10.76)	0.003				
Charlson index >3	14 (42.4)	105 (21.7)	0.54 (1.27-5.07)	0.008	3.02 (1.50-6.09)	0.002	3.69 (1.65-8.24)	0.001
Urinary or biliary source	14 (42.4)	356 (73.7)	0.28 (1.14-0.56)	<0.001	0.35 (0.17-0.74)	0.006	0.23 (0.08-0.61)	0.004
Pitt score >3	10 (30.3)	40 (8.3)	4.33 (2.06-9.10)	<0.001				
Severe sepsis/septic shock	23 (69.7)	151 (31.3)	4.76 (2.26-10.01)	<0.001	3.06 (1.32-7.09)	0.009	3.29 (1.25-8.63)	0.01
SOFA score >4 (day 0)	17 (51.5)	101 (21)	3.81 (1.92-7.54)	<0.001	2.18 (1.03-4.57)	0.03	2.73 (1.20-6.23)	0.01
Empirical meropenem	9 (27.3)	104 (21.5)	1.35 (1.62-2.91)	0.44				
De-escalation								
No de-escalation	17 (51.5)	163 (33.7)	Reference	0.10	Reference	0.41	Reference	
Early de-escalation	10 (30.3)	231 (47.8)	0.42 (0.19-0.93)	0.03	0.58 (0.25-1.31)	0.19	0.69 (0.29-1.65)	0.41
Late de-escalation	6 (18.2)	89 (18.4)	0.65 (0.25-1.66)	0.37	0.89 (0.35-2.26)	0.80	Excluded	
Propensity score[1]							0.81 (0.06-10.42)	0.87

Abbreviations: PS, propensity score; EDE, early de-escalation; NDE, no de-escalation.

[1]Calculated only for patients in the early de-escalation and no de-escalation groups. The variables included in the propensity score were: high-risk hospital, microorganism, gender, age, acquisition, department, Charlson index, previous antibiotic therapy, urinary and biliary source, Pitt score, SOFA score at day 0, severe sepsis and septic shock, and empirical therapy. The AUROC of the PS model was 0.68 (95%CI 0.63-0.73), *p value*=0.001, Hosmer-Lemeshow test=0.84.

[2]The AUROC of the model was 0.64 (0.52-0.75), *p value=0.007*

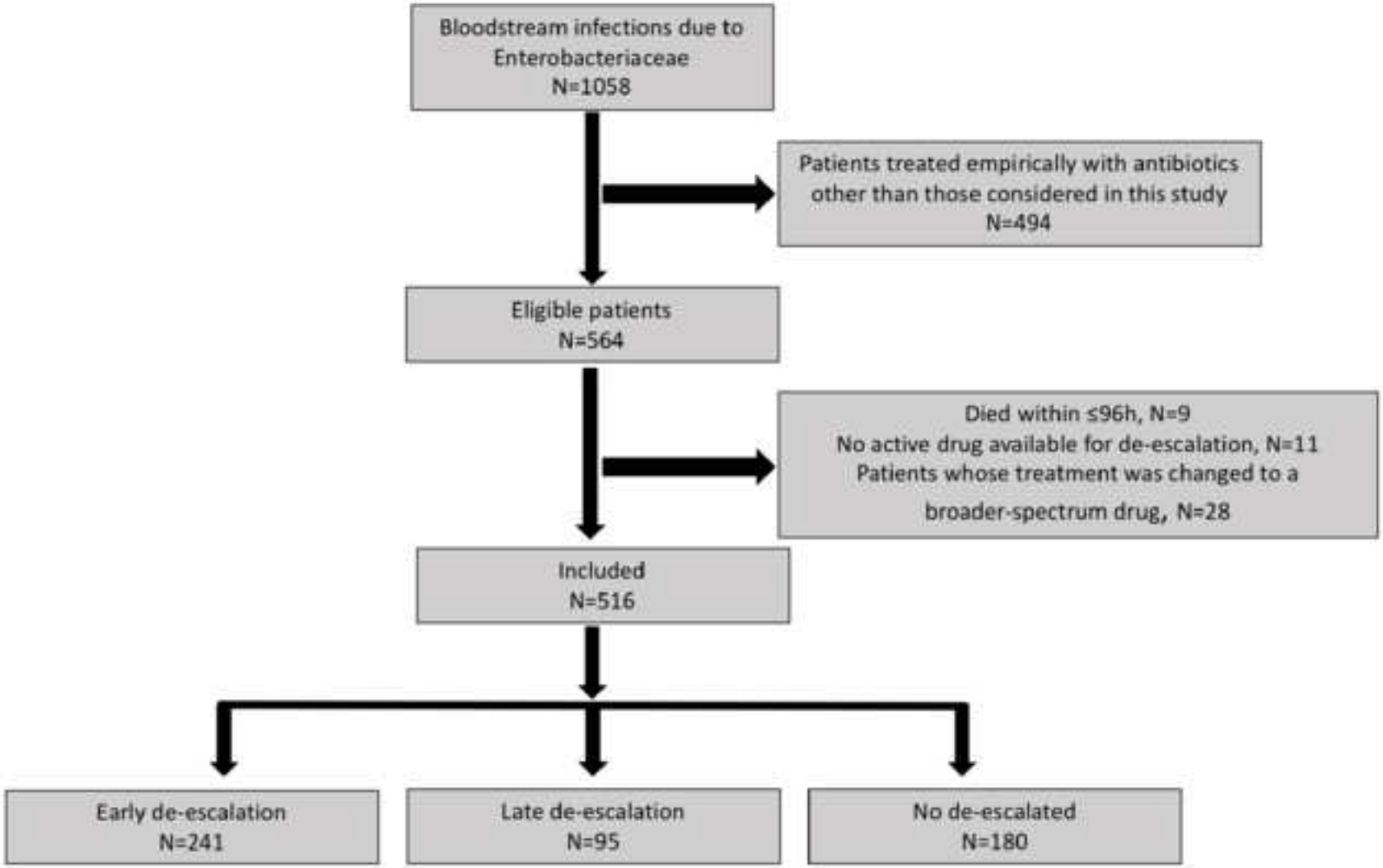
[3]Patients in the late de-escalation group were excluded from this analysis.

Table 4. Univariate and multivariate model of variables associated with failure at the end of antibiotic treatment.

			Crude analysis		Adjusted analysis[1]	
Variable	**Failure (%) (N= 35)**	**Cure (%) (N= 481)**	**OR (95% CI)**	***P value***	**OR (95% CI)**	***P value***
Hospital with high proportion of failure	17 (48.6)	131 (27.2)	2.52 (1.26-5.04)	0.009	1.70 (0.78-3.70)	0.17
Etiology: *Escherichia coli*	20 (57.1)	315 (65.5)	0.70 (0.35-1.40)	0.32		
Male gender	22 (62.9)	317 (65.9)	0.87 (0.43-1.78)	0.71		
Age >60 years	29 (82.9)	363 (75.5)	1.57 (0.63-3.87)	0.32		
Nosocomial acquisition	17 (48.6)	139 (28.9)	2.32 (1.16-4.64)	0.01		
Intensive care unit admission	4 (11.4)	18/ (3.7)	3.31 (1.05-10.40)	0.04		
Charlson index >3	14 (40)	105 (21.8)	2.38 (1.17-4.85)	0.01	2.87 (1.31-6.29)	0.008
Urinary or biliary tract source	14 (40)	356 (74)	0.23 (0.11-0.47)	<0.001	0.24 (0.11-0.52)	<0.001
Pitt score >3	10 (28.6)	40 (4.3)	4.41 (1.97-9.83)	<0.001		
Severe sepsis/septic shock	24 (68.6)	150 (31.2)	4.81 (2.29-10.08)	<0.001	3.09 (1.27-7.50)	0.01
SOFA score >4 (Day 0)	19 (54.3)	99 (20.6)	4.58 (2.27-9.23)	<0.001	2.76 (1.21-6.25)	0.01
De-escalation						
No de-escalation	18 (51.4)	162 (33.7)	Reference		Reference	
Early de-escalation	11 (31.4)	230 (47.8)	0.43 (0.19-0.93)	0.03	0.56 (0.24-1.32)	0.18
Late de-escalation	6 (17.1)	89 (18.5)	0.60 (0.23-1.58)	0.30	0.98 (0.34-2.83)	0.98

Abbreviations: ICU, intensive care unit.

[1]AUROC of this model 0.81 (0.74-0.89), p<0.001, Hosmer-Lemeshow test 0.61.



Supplementary material:

- **Supplementary Table S1**. Checklist of items according to STROBE recommendations.
- **Supplementary Table S2.** Susceptibility data and production of key beta-lactamase among Enterobacteriaceae causing bloodstream infection in the patients included in the study.
- **Supplementary Table S3.** Different de-escalation schemes.
- **Supplementary Table S4.** Comparison of patients matched according to propensity score.
- **Supplementary Table S5.** Univariate analysis of variables associated with length of hospital stay.
- **Supplementary Table S6.** Linear regression model of variables associated with length of hospital stay.
- **Supplementary Table S7.** Susceptibility data and production of key beta-lactamase among Enterobacteriaceae causing bloodstream infection in the whole Bacteremia-MIC cohort and stratified according to the type of acquisition.

Supplementary Table S1. Checklist of items according to STROBE document.

	RECOMMENDATION	ASSESSMENT IN ARTICLE
TITLE AND ABSTRACT	*a*) Indicate the study design with a commonly used term in the title or abstract *b*) Provide an informative and balanced summary in the abstract of what was done and what was found	a) Study design specified in title and abstract b) Balanced summary included in the abstract
BACKGROUND/ RATIONALE	Explain the scientific background and rationale for the investigation being reported	The scientific background and rationale are included in the introduction
OBJECTIVES	State specific objectives, including any pre-specified hypotheses	Pre-specified hypothesis and objectives are stated in Methods
STUDY DESIGN	Present key elements of study design early in the paper	Study design described in the first part of Methods
SETTING	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Described in Methods
PARTICIPANTS	(*a*) Give the eligibility criteria and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	a) Described in Methods b) This is not a matched study
VARIABLES	Clearly define all outcomes, exposures, predictors, potential confounders and effect modifiers. Give diagnostic criteria, if applicable	Defined in Methods
DATA SOURCES/ MEASUREMENT	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Specified in Methods. The same methods for data collection were used in groups.
BIAS	Describe any efforts to address potential sources of bias	Selection bias: inclusion of consecutive cases. Information bias: use of standard, well-defined, easy-to-collect variables (piloted). Use of soft and hard outcome variables.

STUDY SIZE	Explain how the study size was arrived at	Explained in Methods
QUANTITATIVE VARIABLES	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.	Quantitative variables were handled as such. No groupings were made
STATISTICAL METHODS	(*a*) Describe all statistical methods, including those used to control for confounding *b*) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	a) Quantitative variables were handled as such. No groupings were made b) Included in Methods c) Included in Methods d) No patient was lost to follow-up e) Included in methods
PARTICIPANTS	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	a), b) and c) Included in results.
DESCRIPTIVE DATA	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	a), b), c) Table 1
OUTCOME DATA	Report numbers of outcome events or summary measures over time	Table 3
MAIN RESULTS	*(a)* Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized *c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time	a), b), c) Table 3

	period	
OTHER ANALYSES	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Included in Results
KEY RESULTS	Summarize key results with reference to study objectives	Specified in Abstract and Discussion
LIMITATIONS	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Included in Discussion
INTERPRETATION	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Included in Discussion
GENERALIZABILITY	Discuss the generalizability (external validity) of the study results	Included in Discussion
FUNDING	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Included

Supplementary Table S2. Susceptibility data and production of key beta-lactamases among the Enterobacteriaceae causing bloodstream infections in the patients included in the study. Data are number of susceptible isolates (or beta-lactamase producers) per isolates tested (percentage per group).

	Escherichia coli **(N=335)**	***Klebsiella*** **spp. (n=101)**	***Proteus*** **spp. (n=12)**	***Enterobacter*** **spp. (n=40)**	***Serratia*** **spp. (n=14)**	**Others (n=14)**
Amoxicillin-clavulanic acid	163/329 (49.5)	77/101 (76.2)	10/11 (90.9)	3/39 (7.7)	1/14 (7.1)	1/14 (7.1)
Piperacillin-tazobactam	307/329 (93.3)	91/101 (90.1)	11/11 (100)	33/40 (82.5)	12/14 (85.7)	12/14 (85.7)
Cefotaxime	282/334 (84.4)	91/101 (90.1)	12/12 (100)	28/40 (70)	12/14 85.7)	11/14 (78.6)
Cefepime	286/334 (85.6)	95/101 (94.1)	12/12 (100)	33/40 (82.5)	14/14 (100)	14/14 (100)
Ertapenem	334/334 (100)	100/101 (99)	12/12 (100)	38/40 (95)	14/14 (100)	14/14 (100)
Meropenem	334/334 (100)	101/101 (100)	12/12 (100)	40/40 (100)	14/14 (100)	14/14 (100)
Ciprofloxacin	194/334 (58.1)	89/101 (88.1)	11/12 (91.7)	35/40 (87.5)	14/14 (100)	13/14 (92.9)
ESBL-producers	55/335 (16.4)	8/101 (7.9)	0/12 (0)	5/40 (12.5)	0/14 (0)	0/14 (0)
AmpC-producer	12/335 (3.6)	2/101 (2)	0/12 (0)	6/40 (15)	2/14 (14.3)	4/14 (28.6)
Carbapenemase-producer	0/335 (0)	0 (101 (0)	0/12 (0)	0/40 (0)	0/14 (0)	0/14 (0)

Supplementary Table S3. Distribution of de-escalation schemes.

		De-escalation drug					
		Ampicillin (n=5)	**Amoxicillin-clavulanic acid (n=69)**	**Cefotaxime, ceftriaxone (n=112)**	**Ertapenem (n=33)**	**Ciprofloxacin, levofloxacin (n=106)**	**Trimethoprim-sulfamethoxazole (n=10)**
Empirical drug							
Early De-escalation	**Piperacillin-tazobactam (n=124)**	3	21	44	18	34	4
	Ceftazidime (n=10)		2	7	-	1	-
	Cefepime (n=5)	1	-	2	-	2	-
	Ertapenem (n=37)	1	5	19	-	9	3
	Imipenem, meropenem (n=65)	-	15	20	8	22	-
	Total	5	43	92	26	68	7
Late De-escalation	**Piperacillin-tazobactam (n=54)**	-	18	7	2	27	-
	Ceftazidime (n=1)	-	-	1	-	-	-
	Ertapenem (n= 14)	-	4	3	-	4	3
	Imipenem, meropenem (n=25)	-	4	9	5	7	-
	Total	0	26	20	7	38	3

Supplementary Table S4. Comparison of matched patients according to propensity score.

Variable	Early de-escalation (n=130)	No de-escalation (n=130)	*P value*
High mortality hospital	46/130 (35.4)	45/130 (34.6)	0.89
Etiology: *Escherichia coli*	89/130 (68.5)	88/130 (67.7)	0.89
Male gender	82/130 (63.1)	83/130 (63.8)	0.89
Age >60 years	101/130 (77.7)	96/130 (73.8)	0.46
Nosocomial acquisition	40/130 (30.8)	43/130 (33.1)	0.69
ICU admission	7/130 (5.4)	6/130 (4.6)	0.77
Previous surgery	20/130 (15.4)	24/130 (18.5)	0.50
Previous antimicrobial therapy	54/130 (41.5)	52/130 (40)	0.80
Charlson index >3	28/130 (21.5)	31/130 (23.8)	0.65
Source			0.52
Urinary tract	58/130 (44.6)	48/130 (36.9)	
Biliary tract	38/130 (29.2)	45/130 (34.6)	
Other intraabdominal Infection	13/130 (10)	13/130 (10)	
Skin and skin structures	2/130 (1.5)	5/130 (3.8)	
Catheter-related	7/130 (5.4)	6/130 (4.6)	
Respiratory tract	2/130 (1.5)	4/130 (3.1)	
Others	0	2/130 (1.5)	
Unknown source	10/130 (7.7)	7/130 (5.4)	
Pitt score >3	16/130 (12.3)	14/130 (10.8)	0.69
Severe sepsis/septic shock	48/130 (36.9)	47/130 (36.2)	0.89
SOFA score >4 (day 0)	35/130 (26.9)	35/130 (26.9)	1
Empirical therapy			0.83
Piperacillin/tazobactam	66/130 (50.8)	68/130 (52.3)	
Ceftazidime	2/130 (1.5)	5/130 (3.8)	
Cefepime	2/130 (1.5)	2/130 (1.5)	
Ertapenem	19/130 (14.6)	19/130 (14.6)	
Imipenem	14/130 (10.8)	15/130 (11.5)	
Meropenem	27/130 (20.8)	21/130 (16.2)	
Mortality at day 30	7/130 (5.4)	10/130 (7.7)	0.45
Failure at end of treatment	6/130 (4.6)	10/130 (7.7)	0.30
Median days of hospital stay (IQR)	13 (8-26)	15 (10-24)	0.38

IQR: interquartile range

Supplementary Table S5. Univariate analysis of variables associated with length of hospital stay.

Variable	*P* value
Etiology: *Escherichia coli*	0.06[1]
Male gender	0.27[1]
Age >60 years	0.34[1]
Nosocomial acquisition	0.002[1]
Intensive care unit admission	0.01[1]
Charlson index >3	0.001[1]
Urinary or biliary tract source	0.002[1]
Pitt score >3	0.16[1]
Severe sepsis/septic shock	0.001[1]
SOFA score >4 (day 0)	0.06[1]
Empirical treatment with meropenem	0.04[1]
De-escalation	0.02[2]
No de-escalation	
Early de-escalation	
Late de-escalation	
Failure at end of treatment	0.91[1]
Mortality at day 30	0.27[1]

[1]U Mann-Whitney test
[2]Kruskal-Wallis test

Supplementary Table S6. Linear regression model of variables associated with length of hospital stay.

Variable	Coefficient	*P value*	95% CI
Nosocomial acquisition	2.78	0.006	1.17-6.79
Charlson index >3	3.78	<0.001	2.79-8.85
Severe sepsis/septic shock	2.45	0.01	0.67-6.04
Early de-escalation vs. no de-escalation[1]	-1.03	0.56	(-4.51)-2.45
No de-escalation vs. global de-escalation[2]	0.79	0.67	(-2.89)-4.47

[1]This group includes the no de-escalation group and the late de-escalation group
[2]This group includes the early and late de-escalation groups

Supplementary Table S7. Susceptibility data and production of key carbapenemases among Enterobacteriaceae causing bloodstream infection in the whole Bacteremia-MIC cohort and stratified according to the type of acquisition. Data are number of susceptible isolates (or beta-lactamase producers) per isolates tested (percentage).

	All episodes (n=516)	Community-onset episodes (n=190)	Nosocomial episodes (n=157)	Health-care associated episodes (n=169)
Amoxicillin-clavulanic acid	255/505 (50.5)	110/186 (59.1)	64/153 (41.8)	81/166 (48.8)
Piperacillin-tazobactam	466/506 (92.1)	182/186 (97.8)	135/154 (87.7)	149/166 (89.8)
Cefotaxime	438/515 (85)	171/190 (90)	125/156 (80.1)	142/169 (84)
Cefepime	454/515 (88.2)	173/190 (91.1)	133/156 (85.3)	148/169 (87.6)
Ertapenem	509/515 (98.8)	190/190 (100)	153/156 (98.1)	166/169 (98.2)
Meropenem	514/514 (100)	189/189 (100)	156/156 (100)	169/169 (100)
Ciprofloxacin	356/515 (69.1)	146/190 (76.8)	107/156 (68.6)	103/169 (60.9)
ESBL-producer	68/516 (13.2)	24/190 (12.6)	23/157 (14.6)	21/169 (14.6)
AmpC-producer	26/516 (5)	2/190 (1.1)	15/157 (9.6)	9/169 (5.3)
Carbapenemase producers	0/516 (0)	0/190 (0)	0/157 (0)	0/169 (0)

MIC breakpoint for considering susceptible to amoxicillin-clavulanic acid and piperacillin-tazobactam was ≤8 mg/L, for cefotaxime, ceftazidime, cefepime and levofloxacin ≤1 mg/L, for ertapenem and ciprofloxacin ≤0.5 mg/L and for meropenem ≤2 mg/L. Intermediate isolates were considered as resistant for this analysis.
This analysis was performed using EUCAST 2015 breakpoints.

Impact of de-escalation on prognosis of patients with bacteraemia due to Enterobacteriaceae: a post-hoc analysis from a multicenter prospective cohort

Running title: De-escalation in Enterobacteriaceae bacteraemia.

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SUMMARY OF THE MAIN POINTS

De-escalation from empirical ertapenem or antipseudomonal β-lactams to lower spectrum antibiotics in patients with bacteremia due to Enterobacteriaceae was not associated with any detrimental impact in terms of mortality, clinical failure or length of hospital stay

ABSTRACT

Background: More data are needed about the safety of antibiotic de-escalation in specific clinical situations as a strategy to reduce exposure to broad-spectrum antibiotics. The aims of this study were to investigate predictors of de-escalation and its impact on the outcome of patients with bloodstream infection due to Enterobacteriaceae (BSI-E).

Methods: A post-hoc analysis was performed of a prospective, multicenter cohort of patients with BSI-E initially treated with ertapenem or antipseudomonal β-lactams. Logistic regression was used to analyze factors associated with early de-escalation (EDE) and Cox regression for the impact of EDE and late de-escalation (LDE) on 30-day all-cause mortality. A propensity score (PS) for EDE vs. no de-escalation (NDE) was calculated. Failure at end of treatment and length of hospital stay were also analyzed.

Results: Overall, 516 patients were included; EDE was performed in 241 patients (46%), LDE in 95 (18%) and NDE in 180 (35%). Variables independently associated with a lower probability of EDE were multidrug-resistant isolates (OR 0.50, 95% CI 0.30-0.83) and nosocomial infection empirically treated with imipenem or meropenem (OR 0.35, 95% CI 0.14-0.87). After controlling for confounders, EDE was not associated with increased risk of mortality; Hazard ratios (HR) and (95% CI) were: general model, 0.58 (0.25-1.31), model with PS, 0.69 (0.29-1.65), and PS-matched pairs, 0.98 (0.76-1.26). LDE was not associated with mortality. De-escalation was not associated with clinical failure or length of hospital stay.

Conclusions: De-escalation in patients with monomicrobial bacteraemia due to Enterobacteriaceae was not associated with a detrimental impact on clinical outcome.

INTRODUCTION

Patients with sepsis are frequently treated empirically with broad-spectrum drugs (BSD) because the early administration of active drugs has been associated with improved outcome, particularly in the presence of septic shock [1]. This can lead to overuse of these drugs, which is usually considered to be one of the contributing factors for the spread of multidrug-resistant (MDR) bacteria [2]. To minimize this problem, streamlining or de-escalation from broad- to narrower-spectrum drugs is usually advocated once the susceptibility of the causative agent of the infection is known, and antimicrobial stewardship programs frequently include interventions facilitating or recommending this practice [3]. However, de-escalation is performed less frequently than is desirable. Barriers include uncertainty among many prescribers; indeed, although de-escalation is considered standard of care for most infectious diseases specialists, a recent systematic review concluded that there is no adequate evidence as to whether de-escalation of antimicrobial agents is effective and safe for adults with sepsis [4]. Hence, providing more information about the safety of de-escalation would help increase implementation, and knowledge of the variables influencing the performance of de-escalation would lead to better targeting of interventions promoting this practice.

Bloodstream infections (BSI) are an ideal model for de-escalation, since etiology and susceptibility are known, and a more specialized evaluation of patients is possible [5]. A meta-analysis including studies of sepsis, bacteraemia and pneumonia found a trend towards higher mortality with de-escalation in 3 randomized trials, but lower mortality in observational studies [6]. However, the studies were heterogeneous with respect to type of patient and infection, etiology, definitions used and interventions, which precludes high confidence in the meta-analytic estimates. Studies of specific populations

and etiologies are needed therefore. A randomized trial of patients with bacteraemia due to Enterobacteriaceae is now recruiting [7], although the results will not be available for 2 years. The objectives of this study were to evaluate the frequency of variables associated with de-escalation, and the impact of de-escalation on prognosis only among patients with bacteraemia due to Enterobacteriaceae.

METHODS

Study design, sites and study population

This is a post-hoc analysis of the prospective Bactaeremia-MIC cohort, which included BSI episodes due to Enterobacteriaceae at 13 University hospitals in Spain. The methods are detailed in previous reports [8, 9]. Briefly, consecutive adult patients with monomicrobial bacteraemia due to Enterobacteriaceae who received empirical treatment in the first 12 hours after the blood cultures were drawn were included. The original study was conducted between January 2011 and December 2013. Exclusion criteria were polymicrobial bacteraemia, non-hospitalized patients, do-not resuscitate orders, neutropenia (<500/μL) and survival <24 hours after blood cultures were drawn. For this analysis, patients from the Bacteraemia-MIC cohort were selected if: (1) initial treatment was monotherapy with an in vitro active BSD, including ertapenem or antipseudomonal β-lactams such as meropenem, imipenem, doripenem, ceftazidime, cefepime or piperacillin/tazobactam; and (2) the causative microorganism was susceptible to any of the following narrower-spectrum drugs (NSD): ampicillin, amoxicillin/clavulanic acid, non-antipseudomonal cephalosporins such as cefazolin, cefuroxime, cefotaxime or ceftriaxone, trimethoprim/sulfamethoxazole, aminoglycosides, fosfomycin and fluoroquinolones. The classification of antibiotics as BSD or NSD was based on a

147 previously published consensus ranking of β-lactams according to spectrum and
148 resistance-promoting potential [10]. Exclusion criteria were treatment change to another
149 broader-spectrum drug between days 2 and 5 (as we were unable to rule out patients
150 having secondary infections that would overestimate the comparative efficacy of NSD),
151 and death before the susceptibility tests were available (since these patients did not have
152 the opportunity to de-escalate). All patients were followed for 30 days.

153 The Institutional Review Board of the University Hospital Virgen Macarena,
154 Seville, Spain, approved the study and waived the need to obtain informed consent due
155 to the observational nature of the study. This analysis was reported according to STROBE
156 recommendations (Supplementary Table S1) [11].

157

158 **Variables and definitions**

159 The main outcome variable was 30-day all-cause mortality. Secondary outcomes
160 were: clinical response at day 21, and length of hospital stay among survivors. Clinical
161 response was classified as clinical cure if all signs and symptoms of infection had been
162 completely resolved, and failure if there were any persistent, recurrent or new signs and
163 symptoms related to infection, or if death occurred.

164 The main exposure of interest was de-escalation, defined as switching from the
165 empirical BSD to any of the NSDs, or from piperacillin-tazobactam, imipenem or
166 meropenem to ertapenem. De-escalation was classified as early de-escalation (EDE) if
167 performed in ≤4 days (the day when blood cultures were drawn was considered day 0),
168 late de-escalation (LDE) it was from day 5 to day 7, or non-de-escalation (NDE) if the
169 empirical drug was continued for at least ≥7 days.

170 Other exposure variables included demographic data, type of onset of infection
171 (nosocomial or community-onset, the latter including non-nosocomial but healthare-

associated), chronic underlying conditions and severity according to the Charlson index [12], acute severity of underlying condition according to Pitt score [13] measured on day -1, SOFA score measured on day 0 [14], severe sepsis or septic shock at day 0 [15], source of infection using CDC criteria, [16] and microorganism.

All isolates were sent to the Hospital Universitario Virgen Macarena, where identification was confirmed and susceptibility to antimicrobials was studied using microdilution and interpreted according to EUCAST breakpoints [17]. Extended-spectrum beta-lactamase (ESBL), AmpC and carbapenemase production were studied by phenotypic methods according to EUCAST guideline on detection of resistance mechanisms [18], followed by PCR amplification and molecular sequencing. For the sake of simplicity, isolates producing ESBLs, AmpC or carbapenem resistance were considered as MDR.

Statistical analysis

The chi-square test or Fisher's exact test was used to compare categorical variables. The Mann-Whitney U test was used to compare continuous variables. When appropriate, continuous variables were dichotomized according to their association with death, using Classification and Regression Tree (CART) analysis. Multivariate Cox regression analysis was used to analyze the impact of EDE and LDE on 30-day mortality. Logistic regression and linear regression were used to identify the impact of EDE and LDE on failure and length of hospital stay among survivors, respectively. Variables with a P value of <0.2 in univariate comparisons and those considered of clinical importance were manually entered into the multivariate model. The variables in the models were selected manually using a backward stepwise process. Interactions and collinearity were

196 evaluated. Sensitivity analyses were performed by reclassifying the main exposure as
197 EDE vs LDE+NDE, and as EDE+LDE vs NDE.

198 In addition, a propensity score (PS) was calculated for receiving EDE instead of
199 NDE. Its predictive ability was calculated using the area under the receiver operating
200 curve (AUROC) with 95% confidence intervals (CI), and the Hosmer-Lemeshow test was
201 used for goodness of fit. The PS was used in two ways: as a covariate to control for
202 residual confounding in multivariate models after checking for collinearity, and to
203 perform a matched cohort analysis in which patients undergoing EDE and NDE were
204 matched (1:1) according to their propensity scores using calipers of width 0.007.
205 Statistical analysis was carried out using the SPSS program (SPSS 25.0, IBM Corp,
206 Armonk, NY, USA).

207

208 **RESULTS**

209

210 The Bacteraemia-MIC cohort included 1058 patients with BSI due to
211 Enterobacteriaceae; of these, 516 (48.7%) patients fulfilled the criteria for the de-
212 escalation analysis (Figure 1). The number of patients per hospital ranged from 8 (1.6%)
213 to 69 (13.4%). Overall, 241 (46.7%) patients received EDE, 95 (18.4%) LDE, and 180
214 (34.8%) were not de-escalated. The proportion of EDE among hospitals with >20 cases
215 ranged from 13% to 75.4%. The patients' characteristics are shown in Table 1, and the
216 susceptibility data per microorganism is shown in Supplementary Table S2. Compared to
217 patients who underwent EDE, those in the NDE group more frequently had nosocomial
218 infections, had been admitted to the ICU, had respiratory tract infections and received
219 empiric therapy with meropenem. Overall, 68 (13.2%) isolates were ESBL producers, 26
220 (5%) AmpC producers, and 3 (0.6%) were carbapenem-resistant (none were

carbapenemase producers). Among patients undergoing de-escalation, the most frequent empirical drugs were piperacillin-tazobactam, and imipenem or meropenem and the most frequent drugs used for de-escalation were fluoroquinolones (68 patients in EDE and 38 in LDE), cefotaxime or ceftriaxone (92 and 20) and amoxicillin-clavulanic acid (43 and 26) (supplementary Table S3).

Variables associated with EDE

The association of different variables with EDE is shown in Table 2. The variable "center" was dichotomized into low and high proportions of patients with EDE. In multivariate analysis, bacteraemia caused by MDR isolates and nosocomial episodes empirically treated with imipenem or meropenem were associated with a lower probability of receiving EDE. Even after controlling for these variables, patients hospitalized in centers with a high proportion of EDE still had a higher probability of receiving EDE. The AUROC for the model was 0.72 (95% CI 0.66-0.75).

Mortality analysis

Mortality rates were 4.1% (10/241), 6.3% (6/95) and 9.4% (17/180) in patients with EDE, LDE and NDE, respectively (Table 1). The univariate and multivariate analysis of variables associated with 30-day mortality are shown in Table 3. Source of bacteraemia was dichotomized into urinary or biliary tract vs others, according to their association with mortality. Hospitals were also classified into those with lower and higher mortality, and this variable was retained in the models. Multivariate analysis (Table 3) selected Charlson >3, source other than urinary or biliary tract, presentation with severe sepsis or shock, and SOFA >4 as associated with mortality. Among de-escalated patients, no trend toward higher mortality was found, although the model showed poor

discrimination (AUROC=0.64; 95% CI: 0.52-0.75). In sensitivity analysis, the adjusted HR (95% CI) for mortality were: 0.67 (0.33-1.36, p=0.27) for EDE or LDE vs. NDE, and 0.60 (0.27-1.30, p=0.19) for EDE vs LDE-NDE. In nosocomial episodes, the adjusted HR (95% CI) for mortality in EDE and LDE were 0.46 (0.13-1.60) and 1.78 (0.53-5.92), respectively, and in community-onset, 0.70 (0.22-2.14) and 0.52 (0.10-2.56), respectively. No significant interactions were found in either model.

We then investigated the impact of EDE versus NDE including the PS for EDE (LDE patients were excluded from this analysis) (Table 3). No significant collinearity was found between the PS and other variables. Again, EDE did not show an association with higher 30-day mortality (adjusted HR=0.69; 95% CI: 0.29-1.65; p=0.41); the AUROC of this model was higher (0.72; 95% CI: 0.61-0.82). Finally, we matched 137 pairs of patients receiving EDE or NDE according to PS. Matched sub-cohorts had exposure to all other variables (supplementary Table S4). Mortality was 5.4% (n=7) in EDE and 7.7% in NDE (n=10) (HR=0.98; 95% CI: 0.76-1.26; p=0.84).

Clinical cure and length of stay

Overall, 35 patients showed failure at the end of antibiotic treatment (6.7%): 11/2421 (4.6%) with EDE, 6/95 (6.3%) with LDE, and 18/180 (10%) with NDE. The univariate and multivariate analyses of variables associated with failure are shown in Table 4. The multivariate model showed that Charlson index >3, severe sepsis/septic shock at presentation and SOFA score at day 0 were associated with higher treatment failure, while a urinary or biliary source was protective. The failure rate for these sources was 3.7%, while it was 14.3% for other sources. De-escalation was not found to be associated with failure (Table 4).

The median hospital stay after BSI was 14 days (IQR 9-24) and according to group, it was 14 days (9-28) for EDE, 13 (7-20) for LDE and 15 days (IQR 10-25) for NDE. The univariate analysis of variables associated with length of hospital stay is shown at Supplementary Table S5. Linear regression model of variables associated with length of hospital stay showed that nosocomial acquisition, Charlson index >3 and the presence of severe sepsis/septic shock at presentation were associated with more days of hospitalization (p values 0.006, <0.001 and 0.01 respectively). EDE and NDE were not found to be associated with longer hospital stay (p=0.56 and 0.67, respectively) (Supplementary Table S6).

DISCUSSION

In this cohort, less than half the candidate patients received early de-escalation, and one third of patients were never de-escalated. Patients with MDR isolates or nosocomial infections empirically treated with imipenem or meropenem had a lower probability of de-escalation. Finally, neither EDE nor LDE were shown to be associated with worse outcomes.

To our knowledge, this is by far the biggest study of de-escalation among patients with bacteraemia [6]. It is important to note that we only included non-neutropenic, adult patients with monomicrobial bacteraemia due to Enterobacteriaceae who received early active empirical monotherapy with ertapenem or antipseudomonal beta-lactams. We are not therefore addressing the impact of changing from combination therapy to monotherapy, but only of changes in the empirical drug used. This population is somewhat more homogeneous than those considered in most previous studies. In any setting, the proportion of patients with BSI-E who are candidates to de-escalation in

according to the criteria used would depend on the antibiotics used empirically and the susceptibility of the isolates; to provide more information in this regard, the susceptibility data of the Enterobacteriaceae isolated in the whole Bacteriemia-MIC cohort is shown in Supplementary Table S7.

The definition of de-escalation used is open to debate [19]. Unfortunately, many previous studies did not provide a specific definition of de-escalation and/or the drugs considered. The objective of de-escalation is to reduce exposure at the individual and group levels to drugs with a high negative ecological impact. However, the ecological impact of the drugs may depend on different variables, including local epidemiology, the previous colonization status of patients, microbiota composition, and the dosing or duration of antibiotic therapy. In this study we used a classification of beta-lactams developed by consensus [10]; in this consensus, imipenem and meropenem ranked highest in terms of spectrum width and highest resistance selecting potential, followed by ertapenem and piperacillin-tazobactam or antipseudomonal cephalosporins. As drugs for de-escalation, we included the lower-ranked beta-lactams in the consensus, in addition to other drugs suitable for oral use [20] that would allow the earlier discharge of patients, such as fluoroquinolones and trimethoprim-sulfamethoxazole. We also analyzed late de-escalation.

De-escalation is performed less frequently than is desirable [21]. The main barriers identified for de-escalations are uncertainties about etiology, inadequate empirical therapy and isolation of MDR bacteria [20, 21]. In patients with monomicrobial bacteraemia due to Enterobacteriaceae, the only uncertainty about etiology is the possibility of polymicrobial infection in certain types of infection, typically intraabdominal and some skin/skin structure-associated infections. In our study, source of BSI was not associated with higher rates of de-escalation when controlling for

confounders, and inadequate empirical therapy was an exclusion criterion. However, MDR bacteria were associated with a lower probability of de-escalation. We also identified nosocomial infection as a predictor for no de-escalation when these patients had been empirically treated with imipenem or meropenem, which may be a marker for more complex clinical situations. We suspect that other factors, such as stewardship interventions, less awareness of susceptibility results at weekends, and the training and opinions of individual prescribers could also play a role in de-escalation practice and merit specific studies.

In crude analysis, de-escalation was associated with lower mortality and failure. This was probably due to confounding by indication as the associations were no longer significant when other mortality predictors were considered in multivariate analysis, which is similar to the results found in the meta-analysis by Paul et al for observational studies of patients with severe sepsis or bacteraemia [6]. The results are reinforced by the fact that all our estimates in different analyses were consistent, and that we included mortality, failure of treatment and length of stay as outcome variables. Interestingly, the estimates provided by multivariate analysis were much less accurate than those provided by the PS-based matched pairs analysis. Our results strongly suggest therefore that de-escalation is safe. In fact, theoretically, it may have some individual beneficial effects if secondary infections caused by MDR bacteria are reduced, although demonstrating such an effect would require specific studies with a very large number of patients. Any analysis of population-level benefits would also require specific studies.

Our study has several limitations. Because it is not a randomized controlled trial, unmeasured confounding variables or residual confounding cannot be ruled out. The data were collected several years ago and changes in antimicrobial resistance may influence the results. Moreover, despite being controlled in the analysis, differences in clinical

practice at each center might have influenced the outcomes. Some strengths of the study are its multicenter character, the use of clearly specified definitions, and the use of advance statistical methodologies to control for confounders.

In conclusion, the results of this study reinforce the fact that antibiotic de-escalation in patients with monomicrobial bacteraemia due to Enterobacteriaceae does not have a detrimental impact on outcome, 30-day all-cause mortality, failure, or length of hospital stay when compared with continuation with broad-spectrum antibiotics. These results may be useful for antibiotic stewardship activities.

CONFLICT OF INTEREST

ZRPB has received honoraria for educational talks funded by Gilead. JRB has been an advisor for AstraZeneca, Merck, InfectoPharm, Achaogen and Basilea, and a speaker at educational courses for AstraZeneca and Merck. All other authors declare not to have conflict of interest.

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Impact of de-escalation on prognosis of patients with bacteraemia due to Enterobacteriaceae: a post-hoc analysis from a multicenter prospective cohort

Running title: De-escalation in Enterobacteriaceae bacteraemia.

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SUMMARY OF THE MAIN POINTS

De-escalation from empirical antipseudomonal β-lactams or ertapenem to lower spectrum antibiotics in patients with bacteremia due to Enterobacteriaceae was not associated with any detrimental impact in terms of mortality, clinical failure or length of hospital stay

ABSTRACT

Background: More data are needed about the safety of antibiotic de-escalation in specific clinical situations as a strategy to reduce exposure to broad-spectrum antibiotics. The aims of this study were to investigate predictors of de-escalation and its impact on the outcome of patients with bloodstream infection due to Enterobacteriaceae (BSI-E).

Methods: A post-hoc analysis was performed of a prospective, multicenter cohort of patients with BSI-E initially treated with ertapenem or antipseudomonal β-lactams. Logistic regression was used to analyze factors associated with early de-escalation (EDE) and Cox regression for the impact of EDE and late de-escalation (LDE) on 30-day all-cause mortality. A propensity score (PS) for EDE vs. no de-escalation (NDE) was calculated. Failure at end of treatment and length of hospital stay were also analyzed.

Results: Overall, 516 patients were included; EDE was performed in 241 patients (46%), LDE in 98 (18%) and NDE in 180 (35%). Variables independently associated with a lower probability of EDE were multidrug-resistant isolates (OR 0.50, 95% CI 0.30-0.83) and nosocomial infection empirically treated with imipenem or meropenem (OR 0.35, 95% CI 0.14-0.87). After controlling for confounders, EDE was not associated with increased risk of mortality; Hazard ratios (HR) and (95% CI) were: general model, 0.58 (0.25-1.31), model with PS, 0.69 (0.29-1.65), and PS-matched pairs, 0.98 (0.76-1.26). LDE was not associated with mortality. De-escalation was not associated with clinical failure or length of hospital stay.

Conclusions: De-escalation in patients with monomicrobial bacteraemia due to Enterobacteriaceae was not associated with a detrimental impact on clinical outcome.

INTRODUCTION

Patients with sepsis are frequently treated empirically with broad-spectrum drugs (BSD) because the early administration of active drugs has been associated with improved outcome, particularly in the presence of septic shock [1]. This can lead to overuse of these drugs, which is usually considered to be one of the contributing factors for the spread of multidrug-resistant (MDR) bacteria [2]. To minimize this problem, streamlining or de-escalation from broad- to narrower-spectrum drugs is usually advocated once the susceptibility of the causative agent of the infection is known, and antimicrobial stewardship programs frequently include interventions facilitating or recommending this practice [3]. However, de-escalation is performed less frequently than is desirable. Barriers include uncertainty among many prescribers; indeed, although de-escalation is considered standard of care for most infectious diseases specialists, a recent systematic review concluded that there is no adequate evidence as to whether de-escalation of antimicrobial agents is effective and safe for adults with sepsis [4]. Hence, providing more information about the safety of de-escalation would help increase implementation, and knowledge of the variables influencing the performance of de-escalation would lead to better targeting of interventions promoting this practice.

Bloodstream infections (BSI) are an ideal model for de-escalation, since etiology and susceptibility are known, and a more specialized evaluation of patients is possible [5]. A meta-analysis including studies of sepsis, bacteraemia and pneumonia found a trend towards higher mortality with de-escalation in 3 randomized trials, but lower mortality in observational studies [6]. However, the studies were heterogeneous with respect to type of patient and infection, etiology, definitions used and interventions, which precludes high confidence in the meta-analytic estimates. Studies of specific populations

and etiologies are needed therefore. A randomized trial of patients with bacteraemia due to Enterobacteriaceae is now recruiting [7], although the results will not be available for 2 years. The objectives of this study were to evaluate the frequency of variables associated with de-escalation, and the impact of de-escalation on prognosis only among patients with bacteraemia due to Enterobacteriaceae.

METHODS

Study design, sites and study population

This is a post-hoc analysis of the prospective Bactaeremia-MIC cohort, which included BSI episodes due to Enterobacteriaceae at 13 University hospitals in Spain. The methods are detailed in previous reports [8, 9]. Briefly, consecutive adult patients with monomicrobial bacteraemia due to Enterobacteriaceae who received empirical treatment in the first 12 hours after the blood cultures were drawn were included. The original study was conducted between January 2011 and December 2013. Exclusion criteria were polymicrobial bacteraemia, non-hospitalized patients, do-not resuscitate orders, neutropenia (<500/μL) and survival <24 hours after blood cultures were drawn. For this analysis, patients from the Bacteraemia-MIC cohort were selected if: (1) initial treatment was monotherapy with an in vitro active BSD, including antipseudomonal β-lactams such as meropenem, imipenem, doripenem, ceftazidime, cefepime or piperacillin/tazobactam, or ertapenem; and (2) the causative microorganism was susceptible to any of the following narrower-spectrum drugs (NSD): ampicillin, amoxicillin/clavulanic acid, non-antipseudomonal cephalosporins such as cefazolin, cefuroxime, cefotaxime or ceftriaxone, trimethoprim/sulfamethoxazole, aminoglycosides, fosfomycin and fluoroquinolones. The classification of antibiotics as BSD or NSD was based on a

147 previously published consensus ranking of β-lactams according to spectrum and
148 resistance-promoting potential [10]. Exclusion criteria were treatment change to another
149 broader-spectrum drug between days 2 and 5 (as we were unable to rule out patients
150 having secondary infections that would overestimate the comparative efficacy of NSD),
151 and death before the susceptibility tests were available (since these patients did not have
152 the opportunity to de-escalate). All patients were followed for 30 days.

153 The Institutional Review Board of the University Hospital Virgen Macarena,
154 Seville, Spain, approved the study and waived the need to obtain informed consent due
155 to the observational nature of the study. This analysis was reported according to STROBE
156 recommendations (Supplementary Table S1) [11].

157

158 **Variables and definitions**

159 The main outcome variable was 30-day all-cause mortality. Secondary outcomes
160 were: clinical response at day 21, and length of hospital stay among survivors. Clinical
161 response was classified as clinical cure if all signs and symptoms of infection had been
162 completely resolved, and failure if there were any persistent, recurrent or new signs and
163 symptoms related to infection, or if death occurred.

164 The main exposure of interest was de-escalation, defined as switching from the
165 empirical BSD to any of the NSDs, or from piperacillin-tazobactam, imipenem or
166 meropenem to ertapenem. De-escalation was classified as early de-escalation (EDE) if
167 performed in ≤4 days (the day when blood cultures were drawn was considered day 0),
168 late de-escalation (LDE) it was from day 5 to day 7, or non-de-escalation (NDE) if the
169 empirical drug was continued for at least ≥7 days.

170 Other exposure variables included demographic data, type of onset of infection
171 (nosocomial, healthcare-associated or community), chronic underlying conditions and

severity according to the Charlson index [12], acute severity of underlying condition according to Pitt score [13] measured on day -1, SOFA score measured on day 0 [14], severe sepsis or septic shock at day 0 [15], source of infection using CDC criteria, [16] and microorganism.

All isolates were sent to the Hospital Universitario Virgen Macarena, where identification was confirmed and susceptibility to antimicrobials was studied using microdilution, and interpreted according to EUCAST breakpoints [17]. Extended-spectrum beta-lactamase (ESBL), AmpC and carbapenemase production were studied by phenotypic methods, followed by PCR amplification and molecular sequencing. For the sake of simplicity, isolates producing ESBLs, AmpC or carbapenem resistance were considered as MDR.

Statistical analysis

The chi-square test or Fisher's exact test was used to compare categorical variables. The Mann-Whitney U test was used to compare continuous variables. When appropriate, continuous variables were dichotomized according to their association with death, using Classification and Regression Tree (CART) analysis. Multivariate Cox regression analysis was used to analyze the impact of EDE and LDE on 30-day mortality. Logistic regression and linear regression were used to identify the impact of EDE and LDE on failure and length of hospital stay among survivors, respectively. Variables with a P value of <0.2 in univariate comparisons and those considered of clinical importance were manually entered into the multivariate model. The variables in the models were selected manually using a backward stepwise process. Interactions and collinearity were evaluated. Sensitivity analyses were performed by reclassifying the main exposure as EDE vs LDE+NDE, and as EDE+LDE vs NDE.

In addition, a propensity score (PS) was calculated for receiving EDE instead of NDE. Its predictive ability was calculated using the area under the receiver operating curve (AUROC) with 95% confidence intervals (CI), and the Hosmer-Lemeshow test was used for goodness of fit. The PS was used in two ways: as a covariate to control for residual confounding in multivariate models after checking for collinearity, and to perform a matched cohort analysis in which patients undergoing EDE and NDE were matched (1:1) according to their propensity scores using calipers of width 0.007. Statistical analysis was carried out using the SPSS program (SPSS 25.0, IBM Corp, Armonk, NY, USA).

RESULTS

The Bacteraemia-MIC cohort included 1058 patients with BSI due to Enterobacteriaceae; of these, 516 (48.7%) patients fulfilled the criteria for the de-escalation analysis (Figure 1). The number of patients per hospital ranged from 8 (1.6%) to 69 (13.4%). Overall, 241 (46.7%) patients received EDE, 95 (18.4%) LDE, and 180 (34.8%) were not de-escalated. The proportion of EDE among hospitals with >20 cases ranged from 13% to 75.4%. The patients' characteristics are shown in Table 1. Compared to patients who underwent EDE, those in the NDE group more frequently had nosocomial infections, had been admitted to the ICU, had respiratory tract infections and received empiric therapy with meropenem. Overall, 70 (13.6%) isolates were ESBL producers, 26 (5.1%) AmpC producers, and 3 (0.6%) were carbapenem-resistant (none were carbapenemase producers). Among patients undergoing de-escalation, the most frequent empirical drugs were piperacillin-tazobactam, and imipenem or meropenem and the most frequent drugs used for de-escalation were fluoroquinolones (68 patients in EDE and 38

in LDE), cefotaxime or ceftriaxone (92 and 20) and amoxicillin-clavulanic acid (43 and 26) (supplementary Table S2).

Variables associated with EDE

The association of different variables with EDE is shown in Table 2. The variable "center" was dichotomized into low and high proportions of patients with EDE. In multivariate analysis, bacteraemia caused by MDR isolates and nosocomial episodes empirically treated with imipenem or meropenem were associated with a lower probability of receiving EDE. Even after controlling for these variables, patients hospitalized in centers with a high proportion of EDE still had a higher probability of receiving EDE. The AUROC for the model was 0.72 (95% CI 0.66-0.75).

Mortality analysis

Mortality rates were 4.1% (10/241), 6.3% (6/95) and 9.4% (17/180) in patients with EDE, LDE and NDE, respectively (Table 1). The univariate and multivariate analysis of variables associated with 30-day mortality are shown in Table 3. Source of bacteraemia was dichotomized into urinary or biliary tract vs others, according to their association with mortality. Hospitals were also classified into those with lower and higher mortality, and this variable was retained in the models. Multivariate analysis (Table 3) selected Charlson >3, source other than urinary or biliary tract, presentation with severe sepsis or shock, and SOFA >4 as associated with mortality. Among de-escalated patients, no trend toward higher mortality was found, although the model showed poor discrimination (AUROC=0.64; 95% CI: 0.52-0.75). In sensitivity analysis, the adjusted HR for mortality were: 0.67 (95% CI 0.33-1.36, p=0.27) for EDE or LDE vs. NDE, and

0.60 (95% CI 0.27-1.30, p=0.19) for EDE vs LDE-NDE. No significant interactions were found in either model.

We then investigated the impact of EDE versus NDE including the PS for EDE (LDE patients were excluded from this analysis) (Table 3). No significant collinearity was found between the PS and other variables. Again, EDE did not show an association with higher 30-day mortality (adjusted HR=0.69; 95% CI: 0.29-1.65; p=0.41); the AUROC of this model was higher (0.72; 95% CI: 0.61-0.82). Finally, we matched 137 pairs of patients receiving EDE or NDE according to PS. Matched sub-cohorts had exposure to all other variables (supplementary Table S3). Mortality was 5.4% (n=7) in EDE and 7.7% in NDE (n=10) (HR=0.98; 95% CI: 0.76-1.26; p=0.84).

Clinical cure and length of stay

Overall, 35 patients showed failure at the end of antibiotic treatment (6.7%): 11/2421 (4.6%) with EDE, 6/95 (6.3%) with LDE, and 18/180 (10%) with NDE. The univariate and multivariate analyses of variables associated with failure are shown in Table 4. The multivariate model showed that Charlson index >3, severe sepsis/septic shock at presentation and SOFA score at day 0 were associated with higher treatment failure, while a urinary or biliary source were protective factors. De-escalation was not found to be associated with failure (Table 4).

The median hospital stay after BSI was 14 days (IQR 9-24) and according to group, it was 14 days (9-28) for EDE, 13 (7-20) for LDE and 15 days (IQR 10-25) for NDE. The univariate analysis of variables associated with length of hospital stay is shown at Supplementary Table S4. Linear regression model of variables associated with length of hospital stay showed that nosocomial acquisition, Charlson index >3 and the presence of severe sepsis/septic shock at presentation were associated with more days of

hospitalization (p values 0.006, <0.001 and 0.01 respectively). EDE and NDE were not found to be associated with longer hospital stay (p=0.56 and 0.67, respectively) (Supplementary Table S5).

DISCUSSION

In this cohort, less than half the candidate patients received early de-escalation, and one third of patients were never de-escalated. Patients with MDR isolates or nosocomial infections empirically treated with imipenem or meropenem had a lower probability of de-escalation. Finally, neither EDE nor LDE were shown to be associated with worse outcomes.

To our knowledge, this is by far the biggest study of de-escalation among patients with bacteraemia [6]. It is important to note that we only included non-neutropenic, adult patients with monomicrobial bacteraemia due to Enterobacteriaceae who received early active empirical monotherapy with antipseudomonal beta-lactams or ertapenem. We are not therefore addressing the impact of changing from combination therapy to monotherapy, but only of changes in the empirical drug used. This population is somewhat more homogeneous than those considered in most previous studies.

The definition of de-escalation used is open to debate [18]. Unfortunately, many previous studies did not provide a specific definition of de-escalation and/or the drugs considered. The objective of de-escalation is to reduce exposure at the individual and group levels to drugs with a high negative ecological impact. However, the ecological impact of the drugs may depend on different variables, including local epidemiology, the previous colonization status of patients, microbiota composition, and the dosing or duration of antibiotic therapy. In this study we used a classification of beta-lactams

296 developed by consensus [10]; in this consensus, imipenem and meropenem ranked
297 highest in terms of spectrum width and highest resistance selecting potential, followed by
298 ertapenem and piperacillin-tazobactam or antipseudomonal cephalosporins. As drugs for
299 de-escalation, we included the lower-ranked beta-lactams in the consensus, in addition to
300 other drugs suitable for oral use [19] that would allow the earlier discharge of patients,
301 such as fluoroquinolones and trimethoprim-sulfamethoxazole. We also analyzed late de-
302 escalation.

303 De-escalation is performed less frequently than is desirable [20]. The main
304 barriers identified for de-escalations are uncertainties about etiology, inadequate
305 empirical therapy and isolation of MDR bacteria [19, 20]. In patients with monomicrobial
306 bacteraemia due to Enterobacteriaceae, the only uncertainty about etiology is the
307 possibility of polymicrobial infection in certain types of infection, typically
308 intraabdominal and some skin/skin structure-associated infections. In our study, source
309 of BSI was not associated with higher rates of de-escalation when controlling for
310 confounders, and inadequate empirical therapy was an exclusion criterion. However,
311 MDR bacteria were associated with a lower probability of de-escalation. We also
312 identified nosocomial infection as a predictor for no de-escalation when these patients
313 had been empirically treated with imipenem or meropenem, which may be a marker for
314 more complex clinical situations. We suspect that other factors, such as stewardship
315 interventions, less awareness of susceptibility results at weekends, and the training and
316 opinions of individual prescribers could also play a role in de-escalation practice and
317 merit specific studies.

318 In crude analysis, de-escalation was associated with lower mortality and failure.
319 This was probably due to confounding by indication as the associations were no longer
320 significant when other mortality predictors were considered in multivariate analysis,

which is similar to the results found in the meta-analysis by Paul et al for observational studies of patients with severe sepsis or bacteraemia [6]. The results are reinforced by the fact that all our estimates in different analyses were consistent, and that we included mortality, failure of treatment and length of stay as outcome variables. Interestingly, the estimates provided by multivariate analysis were much less accurate than those provided by the PS-based matched pairs analysis. Our results strongly suggest therefore that de-escalation is safe. In fact, theoretically, it may have some individual beneficial effects if secondary infections caused by MDR bacteria are reduced, although demonstrating such an effect would require specific studies with a very large number of patients. Any analysis of population-level benefits would also require specific studies.

Our study has several limitations. Because it is not a randomized controlled trial, unmeasured confounding variables or residual confounding cannot be ruled out. The data were collected several years ago and changes in antimicrobial resistance may influence the results. Moreover, despite being controlled in the analysis, differences in clinical practice at each center might have influenced the outcomes. Some strengths of the study are its multicenter character, the use of clearly specified definitions, and the use of advance statistical methodologies to control for confounders.

In conclusion, the results of this study reinforce the fact that antibiotic de-escalation in patients with monomicrobial bacteraemia due to Enterobacteriaceae does not have a detrimental impact on outcome, 30-day all-cause mortality, failure, or length of hospital stay when compared with continuation with broad-spectrum antibiotics. These results may be useful for antibiotic stewardship activities.

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Potential Conflicts of Interest

Dr. Zaira Palacios Baena reports personal fees from Gilead, outside the submitted work.

Dr. Rodríguez-Baño reports personal fees from Merck, personal fees from AstraZeneca

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for a nondrug related research projects, and grants from Innovative Medicines Initiative (IMI), outside the submitted work. All other authors have no potential conflict of interest to declare.

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