Intensive Care Med (2014) 40:92–95
DOI 10.1007/s00134-013-3154-y

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What can be expected from antimicrobial de-escalation in the critically ill?

Received: 3 November 2013
Accepted: 4 November 2013
Published online: 19 November 2013

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Antimicrobial de-escalation is a clinical approach to empirical antibiotic treatment of serious infections that attempts to balance the need for appropriate initial therapy with the need to limit unnecessary antimicrobial exposure in order to curtail the emergence of resistance [1]. When risk factors for antibiotic resistance are identified in patients with a serious infection, broad-spectrum antimicrobials should be prescribed. A de-escalation approach usually requires initial combination antimicrobial treatment targeting resistant non-fermenting gram-negative bacilli (NFGNB) (*Pseudomonas aeruginosa*, *Acintobacter* species) and methicillin-resistant *Staphylococcus aureus* [2]. However, depending on clinical presentation, patient risk factors, and local epidemiology, other pathogens such as *Candida* species and *Clostridium difficile*, especially when diarrhea is present, may also need to be covered. Once the microbiologic results are available and the patient's clinical response is observed, the antibiotic regimen can be narrowed on the basis of the susceptibilities of the identified pathogens.

In addition to narrowing antibiotic regimens, de-escalation implies that the shortest course of antibiotic treatment should be prescribed that adequately treats the underlying infection. For uncomplicated nosocomial pneumonia, this may be as little as 7 days of therapy [3]. This is an important aspect of de-escalation, as the duration of antibiotic treatment appears to be one of the most important, if not the most important, determinant for the emergence of antimicrobial resistance in hospitalized patients [4]. Moreover, in order to achieve optimal outcomes, including reductions in mortality and shorter courses of antibiotic administration aimed at minimizing the pressure for resistance to emerge, the initial antibiotic regimen should be administered in a timely manner and appropriate for the underlying infection (i.e., active against the pathogen associated with infection based on in vitro susceptibility testing) [4–6]. Although the concept of antimicrobial de-escalation seems to make intuitive sense, clinicians should ask themselves what the realistic expectations of such a strategy are.

Intensivists should expect that a de-escalation approach to antimicrobial therapy in critically ill patients will optimize patient outcomes. Our local experience, as well as that of other groups, bears this out in demonstrating that the administration of appropriate initial antibiotic therapy is associated with improved survival and shorter hospital stays [2, 5–7]. Recently, Garnacho-Montero et al. [8] evaluated 628 patients with severe sepsis or septic shock at ICU admission who were treated empirically with broad-spectrum antibiotics. Antibiotic therapy was guided by written protocols advocating for de-escalation therapy once the microbiological results became available (day of culture results), although this decision was ultimately the responsibility of the physician in charge of the patient. By multivariate analysis, factors independently associated with in-hospital mortality were septic shock, SOFA score on the day of culture results, and inappropriate empirical antimicrobial therapy, whereas de-escalation of antimicrobial therapy was found to be a protective factor for hospital survival. Additionally, among patients receiving appropriate therapy the only factor independently associated with

mortality was SOFA score on the day of culture results, whereas de-escalation therapy was again found to be a protective factor. These investigators found that 57 of 628 (9.1 %) patients received inappropriate empiric therapy and 246 of 628 (39.2 %) patients had no change in their empiric antibiotic regimens, indicating further opportunity to improve their de-escalation practice.

Several strategies have been employed to optimize the use of antimicrobial de-escalation in critically ill patients. Rello et al. [9] conducted a prospective study utilizing a protocol to guide de-escalation of therapy in patients with ventilator-associated pneumonia (VAP). Changes in empiric antibiotic therapy occurred in 56.2 %, including de-escalation (the most frequent cause) in 31.4 % (increasing to 38 % if isolates were sensitive). De-escalation was lower ($p < 0.05$) in the presence of NFGNB (2.7 vs. 49.3 %) and in the presence of late-onset pneumonia (12.5 vs. 40.7 %). When the pathogen remained unknown, half of the patients died and de-escalation was not performed. Ibrahim et al. [2] conducted a before–after trial of standard therapy versus a de-escalation guideline for the treatment of VAP. De-escalation included both narrowing the spectrum of therapy on the basis of microbiology results and shortening the duration of antibiotic therapy on the basis of the patient's clinical response. These investigators found that the initial administration of appropriate antimicrobial treatment was statistically greater during the after-period compared with the before-period (48.0 vs. 94.2 %, $p < 0.001$) and that the duration of antimicrobial treatment was statistically shorter during the after-period (14.8 ± 8.1 vs. 8.6 ± 5.1 days, $p < 0.001$). Second episodes of VAP also occurred less often among patients in the after-period (24.0 vs. 7.7 %, $p = 0.030$).

Computer decision support systems have also been employed to facilitate de-escalation practices in the ICU setting. Thursky et al. [10] employed a real-time microbiology browser and computerized decision support system for isolate-directed antibiotic prescription. They found a significant reduction in the proportion of patients prescribed carbapenems, third-generation cephalosporins, and vancomycin after adjustment for risk factors including Apache II score, suspected infection, positive microbiology, intubation, and length of stay. The decision support tool was associated with a 10.5 % reduction in both total antibiotic utilization (166–149 defined daily doses/100 ICU bed days) and the highest volume broad-spectrum antibiotics. Our own hospital is developing an automated decision-support system with real-time access to patients'

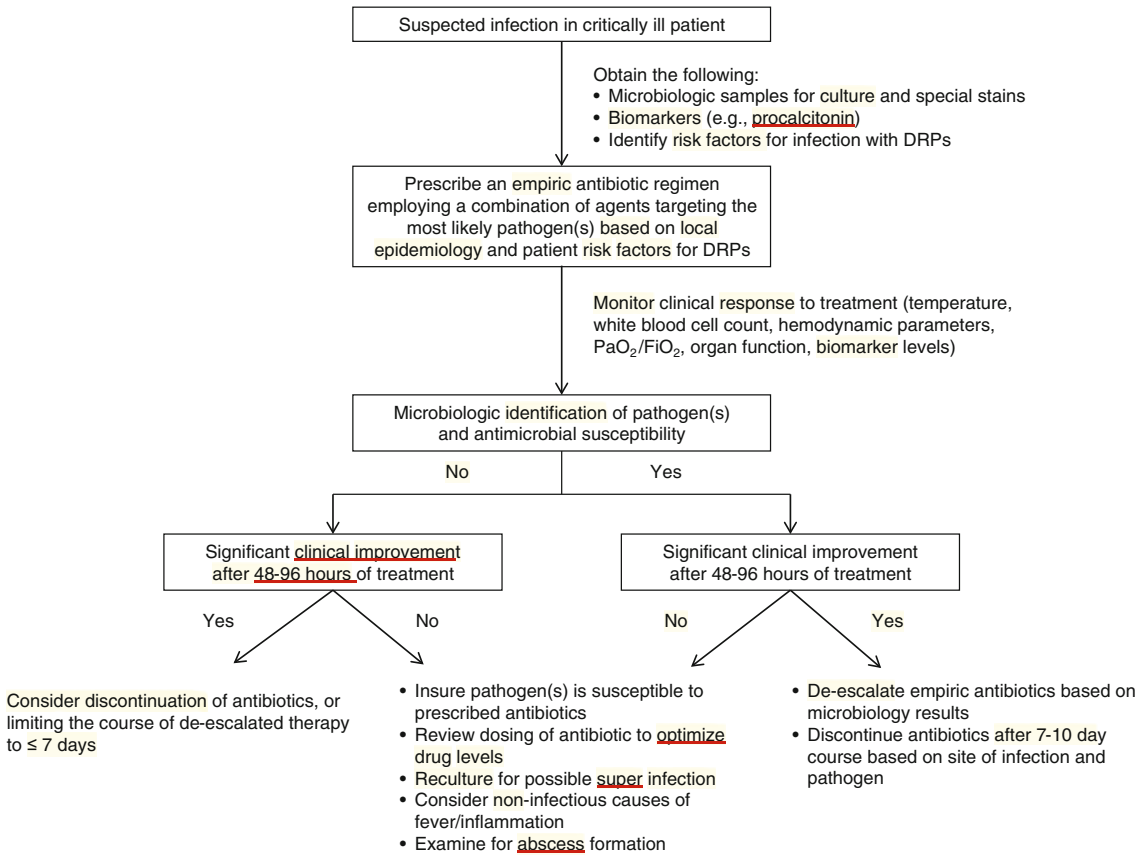

Fig. 1 Schematic outlining a practice of antimicrobial de-escalation. *FiO_2* inspired oxygen fraction, *PaO_2* partial pressure (or tension) of arterial oxygen, *DRPs* drug-resistant pathogens

prior antibiotic exposures and microbiologic results, including those from prior hospitalizations at outside institutions, in order to refine our current empiric antibiotic practices and assist in the performance of de-escalation.

Knowledge of patient risk factors for the presence of infection with antibiotic-resistant pathogens should be a routine part of antibiotic decision-making and can be used in a de-escalation algorithm. For example, community-acquired pneumonia (CAP) drug-resistant pathogens (DRPs) are more commonly found in patients with healthcare-associated risk factors. Shindo et al. [11] demonstrated that independent risk factors for DRPs in both patients diagnosed with CAP and healthcare-associated pneumonia (HCAP) included prior hospitalization, immunosuppression, previous antibiotic use, use of gastric acid-suppressive therapy, tube feeding, and non-ambulatory status. These are similar to independent risk factors identified in a clinical score for assessing the risk of resistant pathogens in patients with pneumonia presenting to the emergency department [12]. Identification of the presence or absence of such risk factors at the time of antibiotic decision-making can obviate the need for broad-spectrum therapy in patients without risk factors for DRPs and avoid having to de-escalate therapy, especially in culture-negative patients. Moreover, biomarkers are increasingly employed to modify empiric antibiotic therapy, including in critically ill patients. Available evidence suggests that biomarker-prompted de-escalation of empiric therapy can be safely applied, although additional trials are needed to confirm this approach [13].

In summary, antibiotic de-escalation should be a routine part of antimicrobial stewardship as it is applied in the ICU. Successful implementation of de-escalation strategies will require a multidisciplinary approach with dedicated efforts and monitoring to insure adherence to its guidance principles [14]. Given the increasing presence of antibiotic-resistant pathogens as a cause of infection in critically ill patients, a practice of de-escalation appears to be the only available practical strategy allowing clinicians to balance the need for empiric appropriate therapy while minimizing the unnecessary use of antibiotics. Certainly, the future development of rapid methods for microbe detection and antimicrobial susceptibility testing will allow for more timely and directed therapy for critically ill patients with serious infections [15]. Until that time, those of us who treat patients in the ICU setting should champion antibiotic de-escalation as a tool to manage our use of antimicrobial agents (Fig. 1).

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Intensive Care Med (2014) 40:32–40
DOI 10.1007/s00134-013-3077-7

ORIGINAL ARTICLE

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De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock

Received: 1 July 2013
Accepted: 10 August 2013
Published online: 12 September 2013

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-013-3077-7) contains supplementary material, which is available to authorized users.

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Abstract *Purposes:* We set out to assess the safety and the impact on in-hospital and 90-day mortality of antibiotic de-escalation in patients admitted to the ICU with severe sepsis or septic shock. *Methods:* We carried out a prospective observational study enrolling patients admitted to the ICU with severe sepsis or septic shock. De-escalation was defined as discontinuation of an antimicrobial agent or change of antibiotic to one with a narrower spectrum once culture results were available. To control for confounding variables, we performed a conventional regression analysis and a propensity score (PS) adjusted-multivariable analysis. *Results:* A total of 712 patients with severe sepsis or septic shock at ICU admission were treated empirically with broad-spectrum antibiotics. Of these, 628 were evaluated (84 died before cultures were available). De-escalation was applied in 219 patients (34.9 %). By multivariate analysis, factors independently associated with in-hospital mortality were septic shock, SOFA score the day of culture results, and inadequate empirical antimicrobial therapy, whereas de-escalation therapy was a protective factor [Odds-Ratio (OR) 0.58; 95 % confidence interval (CI) 0.36–0.93). Analysis of the 403 patients with adequate empirical therapy revealed that the factor associated with mortality was SOFA score on the day of culture results, whereas de-escalation therapy was a protective factor (OR 0.54; 95 % CI 0.33–0.89). The PS-adjusted logistic regression models confirmed that de-escalation therapy was a protective factor in both analyses. De-escalation therapy was also a protective factor for 90-day mortality. *Conclusions:* De-escalation therapy for severe sepsis and septic shock is a safe strategy associated with a lower mortality. Efforts to increase the frequency of this strategy are fully justified.

Keywords Critical care · Sepsis · Empirical therapy · Survival · De-escalation · Infectious diseases

Introduction

Antimicrobial prescription represents a major challenge for clinicians in the daily practice especially in certain difficult clinical scenarios. Thus, in critically ill septic patients, prompt and adequate antimicrobial therapy reduces morbidity and mortality [1–4]. However, once the pathogen(s) are identified and their susceptibilities have been determined, the empiric antibiotic(s) that were started should be stopped or reduced in number and/or narrowed in spectrum. This strategy termed "de-escalation therapy" appears theoretically correct, capable of promoting therapeutic appropriateness and reducing costs.

De-escalating strategies have been evaluated particularly in ventilator-associated pneumonia (VAP), in which the potential implication of multi-drug resistant microorganisms is relatively high. Several studies have shown that de-escalation therapy can be safely provided to patients with ICU-acquired pneumonia and is even associated with lower mortality [5, 6].

The Surviving Sepsis Campaign recommends the use of broad-spectrum antibiotics in the initial management of patients with severe sepsis and septic shock. In addition, the last version of this guideline clearly endorses de-escalation to the most appropriate single therapy as soon as the susceptibility profile is available, although no randomized controlled trials or well-done observational studies have assessed the clinical impact of this strategy in critically ill patients with severe sepsis or septic shock [7]. In a recent study that assessed episodes of hospital-acquired severe sepsis, this strategy was accomplished in approximately 50 % of the cases without impact on the clinical outcomes [8]. Safety and effectiveness of this antibiotic strategy in severe sepsis and septic shock has been recently questioned in a systematic review [9].

The objectives of the present study were to evaluate the impact on in-hospital mortality (primary end-point) and 90-day mortality (secondary end-point) of de-escalation therapy in patients admitted to the ICU with severe sepsis or septic shock. As de-escalation may simply be a marker of early clinical improvement and not be causally related to the outcome, we used two techniques to control for confounders: a multivariable logistic regression model and a propensity score-adjusted regression analysis. We also provide information about the antibiotic strategies used in these critically ill patients.

Patients and methods

Hospital

This is a prospective study carried out in the ICU of the Hospital Virgen del Rocío from January 1, 2008 to May 31, 2012. The ICU is a 40-bed medico-surgical unit in a large University Hospital. The Institutional Review Board of the Hospital approved this protocol waiving the need for informed consent given the observational design of this study.

Study design

All adult patients meeting criteria for severe sepsis or septic shock on admission to the ICU were enrolled. The patients proceeded from the emergency room, operating room, or the general ward. Only the first episode for each patient was included in the analysis. All patients received standard supportive treatment following recommendations of the Surviving Sepsis Campaign released in 2008 [10].

The choice of empirical treatment was made following local guidelines that were elaborated based on local ecology, source of infection, and severity of illness. Broad-spectrum antimicrobial therapy is recommended in all patients with severe sepsis or septic shock. These written protocols clearly advocate for de-escalation therapy once the microbiological results are available (day of culture results), although this decision was finally the responsibility of the physician in charge of the patient.

All patients had a series of blood cultures drawn in the emergency room or at admission to the ICU. Only blood cultures obtained during the first 48 h of the stay in the ICU were considered. Cultures of the infection sources were obtained as clinically indicated. Polymicrobial infection was defined as the isolation of more than one pathogen irrespective of whether the isolates came from blood or the infection site. Episodes caused by ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) that are often resistant to antimicrobials were considered "difficult-to treat infections" [11].

At admission, the severity of the illness was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE) II score considering the worst data point of the first 24 h in the ICU [12]. Underlying chronic organ insufficiencies (liver, renal, pulmonary, cardiovascular, and immuno-suppression) as defined by APACHE II scale and other comorbidities (diabetes mellitus, non-cure malignancy, and previous surgery) were also recorded [13]. Failure of organs and severity of multiple organ dysfunction syndrome was assessed by Sequential Organ Failure Assessment (SOFA) scale on admission and during the subsequent clinical course [14]. The need of mechanical ventilation and SOFA score were noted the day on which culture results were available.

Therapy was considered adequate when at least one effective drug was included in the empirical antibiotic treatment within the first 24 h of the admission to the ICU and the dose and pattern of administration were in

accordance with current medical standards. Antibiotic strategies once culture results were available were classified as: "no change" (empirical therapy was maintained without modification), "escalation of therapy" (the switch to or addition of an antibiotic with a broader spectrum), and "de-escalation" (switch to or interruption of a drug class resulting in a less broad spectrum of coverage). If antimicrobial change consisted of escalation and de-escalation (i.e. switch to or addition of an antibiotic with a broader spectrum but also withdrawal of another antibiotic), the patient was assigned to "escalation group" for statistical analysis.

We grouped de-escalation in the following categories: withdrawal of one antimicrobial (group I); withdrawal of two of the antimicrobials empirically prescribed (group II); switch to a new antimicrobial with narrower spectrum (group III); and withdrawal of at least one antimicrobial plus change of another drug to a new one with narrower spectrum (group IV).

Development of nosocomial infections in the ICU was also noted following previously published definitions [15]. All patients were followed up until death or hospital discharge. Vital status of patients discharged from the hospital before 90 days of admission was ascertained consulting the hospital database or by telephone contact.

Statistical analysis

Discrete variables were expressed as counts (percentage) and continuous variables as medians and interquartile ranges (IQRs). Differences in categorical variables were calculated using a two-sided likelihood ratio Chi square test or Fisher exact test, and the Mann–Whitney *U* test or Kruskal–Wallis test were used for continuous variables, when appropriate.

A logistic regression model was carried out to assess the impact of independent variables on in-hospital mortality (primary goal) and 90-day mortality (secondary goal). We considered the "no change" category as the reference and it was compared with the two others. Variables significantly associated with mortality in the univariate analysis or if they were considered clinically significant were entered into the model (statistical analysis in the ESM).

Furthermore, to assess the impact of treatment (de-escalation use; non de-escalation use) on mortality and to control for confounders, a propensity score adjusted-multivariable analysis was also performed. All information about how the propensity score was constituted and the multivariable model adjusted by the propensity score is described in the statistical analysis section in the ESM [16]. Adjusted OR are presented with corresponding 95 % CI. All reported p values were two-tailed. The threshold for statistical significance was defined as $p < 0.05$. Data analysis was performed using SPSS for Windows 15.0.0 (SPSS, Chicago, IL, USA).

Results

During the study period, 712 patients were admitted to the ICU with the diagnosis of severe sepsis ($n = 278$) or septic shock ($n = 434$). Mean delay to microbiological results was 72 h (48–96). Eighty-four patients died before culture results were available for the clinician in charge of the patient and were excluded from this analysis.

Entire cohort

In these 628 patients in whom evaluation of the empirical therapy could be accomplished, microbiological documentation was obtained in 481 of the episodes (76.7 %). Bacteremia was detected in 241 patients (38.4 %), and 403 patients (87.6 %) received adequate empirical therapy. Pathogens isolated in blood cultures and at the site of infections are depicted in Table 1 of the Electronic Supplementary Material (ESM). In 131 episodes, an organism included in the ESKAPE group was isolated either in blood or in the infectious focus. ICU mortality was 29.5 % (185 patients), in-hospital mortality 33.4 % (210 patients), and 90-day mortality rose up to 35.2 % (221 patients).

Of these 628 patients, 296 (47.1 %) patients received monotherapy in the empirical therapy, 249 (39.7 %) received two antimicrobials, and three or more antimicrobials were used in 83 patients (13.2 %). In patients with monotherapy, the prescribed antibiotics were: piperacillin-tazobactam (72.3 %), followed by a carbapenem (22.2 %), third-generation cephalosporins or cefepime (2.4 %), fluoroquinolones (1.7 %), and others (1.4 %). The most frequently prescribed combinations of antimicrobials were a third-generation cephalosporin or cefepime plus a fluoroquinolone or a glycopeptide followed by a carbapenem plus a glycopeptide. De-escalation therapy was performed in 219 patients (34.9 %) and consisted of: 88 strategy I, 20 strategy II, 80 strategy III, and 31 strategy IV.

Regarding the characteristics of patients according to antibiotic strategy, de-escalation therapy was more commonly performed in medical than in surgical patients (Table 2 of the ESM). Severity of illness in the first 24 h of ICU admission did not influence antimicrobial therapy modification. In contrast, the SOFA score on the day of culture results was higher in those patients in whom therapy was escalated compared with the other two groups. The rate of adequate antimicrobial therapy was lower in those patients for whom the physician in charge

of the patient decided on escalatation. According to patterns of antibiotic strategy (Fig. 1), the hospital mortality rate was 27.4 % in patients in whom therapy was de-escalated, 32.6 % in the category of "no change", and 42.9 % in the escalation group ($p = 0.006$). ICU and 90-day mortalities were also lower in the de-escalation group, intermediate in the group of "no change", and greater in the escalation group.

Bivariate analysis of risk factors associated with mortality is depicted in Table 1. Patients who died in the hospital were significantly older and with a more severe disease at admission assessed by APACHE II and SOFA scores. Similarly, the SOFA score on the day of culture results were significantly greater in patients who died during hospitalization. Rate of de-escalation therapy was significantly higher in patients who survived (38 vs. 28.6 %; $p = 0.019$). APACHE II score at admission to the ICU was divided into four quartiles. The rate of de-escalation was not statistically different among these four quartiles (Fig. 1 of the ESM). By multivariate logistic regression analysis, factors independently associated with mortality were septic shock, SOFA score on the day of culture results, and inadequate empirical antimicrobial therapy, whereas de-escalation therapy was a protective factor (Table 1).

Because of the noted imbalances in baseline characteristics and clinical situation on the day of culture results among patients according to antibiotic strategy, a logistic regression model was developed introducing the probability calculated by the propensity score in an attempt to ameliorate the impact of observed differences. This analysis also identified de-escalation therapy as a protective factor for in-hospital mortality (Table 2).

Regarding mortality at 90 days, factors associated with fatality by multivariate analysis were: septic shock (OR 1.81; 95 % CI 1.10–2.98; $p = 0.019$), inadequate empirical antimicrobial therapy (OR 1.92; 95 % CI 1.02–3.62; $p = 0.043$) and SOFA score on the day of culture results (OR 1.11; 95 % CI 1.06–1.17; $p < 0.001$) whereas de-escalation therapy was a protective factor (OR 0.55; 95 % CI 0.34–0.87; $p = 0.011$). In the propensity score adjusted model, de-escalation therapy was associated with reduced 90-day mortality.

Patients with adequate empirical antimicrobial therapy

We also analyzed the 438 patients with adequate empirical therapy but excluding 35 patients who died before microbiological results were available (Table 3). In the empirical therapy, 184 patients received monotherapy, 161 received combination therapy with two antimicrobials and the initial therapy included three or more antimicrobials in 58 patients. Rate of nosocomial infection in patients with ICU length of stay greater than 5 days was higher in patients in whom antimicrobial therapy was de-escalated compared to the "no change" group although this difference was not statistically significant: 25/148 (16.9 %) vs. 29/116 (25 %); $p = 0.1$. De-escalation therapy was accomplished in 179 patients (44.4 %), in 147 patients (36.5 %) the empirical therapy was maintained and in 77 cases (19.1 %) therapy was escalated although the empirical therapy was adequate. De-escalation consisted in: 68 strategy I, 15 strategy II, 67 strategy III and 29 strategy IV. Figure 1 depicts that the

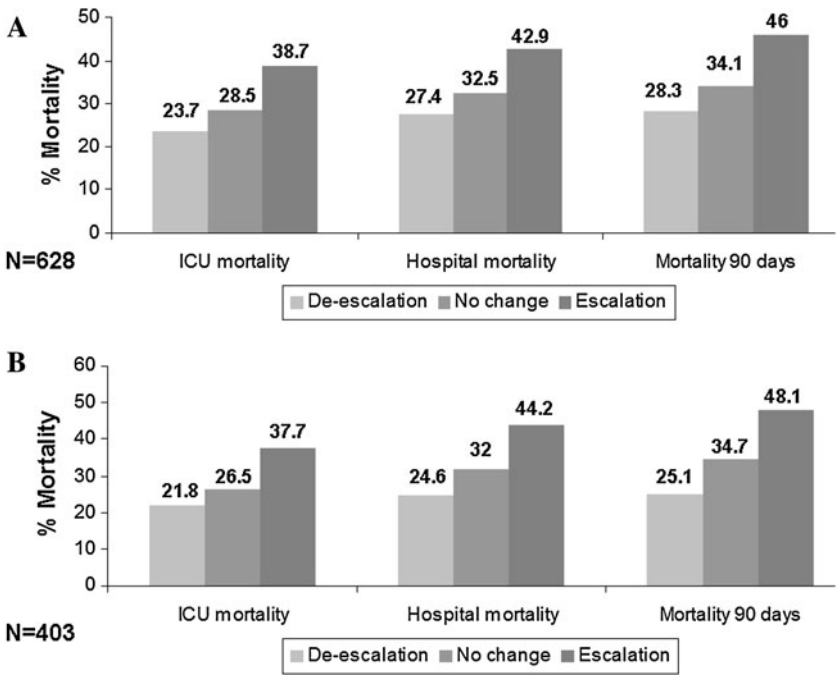

Fig. 1 Mortality rate according to therapeutic strategy: **a** total cohort and **b** patients with adequate empirical antimicrobial therapy

Table 1 Bivariate and multivariate analysis of risk factors associated with hospital mortality in the total cohort

	Alive $n = 418$ (%)	Death $n = 210$ (%)	p	Unadjusted OR (IC 95 %)	p	Adjusted OR (95 % CI)**	p
Age	60 (45–71)	66 (53–75)	<0.001				
Female gender	184 (44)	83 (39.5)	0.282				
APACHE II score[a,b]	15 (11–20)	20 (15–24)	<0.001	1.03 (0.99–1.07)	0.134	1.03 (0.99–1.07)	0.096
SOFA (Median, IQR)[c,b]	6 (3–9)	8 (6–11)	<0.001	–			
SOFA at culture result day[c]	3 (1–7)	9 (5–12)	<0.001	1.12 (1.06–1.19)	<0.001	1.14 (1.08–1.20)	<0.001
Surgical admission	209 (50)	105 (50)	1				
Hospital acquisition	121 (28.9)	69 (32.9)	0.314				
Comorbidities							
Diabetes	89 (21.3)	55 (26.2)	0.168				
COPD	26 (6.2)	20 (9.5)	0.134				
Cirrhosis	10 (2.4)	20 (9.5)	<0.001				
Malignancy	59 (14.1)	48 (22.9)	0.006				
Chronic renal failure	15 (3.6)	16 (7.6)	0.028				
Immunosuppression	39 (9.3)	36 (17.1)	0.004	1.33 (0.68–2.60)	0.401		
Heart failure	17 (4.1)	17 (8.1)	0.035				
Sepsis source							
Chest	89 (21.3)	61 (29)	0.032				
Urinary	48 (11.5)	10 (4.8)	0.006				
Abdomen	181 (43.3)	93 (44.3)	0.814				
Central nervous system	16 (3.8)	4 (1.9)	0.195				
Soft tissue	39 (9.3)	20 (9.5)	0.937				
Catheter	14 (3.3)	5 (2.4)	0.504				
Unidentified	22 (5.3)	11 (5.2)	0.989				
Documented sepsis	319 (76.5)	162 (77.1)	0.857				
Positive blood culture	160 (38.3)	81 (38.6)	0.943				
Septic shock	209 (50.2)	154 (73.3)	<0.001	1.98 (1.01–3.88)	0.044	1.76 (1.05–2.93)	0.030
Inadequate empirical treatment	29 (9.4)	28 (18.3)	0.007	1.95 (1.02–3.71)	0.041	1.98 (1.05–3.75)	0.034
Nosocomial infection	69 (16.6)	63 (30.1)	<0.001	1.51 (0.89–2.54)	0.123		
Antimicrobial treatment							
Escalation	93 (22.2)	70 (33.3)	0.003				
De-escalation	159 (38)	60 (28.6)	0.019	0.58 (0.36–0.94)	0.029	0.58 (0.36–0.93)	0.026
No change	166 (39.7)	80 (38.1)	0.695				

COPD Chronic obstructive pulmonary disease
** Hosmer–Lemeshow test = 8.291; $p = 0.406$
[a] APACHE II denotes Acute Physiology and Chronic Health Evaluation score
[b] Score within the first 24 h after ICU admission
[c] SOFA denotes Sequential Organ Failure Assessment

Table 2 Logistic regression analyses adjusted by the propensity score

	Total cohort ($n = 628$)		Cohort with adequate empirical antimicrobial therapy ($n = 403$)	
	Adjusted by PS OR (95 % CI)	p	Adjusted by PS OR (95 % CI)	p
SOFA day of culture results	1.11 (1.04–1.23)	<0.001	1.18 (1.16–1.29)	<0.001
Septic shock	1.70 (1.03–2.84)	0.043		
Inadequate empirical treatment	2.03 (1.06–3.84)	0.030		
De-escalation	0.55 (0.32–0.98)	0.022	0.57 (0.38–0.94)	0.019

hospital mortality rate was 24.6 % in de-escalation therapy group, 32 % in patients who were kept on broad-spectrum empirical therapy and 44.2 % in the escalation group ($p = 0.008$). We also compared these 179 patients in whom de-escalation was performed with 180 patients without de-escalation despite that the microbiology results allowed simplification of the antimicrobial regimen. APACHE II score and SOFA at admission as well as the SOFA score on the day of culture results were similar in these two groups. In-hospital and 90-day mortalities were higher in patients in whom antimicrobial therapy was de-escalated compared to the "no change" group although only the latter archived statistical significance (24.5 vs. 32.8 %; $p = 0.08$ and 25.1 vs. 36.1 %; $p = 0.024$, respectively).

As shown in Table 3, APACHE II score in the first 24 h and SOFA scores at admission and on the day of culture results were significantly higher in those patients

who died than in patients that were discharged alive from the hospital. As in the entire cohort, the rate of de-escalation was not statistically different among the four APACHE II quartiles (Figure 1 of the ESM). However, SOFA score on the day of culture results was identified as a variable independently associated with in-hospital mortality by multivariate analysis whereas de-escalation therapy was a protective factor. Table 2 shows that the propensity score-adjusted regression model also identified de-escalation therapy as a protective factor for in-hospital mortality. Moreover, in these 403 patients, both regression analyses coincided that de-escalation therapy was associated with lower mortality at 90 days.

Discussion

In this prospective, observational study, rates of de-escalation therapy in patients admitted to the ICU with severe sepsis or septic shock were about 35 %. We corroborate the safety of this antibiotic therapy and, more importantly, that after a strict adjustment for confounding variables including baseline characteristics and severity of illness on the day of culture results, this antibiotic strategy is associated with a lower mortality.

The theory of streamlining antibiotics has been recommended for years, but there are not compelling data to support it in patients with severe sepsis or septic shock. In fact, a recent Cochrane review found insufficient evidence

Table 3 Bivariate and multivariate analysis of risk factors associated with mortality in patients with adequate empirical antimicrobial therapy

	Alive $N = 278$ (%)	Death $N = 125$ (%)	*p*	Unadjusted OR (IC 95 %)	*p*	Adjusted OR (95 % CI)**	*p*
Age	60 (45–71)	65 (54–72)	0.017				
Female gender	119 (42.8)	48 (38.4)	0.406				
APACHE II score[a,b]	16 (11–20)	21 (16–25)	<0.001	1.02 (0.98–1.06)	0.286		
SOFA (Median, IQR)[c,b]	6 (4–9)	9 (6–12)	<0.001	–			
Respiratory Sofa score >2	55 (19.9)	46 (36.8)	<0.001	1.20 (0.67–2.16)	0.531		
Coagulation Sofa score >2	26 (9.4)	27 (21.6)	0.001	1.50 (0.73–3.09)	0.266		
Cardiovascular Sofa score >2	135 (48.9)	88 (71)	<0.001	1.34 (0.64–2.80)	0.433		
SOFA at culture results day	3 (1–7)	9 (5–12)	<0.001	1.13 (1.06–1.20)	<0.001	1.17 (1.11–1.23)	<0.001
Prior antibiotic	49 (17.6)	31 (24.8)	0.095				
Surgical admission	145 (52.2)	67 (53.6)	0.789				
Hospital acquisition	81 (29.1)	43 (34.4)	0.290				
Comorbidities							
Diabetes	62 (22.3)	29 (23.2)	0.842				
COPD	18 (6.5)	13 (10.4)	0.171				
Cirrhosis	8 (2.9)	14 (11.2)	0.001				
Malignancy	38 (13.7)	34 (27.2)	0.001				
Chronic renal failure	13 (4.7)	10 (8)	0.183				
Immunosuppression	29 (10.4)	22 (17.6)	0.045				
Heart failure	11 (4)	7 (5.6)	0.460				
Sepsis source							
Chest	49 (17.6)	30 (24)	0.136				
Urinary	35 (12.6)	5 (4)	0.008				
Abdomen	127 (45.7)	57 (45.6)	0.988				
Central nervous system	12 (4.3)	2 (1.6)	0.168				
Soft tissue	28 (10.1)	16 (12.8)	0.417				
Catheter	13 (4.7)	5 (4)	0.761				
Unidentified	9 (3.2)	7 (5.6)	0.261				
Documented sepsis	276 (99.3)	124 (99.2)	0.931				
Positive blood culture	139 (50)	69 (55.2)	0.334				
Septic shock	139 (50)	91 (72.8)	<0.001	1.20 (0.58–2.49)	0.607		
Mechanical ventilation[d]	79 (29.2)	93 (75.6)	<0.001				
Antimicrobial treatment							
Escalation	43 (15.5)	34 (27.2)	0.006				
De-escalation	135 (48.6)	44 (35.2)	0.013	0.50 (0.30–0.83)	0.008	0.54 (0.33–0.89)	0.016
No change	100 (36)	47 (37.6)	0.753				

COPD chronic obstructive pulmonary disease

** Hosmer–Lemeshow test = 9.131; p = 0.516

[a] APACHE II denotes Acute Physiology and Chronic Health Evaluation score

[b] Score within the first 24 h after ICU admission

[c] SOFA denotes Sequential Organ Failure Assessment

[d] Mechanical ventilation on the day of culture results

to recommend for or against antimicrobial de-escalation in adults with a diagnosis of sepsis, requiring further research via randomized controlled trials or large cohort studies [9].

De-escalation therapy has been predominantly evaluated in patients with hospital-acquired pneumonia. Kollef et al. [6] reported in 398 patients with severe sepsis or septic shock and the ICU mortality rate was significantly lower among patients in whom therapy was de-escalated compared with those experiencing therapy escalation or those in whom therapy remained unchanged. Similarly, Rello et al. [5] observed that the ICU mortality rate of patients with de-escalation therapy was significantly lower than in patients in whom the empirical therapy was maintained. In 137 patients diagnosed with ICU-acquired pneumonia, the de-escalation group showed significantly lower crude and pneumonia-related mortality rates by day 30 after pneumonia diagnosis [17]. Nevertheless, this strategy was not identified as a protective factor by the multivariate analysis. In another study that included microbiologically confirmed episodes of VAP, patients in whom treatment was de-escalated had significantly reduced 15-day and 28-day mortality, compared to patients who were kept on broad-spectrum empirical therapy [18].

De-escalation therapy has also been assessed in other populations. Thus, in non-immunosuppressed patients with bacteremia treated adequately in the initial regimen, de-escalation was safe and associated with a trend towards lower mortality and treatment failure rates, although mortality was very low (3.5 %) [19]. The same group has recently reported that de-escalation therapy is feasible and safe in bacteremia caused by difficult-to-treat Gram-negative bacilli in patients who had received adequate empirical therapy [20].

Data on patients with severe sepsis and septic shock are lacking. In one prospective study that enrolled patients with septic shock, de-escalation therapy was performed in 64 % of cases [21]. Three recent retrospective studies have documented that de-escalation of empirical therapy is accomplished in roughly 50 % of critically ill patients with sepsis [8, 22]. In patients with severe nosocomial infections, escalation was performed more frequently that true de-escalation therapy, reflecting the high rate of multidrug-resistant Gram-negative pathogens found in this multicenter study [23]. However, these studies did not specifically analyze the impact on clinical outcomes, although no excess of mortality was observed even in patients with septic shock [22, 24].

Our rate of de-escalation of the antimicrobial therapy was approximately one-third in the entire cohort and rose to 44.4 % in patients with adequate empirical therapy. Severity of the illness at ICU admission did not influence our decision to de-escalate. As expected, patients in whom the spectrum of antimicrobial therapy was broadened were in a more critical condition than the other two groups of patients. In our series, de-escalation was achieved with the same frequency by reducing the number of drugs and by narrowing the spectrum of antibiotic therapy. Conversely, others have found that de-escalation is achieved more often by reducing the number of drugs [21, 22]. We also found that de-escalation therapy is less frequently accomplished in surgical patients than in medical admissions. Surgical infections (i.e. peritonitis or soft tissue infections) are frequently polymicrobial, which may explain the difficulties in reducing or narrowing the antimicrobial spectrum.

As previously reported [1–4], inadequate empiric antibiotic therapy is also an independent predictor of mortality in critically ill septic patients. More importantly, we have demonstrated that, after controlling for potential confounders including severity of illness on the day of culture results, de-escalation therapy is associated with a lower mortality rate. Interestingly, this survival benefit is also manifest in patients who had received adequate empirical therapy.

Moreover, censoring the mortality data at ICU or hospital discharge may significantly underestimate the medium- and long-term effects of sepsis. In fact, a not insignificant number of septic patients discharged alive from an ICU die in the subsequent months [25]. It is noteworthy that, in our study, the favorable effect in terms of survival of de-escalation therapy persists in the 3-month follow-up.

Several plausible reasons may explain the benefits in terms of survival of de-escalation therapy, especially in comparison with those patients in whom empirical therapy was maintained unaltered. In certain situations, this favorable effect might be produced for the use of less toxic antibiotics (i.e. withdrawal of nephrotoxic agents), by the administration of antibiotics that achieve higher concentrations at the infection focus (i.e. in case of meningitis), or by the election of more active agents. For instance, it is known that beta-lactams are more active than glycopeptides against susceptible Gram-positive cocci. In fact, prognosis of meticillin susceptible *S. aureus* bacteremia is worse in patients treated with vancomycin than in those who received a beta-lactam [26]. Moreover, the risk of nosocomial infection caused by multi-drug resistant pathogen is lower if the spectrum of antimicrobial therapy is narrowed. In our series, the rate of nosocomial infection was similar between these groups although a non-significant trend towards a higher rate of infection acquired in the ICU was documented in patients with adequate therapy and a length of ICU stay longer than 5 days. The highest rate of ICU-acquired infection was observed in the escalation group (53 % of them had received inadequate empirical therapy). Development of nosocomial infection is significantly more frequent in patients with inadequate empirical therapy than in those treated empirically with adequate antibiotics [27].

The deleterious effects of the administration of broad-spectrum antibiotics are well documented [28]. Hence, for critically ill patients without confirmed nosocomial infection, maintenance of the empirical antimicrobial therapy was associated with a higher 28-day mortality rate than for those in whom antibiotics were stopped. When potential confounding variables were controlled for in a multivariable model, the association between continuation of therapy and mortality showed a strong trend towards statistical significance (OR = 3.75, 0.91–15.49, $p = 0.07$) [29].

We admit several limitations of our study. First, the gold standard for demonstrating that a therapeutic intervention impacts on the outcome is a randomized, controlled, blinded trial. When these kinds of trials are lacking, observational studies can provide valuable information about treatment effectiveness. Statistical adjustments using the estimated propensity score have the advantage of balancing recorded covariates, thus producing a situation closer to randomization. However, in our study, we report the conventional regression analysis and the propensity score-adjusted analysis because sometimes the latter may be superior to propensity score methods regarding to precision and bias control [16]. Importantly, both approaches coincide that de-escalation therapy is associated with a lower mortality. Second, a delay of 24 h in starting adequate treatment is not acceptable in case of septic shock because the prognosis of these patients is clearly influenced by the timing of antimicrobial therapy [30]. Third, this is a single-center study carried out in a large academic hospital and our results might not be generalizable to centers that do not share similar characteristics. Fourth, we have not evaluated the applicability of de-escalation therapy in infections caused by multidrug-resistant pathogens in which the use of combination therapy is recommended by most of the experts which makes it generally impossible to stop one antimicrobial [7, 31]. In our study, which included patients at ICU admission, a relatively low prevalence of ESKAPE organisms was observed.

In conclusion, an early and adequate antimicrobial treatment is undoubtedly a major prognostic factor in critically ill septic patients. Moreover, our findings clearly support that the empiric coverage should be refined once culture results are available. Therefore, in patients with severe sepsis and septic shock at admission to the ICU, the optimal management includes the administration of broad-spectrum antibiotics together with reassessment and subsequent narrowing or discontinuation of therapy based on the results of cultures and antibacterial susceptibility tests. All initiatives to improve antibiotic prescriptions in critically ill septic patients are completely warranted and should include the streamlining of empirical antibiotics.

Acknowledgments Supported by Ministerio de Economía y Competitividad, Instituto de Salud Carlos III - co-financed by European Development Regional Fund "A way to achieve Europe" ERDF, Spanish Network for the Research in Infectious Diseases (REIPI RD12/0015).

Conflicts of interest The authors declare that they have no conflict of interest.

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