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

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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'

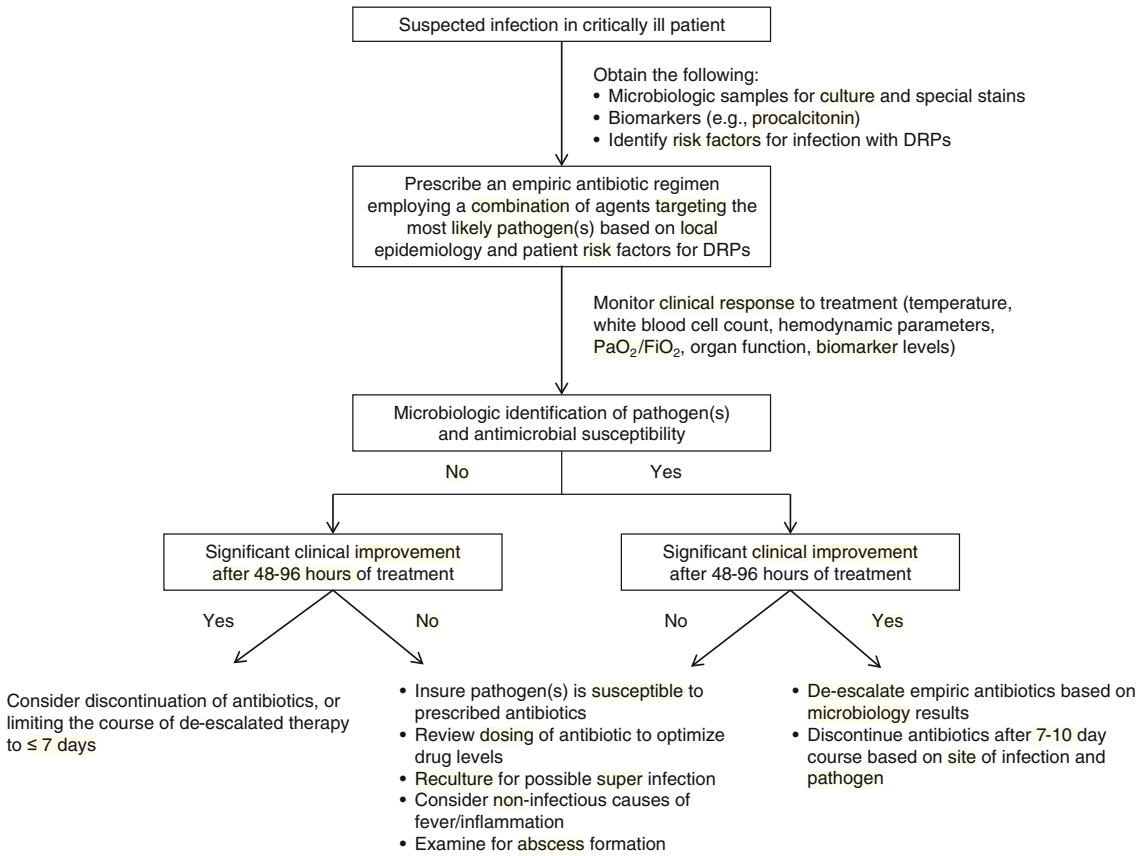

Fig. 1 Schematic outlining a practice of antimicrobial de-escalation. *FiO_2* inspired oxygen fraction, *PaO_2* partial pressure (or tension) of arterial oxygen, *DRPs* drug-resistant pathogens

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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ORIGINAL ARTICLE

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

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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

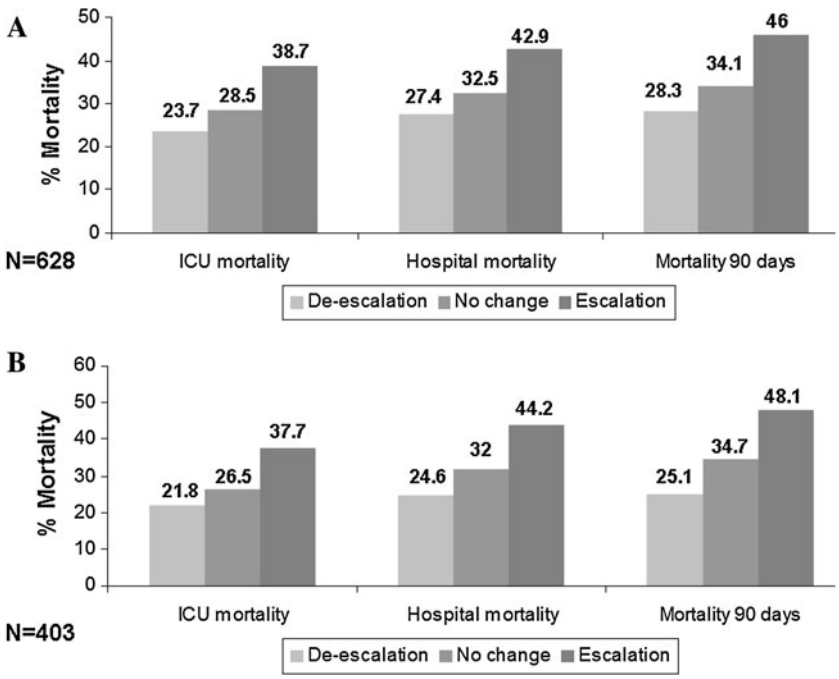

Fig. 1 Mortality rate according to therapeutic strategy: **a** total cohort and **b** patients with adequate empirical antimicrobial therapy

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.

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

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Biomarker-guided de-escalation of empirical therapy is associated with lower risk for adverse outcomes

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Dear Editor,

We would like to congratulate Dr. Garnacho-Montero and colleagues for their prospective study suggesting a mortality benefit for patients in whom antibiotic therapy was de-escalated early [1]. As acknowledged by the authors and due to the observational study design, causal inference remains somewhat unclear. Although the authors used a state-of-the-art statistical approach that includes multivariate regression and propensity score analysis, residual confounding cannot be excluded. Thus, a prospective randomized trial is warranted for ultimate proof.

In line with these authors' study, we have recently analyzed data from similar trials in which patients were treated according to a procalcitonin algorithm for antibiotic de-escalation and control patients were not treated with this approach [2, 3]. We included all published randomized controlled trial data in an individual patient data (IPD) meta-analysis. The main purpose of this analysis was to demonstrate the safety of using procalcitonin protocols. Surprisingly, as demonstrated in Fig. 1, there was a significantly lower risk for treatment failure in patients with community-acquired pneumonia and patients treated in the emergency department when procalcitonin protocols were used for antibiotic stewardship. In terms of the mortality endpoint, there were no significant differences. However, the point estimate of 0.84 for intensive care unit patients with systemic infections treated according to a procalcitonin protocol is reassuring and may prompt future randomized trials to *de-escalate* antibiotic therapy with the aim of reducing mortality and morbidity using a similar biomarker approach.

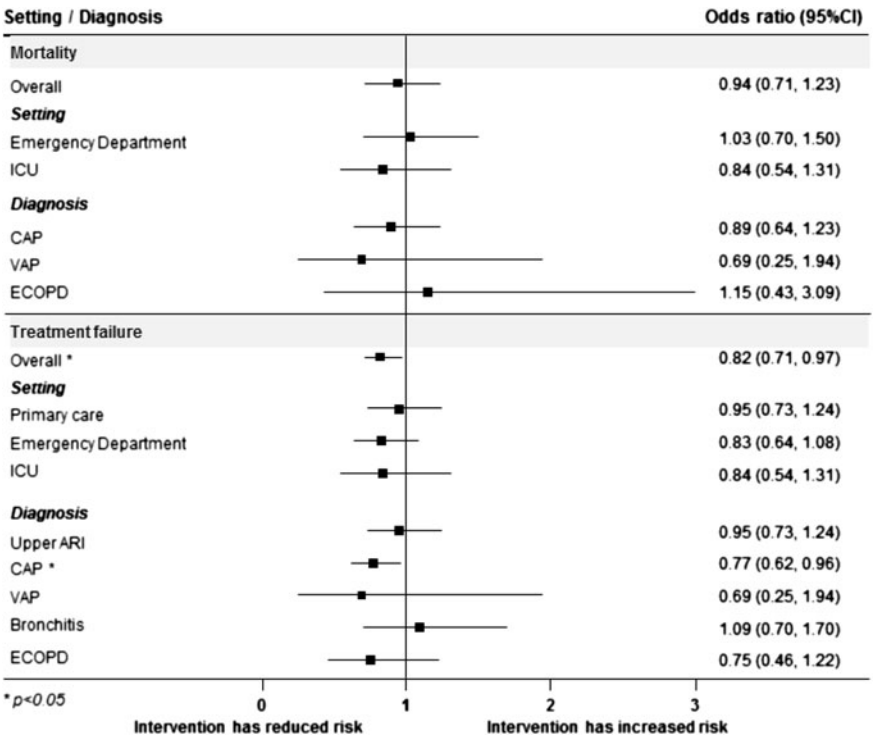

Fig. 1 Mortality and adverse outcomes associated with procalcitonin de-escalation protocols. *ICU* intensive care unit, *CAP* community-acquired pneumonia, *VAP* ventilator-associated pneumonia, *ECOPD* exacerbation of chronic obstructive pulmonary disease, *ARI* acute respiratory infection, *CI* confidence interval

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ORIGINAL ARTICLE

De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study

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Abstract *Background:* In severe sepsis, guidelines recommend de-escalating the empirical antimicrobial treatment as soon as the microbiological results are available. We aimed to determine the rate of de-escalation of the empirical antimicrobial treatment in neutropenic patients with severe sepsis. The characteristics of antimicrobial treatment associated with de-escalation and its impact on short- and long-term survival were also determined. *Methods:* In the intensive care unit (ICU) of a cancer referral center, we prospectively collected observational data related to the antimicrobial management in neutropenic patients who developed severe sepsis and were admitted to ICU for at least 48 h. De-escalation of antimicrobial therapy consisted either of deleting one of the empirical antibiotics of a combined treatment, or, whenever possible, to use a betalactam antibiotic with a narrower spectrum of activity. Multivariate logistic regression was conducted to determine the factors associated with de-escalation, while a Cox proportional hazards model with a time-dependent covariate was fitted to assess the effect of de-escalation on 30-day survival. Finally 1-year survival after ICU discharge was compared across de-escalation groups. *Results:* Cumulative incidence of de-escalation of the empirical antimicrobial treatment among the 101 patients of the cohort was 44 %, [95 % confidence interval (CI) 38–53 %], including 30 (68 %) patients with ongoing neutropenia. A microbiological documentation was available in 63 (63 %) patients. Factors associated with de-escalation were the adequation of the empirical antimicrobial treatment in ICU [OR = 10.8 (95 % CI 1.20–96)] for adequate documented treatment versus appropriate empirical treatment, the compliance with guidelines regarding the empirical choice of the anti-pseudomonal betalactam [OR = 10.8 (95 % CI 1.3–89.5)]. De-escalation did not significantly modify the hazard of death within the first 30 days [HR = 0.51 (95 % CI 0.20–1.33)], nor within 1 year after ICU discharge [HR = 1.06 (95 % CI 0.54–2.08)]. *Conclusion:* Our data suggest that, in ICU, de-escalation of the empirical antimicrobial treatment is frequently applied in neutropenic cancer patients with severe sepsis. No evidence of any prognostic impact of this de-escalation was found.

Keywords Antibiotics · Septic shock · Severe sepsis · Neutropenia · De-escalation

Introduction

In severe sepsis and septic shock, guidelines recommend de-escalating the empirical antimicrobial treatment as soon as the microbiological results are available [1]. This strategy is aimed to reduce the selection pressure and the treatment cost [2, 3]. In intensive care units (ICU), previous studies have shown that de-escalation is safe [4–6]. As routine, de-escalation is performed in around 40 % of septic patients [7].

Neutropenia remains a constant outcome after aggressive chemotherapies as part of bone marrow transplantation, acute leukemia, lymphoma, and certain solid tumor treatments. The price to pay for increasing treatment intensity and duration is a rise in treatment-related toxicity and susceptibility to infection [8, 9]. Thus, in neutropenic patients, suspicion of sepsis should lead to the immediate onset of empirical antimicrobial treatment [10, 11]. In the neutropenic patient with severe sepsis or septic shock, use of broad-spectrum antibiotics is recommended [11]. The changes of empirical antimicrobial treatment should be guided by clinical and microbiological data [12]. To date, there is no study assessing the safety of de-escalation in neutropenic patients with severe sepsis.

Our hypothesis was that de-escalation is feasible in about 40 % of the patients with neutropenia at the onset of severe sepsis. Our first aim was to assess the rate of de-escalation of the first antimicrobial treatment in neutropenic cancer patients with severe sepsis or septic shock admitted to the ICU. Our secondary aims were to test whether characteristics of the empirical antimicrobial treatment (namely, adequation to documentation and compliance to guidelines) were associated with de-escalation, and to determine the impact of the de-escalation on the patient survival.

Methods

All neutropenic cancer patients admitted to the ICU of the Paoli-Calmettes Institute (Marseille, France) from January 2008 to May 2010 and meeting criteria for severe sepsis or septic shock were prospectively included in this observational survey. The patients deceased or discharged alive from the ICU within the first 48 h were excluded from the analysis. All patients were followed over a period of 12 months after ICU admission. The Paoli-Calmettes Institute is a 211-bed cancer referral center. The Institutional Review Board of the Paoli-Calmettes Institute approved this study and waived the need for informed consent due to the observational nature of the study. The methodology adheres to the STROBE statement.

Definitions and data collection

Neutropenia was defined as a neutrophil count below 500 cells/mm^3 or leucocytes below 1,000 cells/mm^3 [12]. Severe sepsis, septic shock, and acute respiratory distress syndrome (ARDS) were defined according to international criteria [13, 14]. Cancer status at ICU admission was graded as follows: newly diagnosed, remission, progression, or unknown. Knaus scale definitions were used to record pre-existing chronic organ failures [15]. Reasons for the ICU admission were categorized as acute respiratory failure, shock, coma, acute kidney injury, severe sepsis, tumor lysis syndrome, and others. Simplified acute physiology score (SAPS) II [16] and sequential organ failure assessment (SOFA) [17] scores were computed on day 1. During the first 5 days after ICU admission, changes in SOFA score (Δ SOFA) were calculated as follows: [score on day 5 (or the day of ICU discharge if discharge occured before day 5) – score on day 1]. When the Δ SOFA was >1, the SOFA score was considered as having worsened. Organ failure was defined as a SOFA score of 3 or more for any system. The patients were included if they had suspected or proven infection. From ICU admission, X-rays, computed tomography scan, and biological and microbiological tests were standardized and performed as indicated by the clinical presentation [12, 18, 19].

In agreement to guidelines, antibiotics were administered as early as possible after ICU admission [12, 20]. Aminoglycosides or fluoroquinolones were added in those patients requiring fluid resuscitation or vasopressors [12, 20]. Antibiotics directed against methicillin-resistant *Staphylococcus aureus* (MRSA) were used as recommended by guidelines [12, 20]. Patients with fever and neutropenia during more than 5 days received an antifungal agent. Our local guidelines recommend continuing antibiotics until clinical resolution was obtained.

For each patient, the episodes of febrile neutropenia were classified as fever of unknown origin, clinically documented or microbiologically documented [21]. A microbiologically documented infection was defined as fever with identification of pathogens in blood samples or samples from the suspected infection site. A clinically documented infection was defined as fever with a focal infection (e.g., pneumonia or skin and soft tissue inflammation) not accessible to specimen sampling or sampled with negative microbiological results. Fever of unknown origin was defined as fever >38 °C over at least 1 h or twice within 12 h, with no detectable cause. Details are available in the Online Supplementary File.

The last antimicrobial treatment before ICU admission and the first antimicrobial treatment after ICU admission were recorded. Antimicrobial treatment were categorized in a 4-class variable according to the existence of microbiological documentation and the compliance with guidelines. Thus, when microbiological documentation

was available, antimicrobial treatment was considered as adequate, inadequate if it was active, or not active against the identified pathogens based on in vitro susceptibility testing. In the absence of microbiological documentation, antimicrobial treatment was considered as appropriate or inappropriate, based on the compliance with guidelines) [12]. For Gram-negative bacilli, monotherapy with aminoglycoside was considered as inappropriate [22].

De-escalation of the empirical antimicrobial treatment consisted of either deleting one of the antimicrobials of a combined treatment including anti-MRSA antibiotics, antifungal treatment, antiviral treatment, or, whenever possible, the use of betalactams with a narrower spectrum of activity [5]. Criteria for narrowing the antimicrobial regimen were based on the results of susceptibility testing of identified bacteria. In our ICU, de-escalation was not performed according to a protocol. It was left to the discretion of the senior intensivist. De-escalation was only evaluated during ICU stay. Escalation of antimicrobial treatment consisted of either the addition of an antibiotic of another family to the betalactam or the use of betalactam with a broader-spectrum of activity. A combination was defined as aminoglycosides or fluoroquinolones given in addition to betalactams.

Statistical analysis

Our hypothesis was that, as reported in non-neutropenic patients [4–7], de-escalation was feasible in 40 % of neutropenic patients with severe sepsis. Thus, the inclusion of 100 patients would permit the estimatation of the proportion of de-escalation with an imprecision [half the width of the 95 % confidence interval (CI)] of <10 %.

All data are presented as percentages for qualitative variables and median (25th–75th percentiles) for quantitative variables. The features of patients during their ICU stay were compared across the groups of patients undergoing de-escalation of the antimicrobial treatment (de-escalation group) and those who did not (non-de-escalation group) by using Fisher's exact test and Wilcoxon rank-sum test. Our second hypothesis was that adequation of antimicrobial treatment was associated with de-escalation. A multivariate logistic model with AIC-based stepwise selection was fitted to identify which of the covariates that described compliance with guidelines was significantly independently associated with de-escalation. The Hosmer–Lemeshow test was used to check goodness-of-fit of the selected logistic model.

Effect of de-escalation on 30-day mortality was assessed by fitting a Cox proportional hazards model using de-escalation as a time-dependent covariate. For patients with de-escalation the same day of antibimicrobial treatment discontinuation (or discharge alive), de-escalation was considered as having been done 12 h before. A sensitivity analysis was performed by considering that, for these patients, no de-escalation was performed. Effect of de-escalation on long-term survival was estimated on the subset of patients discharged alive from ICU, by comparing 1-year survival post-ICU between patients for whom the antimicrobial treatment had or had not been de-escalated.

All tests were two-sided, and p values lower than 0.05 were considered statistically significant. Analysis was performed using SPSS, v.16.0 software (SPSS, Chicago, IL, USA) and R v.2.13 (http://www.R-project.org/).

Results

During the study period, severe sepsis and septic shock were diagnosed in 118 neutropenic patients out of 1,803 patients admitted to ICU. Seventeen (14 %) patients were excluded because they died within the first 48 h after admission. Thus, 101 patients were included in the study. The underlying cancers were acute leukemia ($n = 44$), lymphoma ($n = 24$), myeloma ($n = 12$), and miscellaneous ($n = 21$). Hematopoietic stem cell transplantation was observed in 24 patients, including 14 autologous and 10 allogeneic transplants (Table 1). ICU admission occurred 6 days (2–10) after the onset of neutropenia. Neutropenia duration was 11 days (8–16). In 52 patients, neutropenia was resolutive during the ICU stay. In ICU, granulocyte colony-stimulating factor (G-CSF) was used in 55 patients (Table 2).

Major reasons for ICU admission were acute respiratory failure ($n = 36$) and shock ($n = 32$) (Table 1). At ICU admission, sepsis was identified in 83 patients, and 18 patients developed a subsequent sepsis during the ICU stay. Septic shock and severe sepsis were identified in 54 and 47 patients, respectively (Table 2).

Totals of 63, 21, and 17 patients had microbiologically documented infections, clinically documented infections, and fever of unknown origin, respectively (Table 3). Bacteria ($n = 63$), fungi ($n = 22$), and viruses ($n = 7$) were identified in 59, 18, and 5 patients, respectively. Polymicrobial infection was found in 20 patients. The major sites of infection were lungs ($n = 44$) and abdomen ($n = 11$). Blood cultures were positive in 11 patients (Table 3). The characteristics of the microbiological documentation are available in Electronic Supplementary Material Table 1.

Before ICU admission, antibiotics were administered to 79 (79 %) patients. Betalactams were used in all but one patients. In 74 (94 %) of these 79 patients, they were active against *Pseudomonas aeruginosa*. Vancomycin and linezolid were used in 28 (35 %) and 2 (3 %) patients, respectively. A combined antibiotic was used in 36 (46 %) patients, consisting of aminoglycosides ($n = 18$)

Table 1 Characteristics of patients in the intensive care unit

	All patients ($n = 101$)	No de-escalation ($n = 57$)	De-escalation ($n = 44$)	p
Age (years)	58 (48–67)	60 (51–68)	58 (48–64.25)	0.15
Gender (male)	52	30 (53)	22 (50)	0.84
SAPS II on day 1	49 (42–66)	47 (39–60)	49 (42.75–65.5)	0.097
SOFA score on day 1	8 (6–11)	7 (5–10)	8.5 (6–10.25)	0.37
Time between treatment and the first signs of sepsis in ICU (h)	1.6 (0.7–3.1)	1.8 (0.6–4.1)	1.4 (0.7–2.3)	0.33
Comorbidity (Knaus definitions)				
Chronic respiratory failure	2	0 (0)	2 (5)	0.19
Chronic heart failure	12	7 (12)	5 (11)	1
Chronic renal failure	3	2 (4)	1 (2)	1
Diabetes mellitus	11	7 (12)	4 (9)	0.75
Features at ICU admission				0.51
Shock	32	15 (26)	17 (39)	
Acute respiratory failure	36	21 (37)	15 (34)	
Severe sepsis	12	6 (11)	6 (14)	
Tumor lysis syndrome	11	8 (14)	3 (7)	
Coma	5	4 (7)	1 (2)	
Cardiac arrest	2	1 (2)	1 (2)	
Acute kidney injury	1	0 (0)	1 (2)	
Metabolic	2	2 (4)	0 (0)	
ICU admission for sepsis	83	43 (75)	40 (91)	0.065
Type of cancer				0.86
Acute leukemia	44	26 (46)	18 (41)	
Lymphoma	24	13 (23)	11 (25)	
Chronic leukemia	2	2 (4)	0 (0)	
Myeloma	12	7 (12)	5 (11)	
Other hematologic diseases	7	3 (5)	4 (9)	
Solid tumor	12	6 (11)	6 (14)	
HSCT				0.89
No	77	44 (77)	33 (75)	
Autologous	14	7 (12)	7 (16)	
Allogeneic	10	6 (11)	4 (9)	
Status of cancer disease				0.43
Newly diagnosed	24	15 (26)	9 (20)	
Remission	20	8 (14)	12 (27)	
Progression	49	29 (51)	20 (45)	
Unknown	8	5 (9)	3 (7)	

Data are expressed as number (percentage) or median (25th–75th percentiles)

G-CSF granulocyte-colony stimulating factor, *HSCT* hematopoietic stem cell transplantation, *ICU* intensive care unit, *SAPS II* simplified acute physiology score II, *SOFA* sequential organ failure assessment

and fluoroquinolones ($n = 18$). Antifungal and antiviral agents were given to 30 (38 %) and 14 (18 %) patients, respectively.

In the ward, 79 patients received an empirical antimicrobial treatment. Among them, infection was microbiologically documented in 49 (62 %) patients, with adequate treatment in 27 (55 %) of these patients. The treatment was appropriate for 17 (57 %) out of the 30 patients without microbiological documentation. Twenty-two patients did not receive antibiotics before ICU admission. Among them, infection was microbiologically documented in 15 (68 %) cases.

After ICU admission, antimicrobial treatments were continued in 37 patients and initiated in 22 patients. Changes were performed in 42 patients. The time elapsed between the first antimicrobial therapy and the first signs of severe sepsis in ICU was 1.6 (0.7–3.1) h (Table 1). Betalactams were administered to all patients. They were inactive against *Pseudomonas aeruginosa* in 2 patients. In 57 patients, aminoglycosides ($n = 27$) or fluoroquinolones ($n = 30$) were added. Antibiotics active against MRSA were used in 48 patients. Antifungal and antiviral agents were used in 30 and 17 patients, respectively (Electronic Supplementary Material Table 2). The median duration of antimicrobial treatment was 7 days [4–14] for median duration of ICU stay of 9 days [5–18].

At ICU admission, the empirical antimicrobial treatment was appropriate in 50 patients and adequate in 42 patients. Eight out of the 38 patients without microbiological documentation received an appropriate treatment (Table 4). Of note, in these 38 patients, the anti-pseudomonal antibiotic was appropriate in 31 (82 %).

The empirical antimicrobial treatment was de-escalated in 44 patients of the 101 patients (Electronic Supplementary

Table 2 Organ failure, support care and neutropenia evolution in ICU

	No de-escalation ($n = 57$)	De-escalation ($n = 44$)	p
Time between onset of sepsis and its management in ICU (days)	1 (0–3)	2 (0–7)	0.057
Worsened SOFA score[a]	17 (30)	15 (34)	0.67
MV	20 (35)	15 (34)	1
ARDS	12 (21)	6 (14)	0.43
RRT	15 (26)	11 (25)	1
Hepatic failure	8 (14)	4 (9)	0.54
Cardiac failure	7 (12)	6 (14)	1
Septic shock	29 (51)	25 (57)	0.69
Stress doses corticoids	13 (23)	8 (18)	0.63
Life-sustaining treatment limitation	12 (21)	7 (16)	0.61
Neutropenia status			
Neutropenia recovery in ICU	24 (42)	28 (64)	0.05
Use of G-CSF during ICU stay	26 (46)	29 (66)	0.05
Mucositis	4 (7)	3 (7)	1
Neutropenic colitis	12 (21)	9 (20)	1

Data are expressed as number (percentage) or median (25th–75th percentiles)
ARDS acute respiratory distress syndrome, *ICU* intensive care unit, *MV* invasive mechanical ventilation, *RRT* renal replacement therapy, *SOFA* sequential organ failure assessment
[a] Between day 1 and day 5

Table 3 Characteristics of infection

	No de-escalation ($n = 57$)	De-escalation ($n = 44$)	p
Predominant site of infection			0.64
Pulmonary	24 (42)	20 (45)	
Abdominal	5 (9)	6 (14)	
Bacteremia	6 (11)	5 (11)	
Urinary tract	3 (5)	2 (4)	
Catheter-related infection	3 (5)	2 (4)	
Central nervous system	2 (4)	2 (4)	
Skin and soft tissue infection	0 (0)	2 (4)	
ENT infection	1 (2)	1 (2)	
Unknown	13 (23)	4 (9)	
Infection in the ICU			0.11
Fever of unknown origin	13 (23)	4 (9)	
Clinically documented	13 (23)	8 (18)	
Microbiological documented	31 (54)	32 (73)	
Type of pathogen (among the 63 patients with microbiological documentation)			
Non fermentative Gram-negative bacilli	9 (29)	7 (22)	0.57
Other gram-negative bacilli	7 (23)	9 (28)	0.77
Gram-positive cocci	13 (42)	12 (38)	0.80
Anaerobe	2 (6)	0 (0)	0.24
Fungal	10 (32)	7 (22)	0.41
Viral	2 (6)	3 (9)	1
Polymicrobial infections	12 (21)	8 (18)	0.80
Multiple sites	6 (19)	3 (9)	0.30
Colonization with MDR pathogens at ICU admission	10 (18)	10 (23)	0.62

Data are expressed as number (percentage) or median (25th–75th percentiles)
MDR multi-drug-resistant, *ENT* eye, nose, throat, *ICU* intensive care unit

Material Fig. 1). Cumulative incidence of de-escalation in ICU at day 15 was 44 % (95 % CI 38–53 %) (Fig. 1). De-escalation was performed in 32 of the 63 (51 %) patients with microbiological documentation and 12 of the 38 (32 %) patients without microbiological documentation. The betalactam spectrum was narrowed in 22 (35 %) patients with microbiological documentation and 1 (3 %) patient without microbiological documentation. In 26

Table 4 Compliance with antibiotics guidelines and adequation of antimicrobial treatment to microbiological documentation

	No de-escalation ($n = 57$)	De-escalation ($n = 44$)	p
Empirical antibiotic treatment initiated in ICU			0.075
Documented, adequate	18 (32)	24 (55)	
Documented, inadequate	13 (23)	8 (18)	
Not documented, appropriate	7 (12)	1 (2)	
Not documented, inappropriate	19 (33)	11 (25)	
Compliance with antibiotic guidelines (ICU)			
Empirical anti-pseudomonal betalactam	46 (81)	43 (98)	0.01
Empirical anti Gram positive cocci	39 (68)	25 (57)	0.30
Regarding combination therapy	34 (60)	24 (55)	0.69

Data are expressed as number (percentage) or median (25th–75th percentiles)
ICU intensive care unit

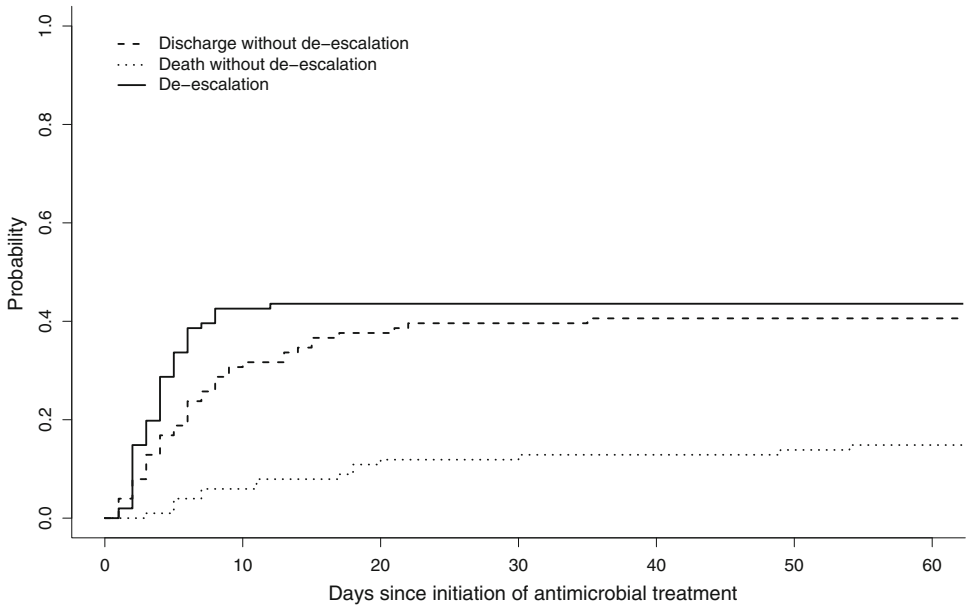

Fig. 1 Cumulative incidence of de-escalation, death in ICU without de-escalation, and discharge alive without de-escalation

patients, the antibiotic directed against MRSA was discontinued. All de-escalation were performed within the first 12 days (Fig. 1). Of note, de-escalation of antifungal and antiviral agents was always concomitant to that of antibiotics. The severity of organ failures at ICU admission was similar in the de-escalation group and the non-de-escalation group (Table 1). The time elapsed between the severe sepsis onset and its ICU management was longer in the de-escalation group, compared to the non-de-escalation group but the difference did not reach statistical significance [2 (0–7) vs. 1 (0–3) days, $p = 0.057$] (Table 2). In 30 (30 %) patients, de-escalation was performed during neutropenia. The rate of escalation after de-escalation was 5 % (Electronic Supplementary Material Table 3).

Using a multivariate analysis, the characteristics of antimicrobial treatment independently associated with de-escalation were adequation of the empirical antimicrobial treatment used in ICU [OR = 10.8 (95 % CI 1.20–96)] for adequate documented treatment versus appropriate empirical treatment), and compliance with guidelines regarding the empirical anti-pseudomonal betalactam used in ICU [OR = 10.8 (95 % CI 1.3–89.5)] (Electronic Supplementary Material Table 4).

The ICU mortality rate was 23 %. The 23 deaths included 6 patients undergoing de-escalation during neutropenia, 2 patients undergoing de-escalation after neutropenia recovery, and 15 patients in the non-de-escalation group ($p = 0.57$). De-escalation was not associated with the hazard of death within the first 30 days [HR = 0.51 (95 % CI 0.20–1.33)], nor within the 1-year post-ICU-discharge [HR = 1.06 (95 % CI 0.54–2.08)] (Electronic supplementary material Fig. 2). Among patients discharged alive, median duration of antibiotherapy in ICU was 9 days [4–12] in the de-escalation group versus 5 days [3–8] in the non-de-escalation group ($p = 0.005$). In the de-escalation group, cancer status and G-CSF use were not associated with ICU death. During the ICU stay, 7 (22 %) out of 32 patients in the

no-remission group died, compared to 1 (8 %) out of 12 patients in the remission group ($p = 0.15$). Five (17 %) out of 29 patients treated with GCS-F and 3 (20 %) out of 15 patients not treated with G-CSF died ($p = 1$).

Discussion

To our knowledge, this study is the first evaluation of de-escalation in neutropenic cancer patients requiring ICU. As expected, the empirical antimicrobial treatment was de-escalated in about 40 % of this population. In ICU, an adequate empirical antimicrobial treatment and the compliance to guidelines regarding the first anti-pseudomonal betalactam agent are critical for initiating the process of de-escalation. De-escalation did not affect the patient outcomes.

In the hematological patients with sepsis and neutropenia, the empirical choice of antimicrobials remains a matter of debate [23]. Two approaches are opposed to each other. The escalation approach consists of avoiding the use of broad-spectrum antibiotics. In this strategy, the treatment is escalated in the patient with clinical worsening or after the identification of a resistant pathogen. This strategy reduces toxicity, selection pressure, and cost. However, the delayed use of an effective treatment can negatively impact the outcomes [24, 25]. In contrast, de-escalation consists of the empirical use of broad-spectrum antibiotics. This strategy is efficient in covering all possible pathogens [2], but it exposes broad-spectrum antibiotics to overuse [24, 26]. Previous studies showed the safety of de-escalation in patients with septic shock, although no randomized clinical trials are available [4].

In our series, the empirical antimicrobial treatment was de-escaladed in 44 % of the neutropenic patients. No apparent effect on mortality was observed. Initial organ failures did not affect the strategy, suggesting that the decision was not guided by the patient severity. The rate of de-escalation did not differ from that reported in non-neutropenic patients [5–7, 27]. Importantly, our study was conducted in ICU. It is important to underline that our patients were continuously monitored. Thus, our results cannot be extrapolated to conventional wards. One should note that 5 % of patients required escalation after de-escalation failure [5, 28]. In a cancer ICU, de-escalation seems feasible and safe.

The neutropenic patients are at high risk of complications, due to altered immune response [29, 30]. Guidelines suggest continuing antimicrobial treatment until neutropenia recovery. They recommend the changing of antibiotics on the basis of microbiological results [11, 12]. There are no data supporting this statement [11, 12]. In our study, 68 % of patients underwent de-escalation during neutropenia. We did not find a deleterious impact of de-escalation on the survival of this specific subgroup. Future studies are required to confirm this finding. In our study, the duration of treatment was increased in the de-escalation group, compared to the non-de-escalation group. Of importance, in the de-escalated patients, treatment was never interrupted before neutropenia recovery. In critically ill neutropenic cancer patients, recovering from neutropenia during the ICU stay is a critical step; before this time, supportive care including antimicrobial treatment is usually maintained [30].

The administration of an adequate empirical antimicrobial treatment was associated with de-escalation. In line with a previous study [1], this finding underlines the need to collect blood samples and specimens from the suspected sources of infection before the antibiotic onset [31]. In cancer patients, a standardized diagnostic approach has been associated with improved outcomes [18, 32]. Using both invasive and non-invasive procedures, this strategy resulted in a microbiological documentation in up to 60 % of patients [18, 32]. Elsewhere, the identification of pathogens has been associated with decreased mortality [33]. In agreement with previous findings, this strategy was associated with a relatively low rate of positive blood culture [18].

The second factor associated with de-escalation was the compliance to guidelines regarding the choice of the antipseudomonal agent [12]. The use of ceftazidime and ticarcillin/clavulanate was not associated with de-escalation. Of note, international guidelines recommend the avoidance of ceftazidime for empirical monotherapy of fever and neutropenia [12]. In contrast, the empirical use of carbapenem was significantly associated with a high rate of de-escalation. This suggests that a guidelines strategy based on an empirical broad-spectrum antimicrobial treatment followed by de-escalation is feasible in neutropenic patients [4].

In the 38 patients without microbiological documentation, the uses of antipseudomonal belactams, anti-MRSA antibiotics, and combined antibiotics were inappropriate in 7 (18 %), 15 (39 %), and 17 (45 %) patients, respectively. Thus, only 8 (21 %) of these patients received an antimicrobial treatment in compliance with the guidelines. In the septic neutropenic patients, initial antimicrobial treatment using combined antibiotics or anti-MRSA drugs remains a matter of debate [20]. In the wards of our institution, anti-MRSA drugs were largely used although MRSA were rarely identified. In ICU, in disagreement with the guidelines, the use of these antibiotics was often interrupted, based on our local ecology and the removal of invasive devices [20]. Surprisingly, we observed a high rate of patients receiving antifungals in the de-escalation group. One possible explanation is that, in those patients, the delay between the onset of sepsis and its ICU management was longer than in the non-de-escalated patients. Thus, an antifungal treatment was prior introduced as the guidelines recommend [11, 34]. Of note,

antifungal treatment was interrupted in 50 % of de-escalated patients.

Our results show that de-escalation did not impact short-term mortality. Several factors can affect the relationship between de-escalation and mortality: early ICU discharge, adequacy of empirical antimicrobial therapy, and timing of antibiotic administration. In our opinion, de-escalation may probably not alter short-term mortality. Indeed, no study has reported significant differences between two adequate antimicrobial treatment in patients with septic shock [35].

Several limitations should be acknowledged. De-escalation was left to the discretion of the senior physician. This represents a confusing factor, limiting the application of this strategy. However, our rate of de-escalation was similar to that reported in previous studies [5–7, 27]. The identification of co-pathogens such as yeasts and viruses has not been reported elsewhere. The actual impact of those pathogens on the de-escalated patient outcomes remains unclear. Finally, our study cannot document the relationship between a potential time-varying confounder such as the evolution of organ failure during ICU and de-escalation.

In conclusion, for the first time, we show that, in ICU, de-escalation is frequently performed in neutropenic cancer patients with severe sepsis. This approach appears not to affect the outcomes. Future studies are required to confirm these preliminary findings.

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