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De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial

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Abstract *Background:* In patients with severe sepsis, no randomized clinical trial has tested the concept of de-escalation of empirical antimicrobial therapy. This study aimed to compare the de-escalation strategy with the continuation of an appropriate empirical treatment in those patients. *Methods:* This was a multicenter non-blinded randomized noninferiority trial of patients with severe sepsis who were randomly assigned to de-escalation or continuation of empirical antimicrobial treatment. Recruitment began in February 2012 and ended in April 2013 in nine intensive care units (ICUs) in France. Patients with severe sepsis were assigned to de-escalation ($n = 59$) or continuation of empirical antimicrobial treatment ($n = 57$). The primary outcome was to measure the duration of ICU stay. We defined a noninferiority margin of 2 days. If the lower boundary of the 95 % confidence interval (CI) for the difference in patients assigned to the de-escalation group was less than 2 days, as compared with that of patients assigned to the continuation group, de-escalation was considered to be noninferior to the continuation strategy. Secondary outcomes included mortality at 90 days, occurrence of organ failure, number of superinfections, and number of days with antibiotics during the ICU stay. *Results:* The median duration of ICU stay was 9 [interquartile range (IQR) 5–22] days in the de-escalation group and 8 [IQR 4–15] days in the continuation group, respectively ($P = 0.71$). The mean difference was 3.4 (95 %

CI −1.7 to 8.5). A superinfection occurred in 16 (27 %) patients in the de-escalation group and six (11 %) patients in the continuation group ($P = 0.03$). The numbers of antibiotic days were 9 [7–15] and 7.5 [6–13] in the de-escalation group and continuation group, respectively ($P = 0.03$). Mortality was similar in both groups. *Conclusion:* As compared to the continuation of the empirical antimicrobial treatment, a strategy based on de-escalation of antibiotics resulted in prolonged duration of ICU stay. However, it did not affect the mortality rate.

Keywords Sepsis · Antibiotics · De-escalation · Empirical · Stewardship

Introduction

The increasing rate of multidrug-resistant pathogens is a major challenge in intensive care units (ICU). Because of the low number of new antibiotics available in the near future, the development of strategies preventing the emergence of resistance is critical. Hand hygiene, contact precautions, isolation of colonized patients, and surveillance are the standards of infection control policies [1]. Antimicrobial stewardship is another important strategy for controlling the risk of emergence of antibiotic resistance [2].

With respect to antimicrobial stewardship, de-escalation of empirical antimicrobial treatment on the basis of culture results and the elimination of redundant combination therapy is a strong recommendation [2, 3]. At the bedside, de-escalation consists either in eliminating one of the antibiotics of the prescribed combination or, whenever possible, using a beta-lactam antibiotic with a narrower spectrum of activity [4]. This recommendation is supported by observational studies [5–11]. De-escalation aims at reducing the use of broad-spectrum antibiotics and therefore the emergence of multidrug-resistant pathogens [12]. Observational studies suggested that this strategy was safe [5–11]. However, there is no adequate, direct evidence as to whether de-escalation of antimicrobial agents is effective and safe for adults with sepsis, severe sepsis, or septic shock [13]. Thus, randomized clinical trials are needed for testing the safety and efficiency of de-escalation of antimicrobial therapy.

Our hypothesis was that de-escalation of empirical antimicrobial therapy in patients with severe sepsis or septic shock was noninferior to the continuation of empirical antimicrobial therapy. The first aim of the study was to demonstrate that de-escalation was noninferior to the continuation of broad-spectrum antibiotics in terms of duration of ICU stay. The secondary aims were to compare the two strategies in terms of mortality, duration of antimicrobial therapy, durations of mechanical ventilation, vasopressor use, numbers of superinfections, organ failure, and *Clostridium difficile* infection.

Methods

We conducted a multicenter non-blinded randomized noninferiority trial comparing de-escalation versus continuation of the appropriate empirical antimicrobial treatment. The trial was registered in ClinicalTrials.gov (NCT01626612).

Patients

Patients were enrolled from 1 February 2012 to 8 April 2013 at nine ICUs (see list of investigators in the Appendix). Eligibility criteria were (1) the presence of severe sepsis requiring an empirical antimicrobial treatment; severe sepsis was defined as systemic inflammatory response syndrome and suspected infection with at least one organ failure including hypotension, respiratory failure, coma, liver failure, thrombocytopenia, and acute renal failure [14]. (2) The appropriateness of empirical antimicrobial therapy and positive microbiological cultures in relation to the suspected location of infection. Definitions of infections are available in Electronic Supplementary Material Table 1. The reasons for exclusion are reported in Fig. 1.

The trial was monitored by an independent data and safety monitoring board consisting of three members (Dr Nathalie Lesavre, MD; Dr Julie Brunet, PharmD; and Patrick Sudour, Senior Research Technician). They checked the quality of data and the safety of procedures during the study. They produced a report for the National Agency of Drug Safety.

Randomization was performed according to an electronic list that was under the responsibility of the Public Health and Medical Information Department (Hôpital Nord, Marseille, France). The electronic list was managed and centralized by the principal investigator who checked the criteria for inclusion before randomization. The study protocol and statistical analysis plan were approved by the ethics committee of the Marseille University Hospital (Comité de Protection des Personnes Sud Méditerranée no. 2011-002297-22). Written informed consent was obtained from the patients or their relatives.

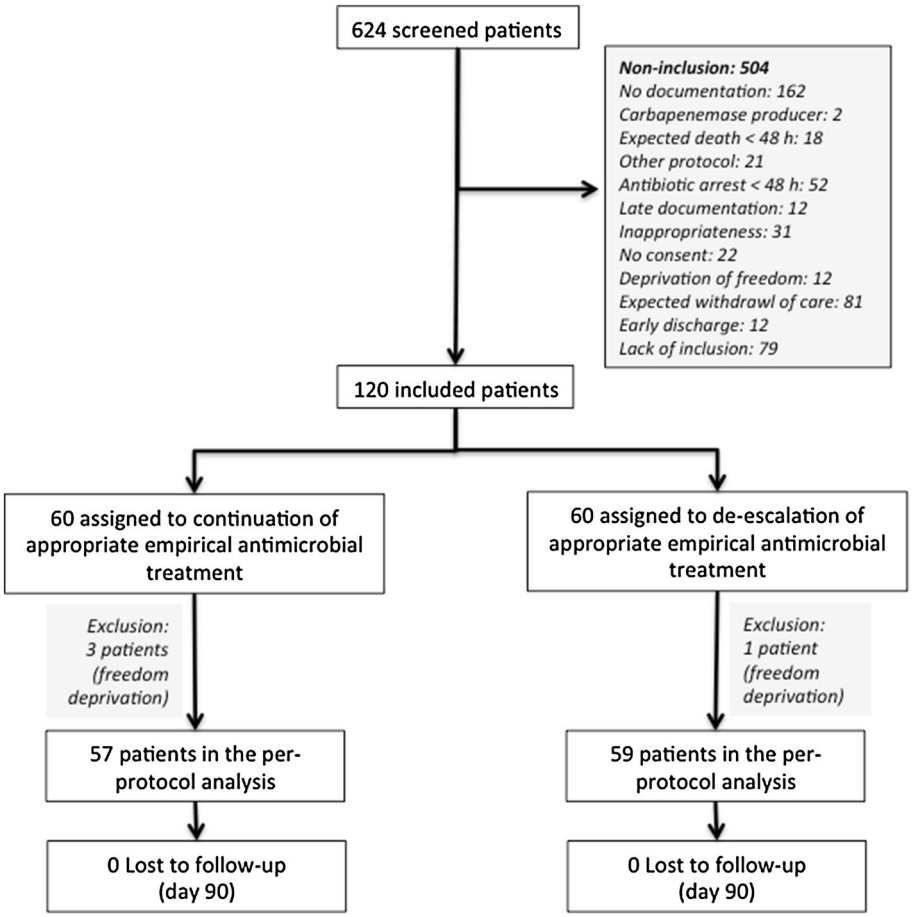

Fig. 1 Flow chart of inclusion and follow-up

Randomization

After the suspected bacteria responsible for infection was identified, the patients/relatives were invited to participate as soon as the antibiogram was available. After the written consent was signed, the eligible patients were randomly assigned (1:1) to be included in either the de-escalation group or the continuation group.

De-escalation strategy

After the results of the antibiogram of the suspected causative bacteria were available, the "pivotal" antibiotic used for empirical treatment was switched to an antibiotic with a spectrum as narrow as possible according to the targeted pathogens [4]. The companion drug (aminoglycoside or fluoroquinolone or macrolide) was stopped at day 3. The choice of antibiotics was based on international guidelines [3, 15–18]. The empirical antibiotics directed against methicillin-resistant *Staphylococcus aureus* (MRSA) were stopped if MRSA was not identified in microbiological cultures. For the purpose of this study, de-escalation was considered if the pivotal antibiotic was switched for an antibiotic with a narrower spectrum than the empirical treatment, according to a ranking of molecules provided in Electronic Supplementary Material Table 2. The companion drug and the antibiotic used against MRSA were eliminated after inclusion.

Continuation strategy

After randomization, the pivotal antibiotic of the empirical treatment was continued for the entire duration of the treatment, independently of microbiological results (although the treatment should be active against the identified pathogen). For prolonged treatment (>15 days), the physician had the choice of de-escalating after 8–15 days of treatment. The companion antibiotic (aminoglycoside or fluoroquinolone or macrolide) was stopped between day 3 and day 5 [3, 15–18]. Empirical antibiotics directed against MRSA were used according to international guidelines [3, 15–18].

Antimicrobial treatment

The antimicrobial treatments were based on the standards of care, in agreement with international guidelines [3, 15–18]. First, the patients with severe sepsis and septic shock received an empirical antimicrobial therapy. The choices of antibiotics were suggested according to the site of infection (Electronic Supplementary Material Table 3) [15–18]. With respect to treatment duration, the study protocol invited the co-investigators to follow international guidelines (Electronic Supplementary Material Table 4) [3, 15–18]. The doses and routes of administration were in accordance with current medical standards. The noninfectious treatments were conducted according to international guidelines [3].

Data collection

Demographic characteristics, physiological variables, coexisting conditions, and medications were collected at inclusion. Risk factors for infection due to multidrug-resistant bacteria were screened at inclusion, according to previous guidelines [15]. Briefly, they consisted of the administration of antimicrobial therapy in the preceding 90 days, current hospitalization of 5 days or more, high frequency of antibiotic resistance in the specific hospital unit, hospitalization for 2 days or more in the preceding 90 days, home infusion therapy, residence in nursing home or extended care facility, and immunosuppressive disease. The local situation of local resistance is summarized in Electronic Supplementary Material Table 5. Microbiological results, duration of antimicrobial treatments, changes in antibiotics occurring after inclusion, and superinfection episodes requiring reintroduction of antibiotics were prospectively collected. Patients were monitored during their ICU stays for signs of organ failures. Organ failure was reported as follows: circulatory failure was defined as systolic blood pressure of 90 mmHg or less or the need for vasopressor therapy. Coagulation failure was defined as a platelet count of 80,000 or less per cubic millimeter. Hepatic failure was defined as a serum bilirubin level of 2 mg/dl (34 μmol/l) or higher. Renal failure was defined as a serum creatinine level of 2 mg/dl (177 μmol/l) or higher.

Study outcomes

Primary outcome

The primary outcome was the number of days between the study inclusion and ICU discharge. For the patients who died during ICU hospitalization, the day of ICU discharge was the day of death.

Secondary outcomes

To complement the primary outcome, the duration of ICU stay was compared in the two groups after adjustment for unbalanced baseline variables. The same procedure was performed on the subgroup of patients alive at ICU discharge.

The other secondary outcomes were the number of ICU-free days (from inclusion to day 28), the day-90 mortality, the numbers of ventilator-free days (from inclusion to day 28), the number of catecholamine-free days (from inclusion to day 28), the number of antibiotic-free days (from inclusion to day 28), the number of days of antibiotic treatment during the ICU stay, and the number of superinfections requiring antibiotics. During the first 8 days after inclusion, changes in SOFA score (D-SOFA) were calculated as follows: [score on day 8 − score on inclusion]. We also collected the number of infections due to *C. difficile* (positivity of toxin A or B in feces).

Post hoc outcomes

A post hoc analysis was conducted in a subgroup of patients with ventilator-associated pneumonia. From inclusion to ICU discharge, we determined the use of antibiotics directed against *Pseudomonas aeruginosa*, carbapenems, and antibiotics directed against MRSA. We also analyzed the number of patients in whom an escalation of treatment was required after inclusion. We conducted an analysis of outcomes in the subgroup of patients not requiring changes in antibiotics after inclusion.

Statistical analysis

Assumptions for the sample-size calculation were based on the durations of ICU stay reported in previous studies [7, 10, 11]. With respect to a mean duration of ICU stay of 10 days in the continuation group [7, 10, 11], a clinically significant noninferiority range of 2 days for 80 % statistical power with a one-sided alpha value of 2.5 %, 51 patients would be needed in each group to establish the noninferiority of de-escalation compared with the continuation of antimicrobial treatment. An additional 15 % was added for loss to follow-up, leading to a total of 120 patients. No interim analysis was planned.

Analysis was performed using SPSS software version 17.0. Statistical significance was defined as $P < 0.05$. The methodology was based on the extension of Consolidated Standards of Reporting Trials Statement (CONSORT, http://www.consort-statement.org/consort-statement/) for reporting of noninferiority randomized trials [19]. In view of the noninferiority hypothesis, we performed a per-

protocol analysis, which excluded patients who were ineligible after randomization. Differences between groups were assessed using a Chi square test, Fisher's exact test, the Student *t* test, and the Mann–Whitney test, as appropriate.

Primary outcome

For each patient, we determined the duration of ICU stay. We defined a noninferiority margin of 2 days. If the lower boundary of the 95 % confidence interval (CI) for the difference in the duration of ICU stay in patients assigned to the de-escalation group was less than 2 days, as compared with the duration in patients assigned to the continuation group, we would consider de-escalation as noninferior to the continuation strategy. The duration of ICU stay was expressed as median and interquartile range (IQR) for both groups, as the mean difference and the 95 % CI (de-escalation group minus continuation group).

To complement the primary analysis on the duration of ICU stay, we performed a linear regression model after adjustment for baseline simplified acute physiology score (SAPS) II, (1) in the whole sample; (2) in the subgroup of patients alive at ICU discharge; beta standardized coefficients were presented.

Secondary outcomes

The 90-day mortality rate was compared between the two groups. The 90-day survival rate was also compared between the two groups using the Renyi test [20]. Cox models were performed for adjustment on SAPS II. Modified SAPS II (SAPS II excluding the age variable) was calculated. Cox models were performed for adjustment on modified SAPS II, age, and treatment group. Hazard ratios (HR) and 95 % CI were presented. Median D-SOFA (inclusion to day 8), ventilator-free days, catecholamine-free days, antimicrobial-free days (day 1 to day 28), proportions of superinfection (defined by the occurrence of an infection with the identification of a pathogen and the need to introduce a new antimicrobial treatment) and infections due to *Clostridium difficile* were compared between the two groups. The follow-up was completed at day 90.

Post hoc analysis

In order to assess the effect of source of infection, we performed a multivariate linear regression including the modified unbalanced variables (SAPS II, age, chronic arterial hypertension, source of infection, and treatment group). Then, we determined the duration of ICU stay in the subgroup of patients with lung infection. Similarly, we determined the duration of ICU stay in the patients with risk factors for multidrug-resistant bacteria.

Results

Baseline characteristics

Nine ICUs enrolled 120 patients. Four patients were secondarily excluded because they were placed in the care of a guardian. Thus, the per-protocol analysis included 116 patients. Of the 116 patients, 59 and 57 were randomly assigned to the de-escalation group and the continuation group, respectively (Fig. 1). The two groups differed in age (58 ± 17 years old vs. 67 ± 15 years old, $P = 0.003$), SAPS II (44 ± 19 vs. 51 ± 19, $P = 0.03$), and proportion of prior history of hypertension (Table 1). Risk factors for multidrug-resistant bacteria were found in 93 (80 %) patients (Table 1). At inclusion, the SOFA score was 6.4 ± 3.8 (Table 2). Empirical antimicrobial treatment did not differ in either group (Table 2). Blood culture was positive in 39 (34 %) patients. Pathogens were mostly isolated in bronchial and urine samples (Electronic Supplementary Material Table 6).

Empirical treatment was based on combination of antibiotics in 52 (88 %) patients in the de-escalation group, as compared with 52 (91 %) in the continuation group ($P = 0.58$) (Table 2). Aminoglycosides were used in 33 (56 %) patients and 35 (61 %) patients in the de-escalation group and continuation group, respectively ($P = 0.55$). The duration of companion antibiotics was 2.0 [2.0–3.0] days and 3.0 [2.8–3.0] days in the de-escalation group and the continuation group, respectively ($P = 0.002$).

Empirical antimicrobial treatment was de-escalated at a median day 3 and IQR 2–4 after the onset of treatment. The latest day for de-escalation was day 9 in one patient. Details of de-escalation are shown in Electronic Supplementary Material Table 7. After randomization, the companion drugs [i.e., aminoglycoside ($n = 34$), fluoroquinolones ($n = 8$), and macrolides ($n = 3$)] were stopped in all cases but one. An antibiotic directed against MRSA was empirically used in 25 (42 %) patients, respectively linezolid ($n = 19$) and vancomycin ($n = 6$). In all patients, these antibiotics were stopped after randomization.

Primary outcome

In the per-protocol population, the median duration between inclusion and ICU discharge was 9 [5–22] days in the de-escalation group and 8 [4–15] days in the continuation group ($P = 0.71$) (Table 3). The mean

Table 1 Baseline characteristics of study participants

Characteristics	De-escalation group ($n = 59$)	Continuation group ($n = 57$)	P
Age (years)	57.9 ± 17.0	66.8 ± 14.9	0.003
Male sex (%)	62.7	66.7	0.66
SAPS II[a]	43.6 ± 18.5	51.4 ± 18.7	0.03
Modified SAPS II[a]	33.9 ± 17.5	38.1 ± 18.3	0.20
Body mass index	26.8 ± 6.4	27.4 ±7.4	0.65
Admission cause			0.56
Medicine (%)	52.5	54.4	
Trauma (%)	8.5	15.8	
Scheduled surgery (%)	10.2	7.0	
Emergent surgery (%)	28.8	22.8	
Co-morbidities			
Chronic obstructive pulmonary disease (%)	15.3	15.8	0.94
Diabetes (%)	18.6	28.1	0.23
Arterial hypertension (%)	30.5	50.9	0.03
Chronic heart failure (%)	10.2	8.8	0.80
Prior stroke (%)	3.4	7.0	0.38
Risk factors for multidrug-resistant pathogen[b] (%)	83.1	77.2	0.43
Time between onset of empirical treatment and inclusion (days)[c]	3.0 ± 1.7 3.0 [2.0–4.0]	2.7 ± 1.4 2.0 [2.0–3.5]	0.25
Time between sepsis and inclusion (days)[c]	3.2 ± 1.6 3.0 [2.0–4.0]	2.7 ± 1.4 2.0 [2.0–3.0]	0.05

Data are means ± SD unless otherwise specified

[a] SAPS denotes simplified acute physiology score. Modified SAPS II means SAPS II without age inclusion

[b] Includes antimicrobial therapy in preceding 90 days, current hospitalization of 5 days or more, high frequency of antibiotic resistance in the community or in the specific hospital unit, hospitalization for 2 days or more in the preceding 90 days, resident in nursing home or extended care facility, chronic dialysis within 30 days, home wound care, family member with multidrug-resistant pathogen, immunosuppressive disease and/or therapy

[c] Data include medians [interquartile]

Table 2 Criteria at inclusion

Characteristics	De-escalation group ($n = 59$)	Continuation group ($n = 57$)	P
SOFA[a]	6.3 ± 2.9	6.4 ± 4.0	0.78
Catecholamines (%)	54.2	54.4	0.99
Mechanical ventilation (%)	71.2	59.6	0.19
Site of infection			
Lung (%)	57.6	40.4	0.06
Urine (%)	20.3	22.8	0.75
Abdomen (%)	15.3	21.2	0.42
Skin and tissue (%)	5.1	10.5	0.32
Catheter (%)	1.7	1.8	1.00
Positive blood culture (%)	32.2	35.1	0.74
Empirical antibiotics			0.54
Combined therapy (%)	88	91	0.58
Carbapenems (%)	39.0	17.5	0.01
Ureidopenicillin plus inhibitor (%)	35.6	50.9	0.09
Third-generation cephalosporin (%)	25.4	29.8	0.59
Aminoglycoside (%)	56.0	61.4	0.55
Fluoroquinolone (%)	13.6	29.8	0.03
Vancomycin (%)	11.9	12.3	0.94
Linezolid (%)	23.7	12.3	0.11
Fluconazole (%)	3.3	3.5	1.0
Echinocandin (%)	0.0	1.8	0.49

[a] SOFA denotes sequential organ failure assessment

difference between de-escalation group and continuation group was 3.4 (95 % CI −1.7 to 8.5). After adjustment for baseline SAPS II, neither the treatment group nor the SAPS II was linked to the duration of ICU stay ($\beta = -0.10$; $P = 0.28$, $\beta = -0.09$; $P = 0.33$, respectively). The estimated marginal means and standard errors were 14.9 ± 1.8 days and 12.1 ± 1.7 days for the de-escalation group and continuation group, respectively.

Table 3 Outcomes of patients included in the two groups

Duration	De-escalation group ($n = 59$)	Continuation group ($n = 57$)	P
Duration of ICU stay (days)			
From inclusion to discharge	15.2 ± 15.0 9 [1–79]	11.8 ± 12.6 8 [1–60]	0.71
From admission to discharge	29.1 ± 50.0 13 [1–375]	18.1 ± 15.7 12 [3–67]	0.11
Number of ICU-free days[a]	13.2 ± 10.6 18 [0–23]	15.0 ± 11.3 21 [0–25]	0.21
Ventilator-free days[a]	18.9 ± 11.6 23 [6–29]	19.3 ± 11.8 26 [6–29]	0.55
Catecholamine-free days[a]	22.3 ± 10.3 28 [21–29]	21.6 ± 11.2 28 [16–29]	0.93
Number of antibiotic days	14.1 ± 13.4 9 [7–15]	9.9 ± 6.6 7.5 [6–13]	0.04
Number of companion antibiotic days	2.3 ± 0.8 2.0 [2.0–3.0]	3.2 ± 1.7 3.0 [2.8–3.0]	<0.00
Number of antibiotic days for the initial episode	7.9 ± 5.2	8.0 ± 4.3	0.94
Number of antipseudomonal agent-free days[a]	23.6 ± 9.2 29 [24–29]	20.1 ± 9.6 24 [15–28]	<0.001
Number of carbapenem-free days[a]	25.6 ± 7.3 29 [26–29]	23.5 ± 8.4 29 [19–29]	0.17
Number of anti-MRSA drug-free days[a]	25.8 ± 7.1 29 [27–29]	24.1 ± 8.4 29 [21–29]	0.30

Data are means ± SD, followed by medians [interquartile]. Durations are determined after study inclusion

MRSA methicillin-resistant *Staphylococcus aureus*

[a] Free days were calculated from inclusion (day 1) to day 28

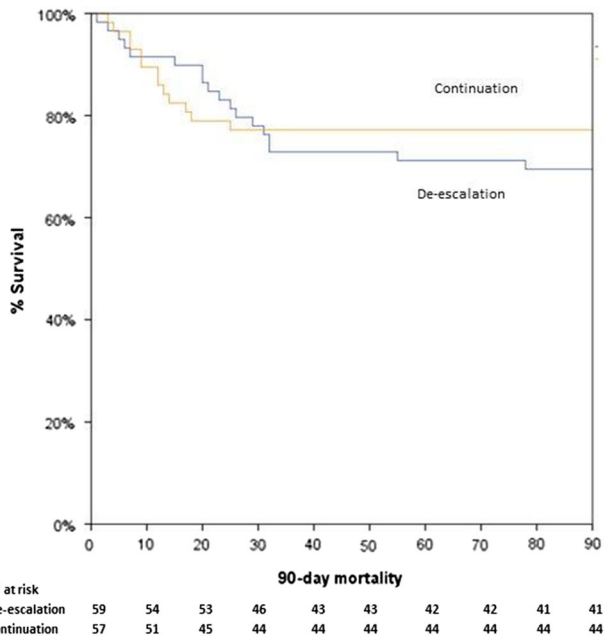

Fig. 2 Cumulative survival curves: no difference was observed in the groups

Secondary prespecified outcomes

Regarding the initial episode of severe sepsis or septic shock, the duration of antibiotic treatment was similar in both groups ($P = 0.94$). For the patients discharged alive from the ICU, the mean duration from inclusion to discharge did not differ in either group (9 [1–79] days vs. 6 [1–60] days, $P = 0.28$). In the de-escalation group, severe sepsis or septic shock was diagnosed 5 [3–10] days after ICU admission, as compared with 4 [3–8] days in the continuation group ($P = 0.24$). The number of hospital days after inclusion was 24 [2–120] days in the de-escalation group and 20 [4–134] days in the continuation group ($P = 0.26$).

Death at 90 days was reported in 18 (31 %) patients in the de-escalation group and 13 (23 %) patients in the continuation group ($P = 0.35$) (Fig. 2). The 90-day mortality did not differ in either group (HR = 1.31, 95 % CI 0.64–2.67, $P = 0.49$). After adjustment for modified SAPS II, age, and treatment group, the Cox regression model yielded an HR for death at day 90 of 1.01 (95 % CI, 0.99–1.03, $P = 0.30$) for modified SAPS II, 1.02 (95 % CI 1.00–1.05, $P = 0.06$) for age, and 1.7 (95 % CI 0.79–3.49, $P = 0.18$) for treatment group.

In the 66 patients with an ICU stay of more than 7 days, the median D-SOFA score was similar in both groups (3 [0; 4] vs. 2 [−1; 3], $P = 0.63$). At day 28, the numbers of ventilator-free days and of catecholamine-free days did not differ significantly in either group (Table 3). Of the 86 patients discharged alive from hospital, 15 (36 %) patients in the de-escalation group and 14 (32 %) patients in the continuation group were re-admitted to hospital ($P = 0.64$). Globally, five patients in the de-escalation group and one patient in the continuation group required ICU readmission, respectively ($P = 0.1$).

The number of days of antimicrobial use was 9 [2–66] days in the de-escalation group and 8 [2–34] days in the continuation group ($P = 0.11$). During ICU stay, superinfection episodes requiring antibiotics were identified in 16 (27 %) patients in the de-escalation group and six (11 %) patients in the continuation group ($P = 0.03$). This was related to the same bacteria in seven (44 %) of the 16 episodes in the de-escalation group and four (67 %) of the six episodes in the continuation group ($P = 0.64$). The locations of superinfection were lungs ($n = 13$), abdomen ($n = 2$), bloodstream ($n = 2$), urine ($n = 2$), and catheter-related infection ($n = 1$). No *C. difficile* infection was reported in the included patients.

Secondary post hoc outcomes

Because lung infection was unbalanced between groups, we performed a multivariate analysis with modified SAPS II, age, chronic arterial hypertension, and source of infection. Lung as source of infection was an independent variable linked to the duration of ICU stay. Thus, we assessed the impact of de-escalation in the 56 patients with lung infection. The durations of ICU stay were 14 [9–31] days and 15 [8–21] days in the de-escalation group and the continuation group, respectively ($P = 0.53$). Thirteen (39 %) and five (22 %) superinfection episodes were reported in the de-escalation group and continuation group ($P = 0.2$).

In the 93 patients with risk factors for multidrug-resistant bacteria carriage, the duration of ICU stay was 10 [5–25] days and 8 [4–16] days in the de-escalation group and continuation group, respectively ($P = 0.71$).

After inclusion, the antibiotics directed against *P. aeruginosa* were used for 12 [5–22] days in the de-escalation group and 6 [3–12] days in the continuation group ($P = 0.03$). The duration of the use of carbapenems and antibiotics directed against MRSA were similar in both groups (Table 3).

After inclusion, antimicrobial treatment was escalated in eight (14 %) patients in the de-escalation group and five (8.8 %) patients in the continuation group ($P = 0.41$). We assessed the duration of ICU stay, mortality rate, and number of superinfections in the 103 patients in whom the antimicrobial treatment remained unchanged after inclusion. No significant difference was reported in either group, including the number of superinfection episodes (10 (19 %) episodes vs. four (8 %) episodes, $P = 0.08$).

Discussion

For the first time, de-escalation of antimicrobial treatment was tested in a randomized clinical trial. In terms of duration of ICU stay we cannot conclude that the de-escalation strategy was noninferior to the continuation of an appropriate empirical treatment. De-escalation was associated with an increased number of superinfection episodes, but it did not affect the number of organ failures and mortality.

The strength of our study was to randomize de-escalation as compared to the continuation of an appropriate empirical treatment. Although guidelines recommend a strategy based on de-escalation [2, 3], such a strategy has never been tested in a randomized clinical trial [13]. The guidelines are supported by observational studies [5–11], in which several biases may affect the results [21]. The present randomized clinical trial did not confirm the findings of observational studies. Nevertheless, our pragmatic study protocol aimed at reflecting real-life conditions, including uncertainty about diagnosis and adequate treatment of infections. The study was performed in nine multidisciplinary ICUs. This suggests that our results can be exported to other ICUs.

In the de-escalation group, we observed an increased number of superinfections. This finding probably explains the increased use of antibiotics in this group. The duration of treatment of the initial episode was similar in both groups, suggesting that superinfection episodes were responsible for prolonged antimicrobial use in the de-escalation group. Of note, in this group, new pathogens were responsible for 56 % of the superinfection episodes.

De-escalation did not affect the mortality rate. In our study, we observed a 27 % mortality rate at day 90. This rate is consistent with the selection of patients with severe sepsis [22]. Although the study was not designed to assess this endpoint, we did not observe any difference in the 90-day mortality in either group. Our findings are in accordance with the results of several observational studies [6, 11]. In contrast, an observational study concluded that de-escalation was a protective factor for mortality [10]. Unexpected bias can affect the findings of observational studies [21, 23]. The appropriateness of antimicrobial treatment is probably critical for reducing the mortality related to severe sepsis [10, 24–27]. Here we found that de-escalation was not associated with a significant change in mortality.

The study was designed on a noninferiority model. This choice was based on the analysis of observational studies [5–11]. Most of those studies did not report significant effects of de-escalation in terms of ICU duration. Importantly, this design cannot serve to state that continuing the empirical antimicrobial treatment was associated with a shorter duration of ICU stay than de-escalating the empirical antimicrobial treatment.

Limitations of our study include the lack of blind treatment. The open design probably may have influenced many important variables. As we compared different strategies, it was technically difficult to conduct blind treatment. Although we designed the study to reach a power of 80 %, the number of patients remains relatively small. Mode of administration was not collected, but most treatments were given according to international guidelines [2,

3]. The inclusion of patients with severe sepsis independently of the site of infection could be viewed as a limitation. However, guidelines recommend de-escalating the empirical antimicrobial treatment in all patients with severe sepsis, wherever the source of infection [2, 3]. Of note, no significant difference was reported in the patients with lung infection. Finally, there is an arbitrary dimension in the definition of de-escalation. Future consensus is required in order to provide a definition for this process.

Our study was not designed to measure the effect of de-escalation on local ecology. We collected samples from patients at inclusion and on day 8. We did not find significant differences in either groups (data not shown). In addition, no *C. difficile* infection was diagnosed in our patients. Larger samples of patients are probably required to explore this issue accurately [26]. Time of inclusion is another limitation. However, the time between onset of sepsis and antibiotic administration was similar in both groups. Randomization resulted in imbalances between the groups in age that could have influenced the findings. After adjustment, the differences in hospital stay and mortality were unchanged. One can note that lung as a source of infection impacted the duration of ICU stay. However, in this subgroup, the duration of ICU stay tended also to be longer in the de-escalation group than in the continuation group. In line with prior findings [28], a similar trend was found in the analysis of patients with risk factors of infection due to multidrug-resistance bacteria. According to guidelines [2, 3], antibiotics directed against MRSA were empirically used in our patients with severe sepsis and septic shock. However, as there is no option for de-escalating linezolid or vancomycin, no patient with MRSA infection was included. Of note, in a previous study [29], we assessed the rate of patients with ventilator-associated pneumonia in three out of the nine ICUs of our present study. We noted a 1.6 % prevalence of MRSA, suggesting that this pathogen is rare in our area. In the present study, we screened two patients with MRSA infection.

In conclusion, for the first time, this multicenter trial randomly assigned de-escalation or continuation strategy. In terms of duration of ICU stays, de-escalation was inferior to continuation of the appropriate empirical treatment. De-escalation was associated with an increased number of superinfections, but it did not affect mortality.

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The following data are reported as "unit, hospital, city (number of patients included): names of co-investigators":

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References

1. Maragakis LL (2010) Recognition and prevention of multidrug-resistant Gram-negative bacteria in the intensive care unit. Crit Care Med 38(8 Suppl): S345–S351
2. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeter M, Hooton TM (2007) Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 44:159–177
3. Dellinger RP, Levy MM, Rhodes A et al (2013) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39:165–228
4. Kollef MH (2001) Hospital-acquired pneumonia and de-escalation of antimicrobial treatment. Crit Care Med 29:1473–1475

5. Rello J, Vidaur L, Sandiumenge A, Rodríguez A, Gualis B, Boque C, Diaz E (2004) De-escalation therapy in ventilator-associated pneumonia. Crit Care Med 32:2183–2190
6. Leone M, Bourgoin A, Cambon S, Dubuc M, Albanèse J, Martin C (2003) Empirical antimicrobial therapy of septic shock patients: adequacy and impact on the outcome. Crit Care Med 31:462–467
7. Morel J, Casoetto J, Jospé R, Aubert G, Terrana R, Dumont A, Molliex S, Auboyer C (2010) De-escalation as part of a global strategy of empiric antibiotherapy management. A retrospective study in a medico-surgical intensive care unit. Crit Care 14:R225
8. Heenen S, Jacobs F, Vincent JL (2012) Antibiotic strategies in severe nosocomial sepsis: why do we not de-escalate more often? Crit Care Med 40:1404–1409
9. Shime N, Kosaka T, Fujita N (2013) De-escalation of antimicrobial therapy for bacteraemia due to difficult-to-treat Gram-negative bacilli. Infection 41:203–210
10. Garnacho-Montero J, Gutiérrez-Pizarraya A, Escoresca-Ortega A, Corcia-Palomo Y, Fernández-Delgado E, Herrera-Melero I, Ortiz-Leyba C, Márquez-Vácaro JA (2014) De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. Intensive Care Med 40:32–40
11. Mokart D, Slehofer G, Lambert J, Sannini A, Chow-Chine L, Brun JP, Berger P, Duran S, Faucher M, Blache JL, Saillard C, Vey N, Leone M (2014) De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study. Intensive Care Med 40:41–49
12. Niederman MS (2006) De-escalation therapy in ventilator-associated pneumonia. Curr Opin Crit Care 12:452–457
13. Silva BN, Andriolo RB, Atallah AN, Salomão R (2013) De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock. Cochrane Database Syst Rev 3:CD007934
14. Calandra T, Cohen J, International Sepsis Forum Definition of Infection in the ICU Consensus Conference (2005) The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med 33:1538–1548
15. American Thoracic Society; Infectious Diseases Society of America (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171:388–416
16. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, O'Neill PJ, Chow AW, Dellinger EP, Eachempati SR, Gorbach S, Hilfiker M, May AK, Nathens AB, Sawyer RG, Bartlett JG (2010) Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 50:133–164
17. Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, Rice JC, Saint S, Schaeffer AJ, Tambayh PA, Tenke P, Nicolle LE (2010) Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis 50:625–663
18. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC (2005) Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis 41:1373–1406
19. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG, CONSORT Group (2012) Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA 308:2594–2604
20. Renyi A (1953) On the theory of order statistics. Acta Math Acad Sci Hungar 4:191–231
21. Ellenberg JH (1994) Selection bias in observational and experimental studies. Stat Med 13:557–567
22. Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, Gårdlund B, Marshall JC, Rhodes A, Artigas A, Payen D, Tenhunen J, Al-Khalidi HR, Thompson V, Janes J, Macias WL, Vangerow B, Williams MD (2012) Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med 366:2055–2064
23. Leibovici L (2009) Non-antibiotic treatment for bacterial infections: how to validate chance findings. Clin Microbiol Infect 15:298–301
24. Retamar P, Portillo MM, López-Prieto Rodríguez-López F, de Cueto M, García MV, Gómez MJ, Del Arco A, Muñoz A, Sánchez-Porto A, Torres-Tortosa M, Martín-Aspas A, Arroyo A, García-Figueras C, Acosta F, Corzo JE, León-Ruiz L, Escobar-Lara T, Rodríguez-Baño J (2012) Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. Antimicrob Agents Chemother 56:472–478
25. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH (2000) The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 118:146–155
26. Kerry SM, Bland JM (1998) Trials which randomize practices II: sample size. Fam Pract 15:84–87
27. Garcin F, Leone M, Antonini F, Charvet A, Albanèse J, Martin C (2010) Non-adherence to guidelines: an avoidable cause of failure of empirical antimicrobial therapy in the presence of difficult-to-treat bacteria. Intensive Care Med 36:75–82
28. Martin-Loeches I, Deja M, Koulenti D, Dimopoulos G, Marsh B, Torres A, Niederman MS, Rello J, EU-VAP Study Investigators (2013) Potentially resistant microorganisms in intubated patients with hospital-acquired pneumonia: the interaction of ecology, shock and risk factors. Intensive Care Med 39:672–681
29. Leone M, Malavieille F, Papazian L, Meyssignac B, Cassir N, Textoris J, Antonini F, La Scola B, Martin C, Allaouchiche B, Hraiech S (2013) Routine use of Staphylococcus aureus rapid diagnostic test in patients with suspected ventilator-associated pneumonia. Crit Care 17:R170