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Selective digestive decontamination and empirical antimicrobial therapy of late-onset ventilator-associated pneumonia in trauma patients

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ABSTRACT

Objective: To assess the appropriateness of empirical antimicrobial therapy in trauma patients treated with selective digestive decontamination (SDD) who developed ventilator-associated pneumonia (VAP). **Methods:** Retrospective study comparing 199 trauma patients receiving SDD and 99 non-trauma patients not receiving SDD hospitalized in a polyvalent intensive care unit (ICU) of a university hospital. **Results:** Early-onset VAP were recorded in 76 (35%) patients. Late-onset VAP occurred in 86 (72%) trauma patients receiving SDD and 56 (56%) non-trauma patients not receiving SDD (P = 0.02). The empirical antimicrobial therapy was appropriate in 108 (91%) trauma patients receiving SDD and 82 (83%) non-trauma patients not receiving SDD (P = 0.1). In the patients who developed late-onset VAP, the empirical antimicrobial therapy was appropriate in 77 (90%) trauma patients receiving SDD and 49 (88%) non-trauma patients not receiving SDD (P = 0.9). De-escalation was performed in 52 (44%) trauma patients receiving SDD and 37 (37%) non-trauma patients not receiving SDD (P = 0.4). Recurrences were observed in 26 (22%) trauma patients receiving SDD and 18 (18%) non-trauma patients not receiving SDD (P = 0.6). These episodes were due to easy-to-treat pathogens in 75 (63%) trauma patients and 33 (33%) non-trauma patients (P = 0.01). **Conclusions:** SDD is not associated with a rise in the rate of inappropriateness of the empirical antimicrobial therapy in trauma patients developing late-onset VAP.

1. Introduction

Ventilator-associated pneumonia (VAP) is the most common cause of infection in the intensive care unit (ICU). Amongst ICU patients, the rate of VAP is higher in the patients with trauma than in those with medical or surgical conditions[1]. Prompt initiation of an appropriate antimicrobial therapy for VAP is the key determinant for patient outcome[2,3]. We previously showed that a strategy based on the knowledge of local ecology and consideration of patient medical history led to a high rate of appropriateness of the empirical antimicrobial therapy in patients with VAP[4].

In ICU, the use of selective digestive decontamination (SDD) reduces the bacterial inoculum stagnant in the oropharyngeal and digestive reservoirs[5]. SDD regimen has been associated with a reduction of mortality[6]. This benefit has been historically demonstrated in trauma patients[7]. On the other hand, SDD can result in the emergence of multidrug resistant pathogens[8]. Thus, the rate of appropriateness of the empirical antimicrobial therapy can be impaired in the patients receiving SDD and developing late-onset VAP. The objective of our study was to assess whether the use of SDD was associated with an increased rate of inappropriateness of the empirical antimicrobial therapy in patients who developed VAP.

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2. Materials and methods

The retrospective study was conducted in a polyvalent 16-bed ICU in an 800-bed university hospital (Hôpital Nord, Marseille, France). This hospital is a level I trauma center and a major regional referral center for acute surgical disease. Informed consent and approval by the Ethics Committee were waived due to the observational nature of the study.

Patients. All adult patients admitted to the ICU requiring tracheal intubation and mechanical ventilation for more than 48 h during a 6-year period (January 2001 to January 2007) were eligible for inclusion. Trauma patients receiving SDD and non-trauma not receiving SDD who developed VAP were included in the cohort. The diagnosis of VAP[9] was established when the following criteria were fulfilled: (i) purulent bronchial sputum; (ii) body temperature >38 ℃ or <36 ℃; (iii) white blood cells >10 000 per mm^3 or <4 000 per mm^3; (iv) chest radiograph showing new or progressive infiltrates; (v) presence of at least one microorganism at a concentration of $\geqslant 10^4$ colony-forming units (cfu) per mL in bronchoalveolar lavage, or 10^6 cfu per mL in tracheal aspirates. We excluded episodes in which the final diagnosis was rejected or undetermined due to the presence of an alternative cause, or in which no agreement on diagnosis was reached. Senior intensivists and microbiologists rejected or determined the final diagnosis of VAP.

The unit is set up on a closed organizational format, with two weekly staff meetings, including a meeting with the microbiology physicians. The plan of care was decided during the daily round by the attending physician. The duration of prior antibiotic exposure was recorded as a dichotomous variable with a threshold to three days to discriminate antimicrobial prophylaxis for trauma patients and prior use of antimicrobial therapy. Prior broad-spectrum antimicrobial therapy (third-generation cephalosporin, amoxicillin-clavulanate association, fluoroquinolone, and antipseudomonal antibiotics) before VAP onset was regrouped to constitute a new variable. Stress-ulcer prophylaxis was used in patients with a past medical history significant for ulcer and in those who were not enterally fed. If needed, proton pump inhibitor stress was administered for bleeding prophylaxis. Enteral nutrition was initiated as soon as feasible. The patients underwent mechanical ventilation with the ventilator set in volume-controlled mode. Mechanical ventilation was protocol-driven, with standard orders for semi-recumbent position, daily interruption of sedation, daily oral hygiene, and spontaneous breathing trials when patients met criteria for weaning. The decision to extubate a patient was made by daily evaluations of spontaneous breathing trials. Heat and moisture exchanger bacterial filters (Gibeck, Stockholm, Sweden) were inserted between the endotracheal tube and the ventilator circuit except in patients with acute respiratory distress syndrome.

The trauma patients requiring tracheal intubation received SDD consisting of polymyxin E, gentamicin, and amphotericin B, as described elsewhere[10]. A 2% mixture of these drugs in Orabase paste was applied on the buccal mucosa, and a suspension of the same drugs (respective doses 200, 80, and 500 mg) was provided in the nares and digestive tract at 6 h intervals. SDD was started on the day of admission and was continued until the patients were weaned from mechanical ventilation. For the first three days, systemic cefazolin (1 g three times a day) was provided to all trauma patients. Importantly, this regimen was not administered to the surgical and medical patients.

Empirical antimicrobial therapy. Antimicrobial therapy was administered according to our local written guidelines, as described elsewhere[4]. Empirical antimicrobial therapy was initiated just after microbiological sample collection. Ceftriaxone or amoxicillin-clavulanate was used in the patients with early-onset VAP (< 5 d) without recent prior hospitalization, including long-term care facilities (within 30 d), or prior antibiotic treatment (within 15 d). Gentamicin was combined with a beta-lactam in patients with severe sepsis and septic shock. In patients with late-onset VAP, beta-lactams with activity against *P. aeruginosa* (piperacillin-tazobactam or ceftazidime) were used at the discretion of the attending physicians (antipseudomonal antibiotics). Carbapenems were kept as last-line therapy. Amikacin or levofloxacin was added when criteria for severe sepsis or septic shock were diagnosed. Vancomycin or linezolid was prescribed when oxacillin-resistant Staphylococcus aureus (ORSA) was suspected. Empirical antimicrobial therapy was systematically reassessed from the moment the microbiological results were available (*i.e.*, on days 2-3). Microbiological findings were used to determine whether the empirical treatment targeted the identified bacteria. The clinical status of patients was evaluated taking into account the evolution of prior organ dysfunction and plasma lactate levels. According to the antimicrobial susceptibility of the identified bacteria and clinical progress, a decision was made to perform escalation, de-escalation or maintain the initial treatment.

Definitions. "Trauma" was defined as the presence of injury to more than one body area or system or the presence of major cranial trauma alone. The injury severity score (ISS) was used to determine the severity of trauma[11]. The "non-trauma" group included surgical and medical patients requiring mechanical ventilation. Severity of underlying disease was evaluated with the simplified acute physiologic score (SAPS II) for each patient in the first 24 h after ICU admission[12].

VAP due to "difficult-to-treat bacteria" referred to VAP due to ORSA, *P. aeruginosa* and *A. baumannii*. "Easy-to-treat bacteria" designated a group of microorganisms eligible to a short-course of eight days of appropriate antimicrobial therapy. "Anti-pseudomonal antibiotics" referred to antibiotics with activity against *P. aeruginosa* including imipenem-cilastatin, piperacillin-tazobactam, ceftazidime or ciprofloxacin, whereas "broad-spectrum

antimicrobial therapy" designated combination of antibiotics with activity against *P. aeruginosa*, *A. baumannii* and ORSA. In particular, the addition of aminoglycosides to beta-lactams was considered as a broad-spectrum therapy. "Limited-spectrum antibiotics" referred to beta-lactams without activity against *P. aeruginosa* (essentially, ceftriaxone and amoxicillin-clavulanate) used alone.

"Appropriateness" was defined as prescription of antimicrobial therapy with activity against pathogens cultured by lower airway sampling in the same patient. "Inappropriate empirical antimicrobial therapy" was defined as follows: (i) absence of antimicrobial agents directed against a specific class of microorganisms; and (ii) administration of an antimicrobial agent to which the microorganism responsible for VAP was resistant[4] "De-escalation" of antibiotic therapy consisted on either discontinuing one of the antibiotics of the prescribed combination or, whenever possible, using a beta-lactam with a narrower spectrum of activity. The criteria for narrowing the antimicrobial regimen were based on the results of susceptibility testing of isolated bacteria. "Escalation" of antibiotic therapy consisted of either adding an antibiotic of another family to the pivotal beta-lactam left, or using a beta-lactam with a broader spectrum of activity. The criteria for escalation were the lack of susceptibility of isolated bacteria and/or inappropriate clinical response or clinical worsening.

"Recurrence" was defined as the development of a new episode of pulmonary infection after 48 h or more of complete resolution of the original VAP. The clinical pulmonary infection score (CPIS) was used to assess the clinical response of patients to treatment[13]. "Adequacy" designated a favorable clinical response after eight days of treatment, defined as a CPIS value under 6 at day 8. "Clinical resolution" was defined as a complete resolution of all signs and symptoms of pneumonia in conjunction with an improvement or stabilization of all abnormalities on chest radiograph. Death was related to VAP if the pulmonary infection was a contributing factor to death in patients with co-morbidity.

Microbiology. Data were extracted from the microbiology laboratory database. When indicated, samples from catheters, wounds, and blood were taken and cultured. All samples were submitted to routine Gram staining. The material was inoculated onto free growth culture media and onto selective differential media for the isolation of Gram-negative and Gram-positive microorganisms. Cultures were incubated at 35 ℃ and examined after 18-24 h. Identification of microorganisms and antibiotic sensitivity testing were performed according to internationally accepted laboratory procedures. Importantly, cross-transmission of epidemic strains was a rare event in this ICU during the study period.

Variables. The following variables were recorded at ICU admission: age, gender, comorbidities, prior hospitalization within 30 d, case mix, Glasgow Coma Scale score, prior antibiotic treatment within 15 d, and SAPS II. The following variables were recorded on the day of sample collection: body temperature, white blood cell count, PaO_2/FIO_2 ratio, lactate plasma level > 2 mmol/L. The duration of mechanical ventilation and length of ICU stay were also recorded. Four groups were created on the basis of mechanical ventilation (> 5 d) before VAP onset and prior antibiotic exposure (within 15 d). Clinical outcomes were compared in each of these four groups based on presence or absence of trauma.

Statistical analysis. A descriptive analysis was performed. Statistical calculations were performed using SPSS software version 15.0. The distribution of continuous variables was checked; if the distribution was normal, data were expressed as mean values ± standard deviation [SD]. For ordinal variables or if the distribution was not normally distributed, data were expressed as median values with interquartile range [IQR] (quartile 25%-75%). For categorical variables, percentages were computed. Comparisons of quantitative

Table 1.
Characteristics of patients with ventilator-associated pneumonia.

Variables	Trauma patients receiving SDD(n = 119)	Non-trauma patients receiving SDD(n = 99)	P
SAPS II, years (mean±SD)	43±12	43±16	0.800
Gender (male/female)	104/15	64/35	0.001
Age, years (mean±SD)	36±15	51±15	0.001
COPD, n (%)	10 (8)	30 (30)	0.001
Congestive heart failure, n (%)	2 (2)	13 (13)	0.002
Chronic renal failure, n (%)	1 (1)	6 (6)	0.070
Diabetes mellitus, n (%)	7 (6)	7 (7)	0.900
Immunocompromised, n (%)	1 (1)	9 (10)	0.010
Recent steroid use, n (%)	18 (15)	32 (32)	0.004
Prior antibiotic use, n (%) *	14 (12)	36 (36)	0.001
Prior hospitalization, n (%)	4 (3)	45 (45)	0.001
Glasgow coma scale, median [IQR]	6 [4-10]	12 [6-15]	0.001
Onset of VAP, days, median [IQR]	7 [4-10]	6 [3-9]	0.020

SAPS: simplified acute physiologic score; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; VAP: ventilator-associated pneumonia; SDD: selective digestive decontamination.
*Except selective digestive decontamination.

values of dichotomous variables were performed with the Student's t test or Mann-Whitney U test for non-normally distributed variables. Comparisons of percentages were performed with Fisher's exact test.

3. Results

Patient and illness characteristics. During the study period, 218 mechanically ventilated patients meeting the inclusion criteria were included in the study. The population consisted of 119 trauma patients receiving SDD and 99 non-trauma patients not receiving SDD. The ISS of our trauma patients was of 38 [30-59]. The most important injuries consisted of severe head trauma (n = 85 (71%)) and chest trauma (n = 65 (58%)). The non-trauma patients not receiving SDD were admitted for surgical (n = 33) and medical (n = 66) reasons. Demographic characteristics of patients are reported in Table 1. Although the trauma patients receiving SDD were younger than the non-trauma patients not receiving SDD, the severity of disease was similar in both groups (Table 1). With regard to the past medical history, prior hospitalization (< 3 months) was identified in four (3%) trauma patients receiving SDD and 45 (45%) non-trauma patients not receiving SDD (P < 0.001). Except SDD, 14 (12%) trauma patients receiving SDD were exposed to prior antimicrobial therapy (< 2 weeks), as compared with 36 (36%) non-trauma patients not receiving SDD (P < 0.001).

VAP and microbiological patterns. Early-onset VAP were recorded in 76 (35%) patients. Late-onset VAP occurred in 142 (65%) patients, respectively 86 (72%) trauma patients receiving SDD and 56 (56%) non-trauma patients not receiving SDD (P = 0.02). A total of 271 microorganisms were identified on quantitative lower airway cultures (Table 2). Fifty-seven episodes of VAP were polymicrobial, respectively 28 (24%) in the trauma patients receiving SDD and 29 (24%) in the non-trauma patients not receiving SDD (29%) (P = 0.6). The pathogens responsible for VAP are shown in Table 2. *P. aeruginosa*, *A. baumanii*, and ORSA represented 53 (20%) isolates. In the trauma patients receiving SDD, they were identified in 22 (19%) episodes, as compared with 28 (28%) episodes in the non-trauma patients not receiving SDD (P = 0.1).

Appropriateness of empirical antimicrobial therapy. The empirical antimicrobial therapy was appropriate in 190 (87%) patients, including 108 (91%) trauma patients receiving SDD and 82 (83%) non-trauma patients not receiving SDD (P = 0.1). In the patients with late-onset VAP, the empirical

Table 2.
Microbiological pathogens associated with ventilator-associated pneumonia.

Microorganisms	Overall (n = 271)	Trauma receiving SDD (n = 146)	Non-trauma patients not receiving SDD (n = 125)
Difficult-to-treat-bacteria			
ORSA	9	3	6
A. baumannii	13	8	5
P. aeruginosa	31	12	19
Non-difficult-to-treat-bacteria			
OSSA	76	42	34
S. pneumoniae	37	22	15
H. influenzae	43	29	14
Enterobacteriae	57	28	29
K. pneumoniae	11	5	6
E. coli	16	10	6
P. mirabilis	13	8	5
Enterobacter spp	16	5	11
S. marcescens	1	0	1
Others	5	2	3

ORSA: oxacillin-resistant *S. aureus*; OSSA: oxacillin-susceptible *S. aureus*; SDD, selective digestive decontamination.

Table 3.
Outcomes of patients with ventilator-associated pneumonia.

Variable	Trauma patients receiving SDD (n=119)	Non-trauma patients receiving SDD (n=99)	P
Duration of antibiotic treatment, days, median [IQR]	8 [7-11]	8 [7-12]	0.50
Duration of mechanical ventilation, days, median [IQR]	12 [8-18]	12 [7-23]	0.90
Recovery, n (%)	99 (83)	75 (76)	0.20
ICU death, n (%)	28 (23)	39 (39)	0.01
Death related to VAP, n (%)	14 (12)	15 (15)	0.20
Discontinuation of life support therapy, n (%)	6 (5)	22 (22)	0.03

IQR, interquartile range; ICU, intensive care unit; SDD, selective digestive decontamination; VAP, ventilator-associated pneumonia.

antimicrobial therapy was appropriate in 77 (90%) trauma patients receiving SDD and 49 (88%) non-trauma patients not receiving SDD (P = 0.9).

The causes of inappropriateness in the trauma patients receiving SDD were the lack of antibiotic coverage in six (5%) cases and bacterial resistance in five (4%) cases. Non-adherence to our local guidelines was responsible for eight (7%) cases of inappropriateness. In the non-trauma patients not receiving SDD, the causes of inappropriateness were respectively the bacterial resistance for nine (9%) patients and the lack of antibiotic coverage for eight (8%) patients. Non-adherence to our local guidelines was observed in four (4%) of these patients.

Re-evaluation of empirical antimicrobial therapy. After culture results were available, the antibiotic regimen was reassessed in 71 (60%) trauma patients receiving SDD and 61 (62%) non-trauma patients not receiving SDD (P = 0.9). The empirical antimicrobial therapy was de-escalated in 89 patients (41%) on day 3 (3 - 5), in 52 (44%) trauma patients receiving SDD and in 37 (37%) non-trauma patients not receiving SDD, respectively (P = 0.4). The empirical treatment was escalated in 43 (20%) patients on day 4 (3 - 7), due to the lack of appropriate empirical antimicrobial therapy (n = 28) and a poor clinical response (n = 15). This occurred in 19 (16%) trauma patients receiving SDD and 24 (24%) non-trauma patients not receiving SDD (P = 0.2). The median duration of the antibiotic treatment was of 8 (7 - 11) d independently of patient characteristics or appropriateness of empirical antimicrobial therapy.

Clinical response to treatment. Adequacy to treatment (*i.e.* CPIS < 6 at day 8) was higher in the trauma patients receiving SDD than in the non-trauma patients not receiving SDD (63% *vs.* 48%, P = 0.04). The VAP were recurrent in 26 (22%) trauma patients receiving SDD and 18 (18%) non-trauma patients not receiving SDD (P = 0.6). These episodes were due to easy-to-treat pathogens in 75 (63%) trauma patients receiving SDD and 33 (33%) non-trauma patients not receiving SDD (P = 0.01).

Outcome. With respect to the duration of antimicrobial therapy, mechanical ventilation and length of ICU stay, no significant differences were found between the trauma patients receiving SDD and the non-trauma patients not receiving SDD (Table 3). The ICU mortality was lower in the trauma patients receiving SDD than in the non-trauma patients not receiving SDD (23% *vs.* 39%, P = 0.01).

4. Discussion

In our study, the rate of appropriateness of empirical antibiotic therapy was similar in the trauma patients receiving SDD and the non-trauma patients not receiving SDD. The use of medical resources was similar in both groups. The clinical response to appropriate treatment was delayed in the non-trauma patients not receiving SDD, as compared with that of the trauma patients receiving SDD. Despite a higher rate of late-onset VAP, the crude mortality rate was lower in the trauma patients receiving SDD than in the non-trauma patients not receiving SDD (23% *vs.* 39%, P = 0.01). Of note, no difference was found in death-related to VAP. This finding confirms that VAP poorly affects mortality in trauma patients[14-16].

In the ICU, the use of SDD has been associated with a reduced mortality[6]. However, the administration of antibiotics may be associated with the emergence of multidrug resistant pathogens[8,17]. Thus, one can expect an increase in the number of cases of late-onset VAP due to difficult-to-treat bacteria, resulting in a rise of inappropriate empirical antimicrobial therapy when SDD is administered to our trauma patients. Our finding does not support this hypothesis since the rate of appropriateness is of about 90% in trauma patients receiving SDD who developed a late-onset VAP, without significant difference with our non-trauma patients not receiving SDD (88%). Hence, the present study adds arguments for the safety of SDD in clinical practice.

The distribution of pathogens is similar in patients receiving or not SDD who developed a late-onset VAP. We previously showed the weak impact of the use of SDD on our ecology[10]. In the present study, we confirm this finding by focusing on a defined clinical endpoint, *i.e.* the appropriateness of the empirical antimicrobial therapy directed against late-onset VAP. One may suggest that trauma patients have a lower risk for carrying difficult-to-treat bacteria than medical or surgical patients. Several studies have reappraised this statement. They report significant numbers of difficult-to-treat pathogens responsible for late-onset VAP in trauma patients[18-20]. Thus, SDD was not associated with an increased risk of inappropriateness of the empirical antimicrobial therapy in our trauma patients developing late-onset VAP.

Empirical antimicrobial therapy was de-escalated in about 40% of our patients. As described elsewhere, de-escalation is a part of an integrative strategy of dynamic management of antibiotic treatment for patients with VAP[4,21]. This strategy includes a rational use of empirical antibiotic therapy considering local patterns of susceptibility of pathogens, prior history of patients, and clinical status, followed by an early reassessment to focus on the bacteria responsible for VAP. In previous studies, de-escalation therapy was not associated with recurrent pneumonia or increased mortality in patients with VAP[22-24]. This strategy should be used whenever possible in patients with VAP[22-24]. Our findings show that SDD did not alter this practice in our trauma patients who developed late-onset VAP.

Our study has several limitations. First, because it was a single ICU study, these findings may not be applicable to other ICU. Second, we cannot exclude the role of unknown variables. One can note that the two groups of patients are dissimilar. However, in the trauma patients receiving

SDD, our study clearly shows that SDD is safe in terms of outcomes. Third, the value of regular surveillance cultures for guiding the empirical therapy was not evaluated in the present study. Indeed, the regular surveillance of cultures is critical to revise the protocol according to local ecology changes.

In conclusion, in our trauma patients receiving SDD, a high rate of late-onset VAP was noted. Despite this finding, the use of SDD appears to be safe. Indeed, SDD was not associated with an increased rate of inappropriate antimicrobial therapy in patients who developed late-onset VAP. Thus, in this population, SDD does not seem to interfere with the appropriateness of empirical antimicrobial therapy and the process of de-escalation.

Conflict of interest statement

We declare that we have no conflict of interest.

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