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Management of ventilator-associated pneumonia in a multidisciplinary intensive care unit: does trauma make a difference?

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Abstract *Objective:* Antibiotic exposure and timing of pneumonia onset influence ventilator-associated pneumonia (VAP) isolates. The first goal of this investigation was to evaluate whether trauma also influences prevalence of microorganisms. *Design:* A retrospective, single-center, observational cohort study. *Setting:* Multidisciplinary teaching ICU. *Patients:* Adult patients requiring mechanical ventilation identified as having VAP. *Interventions:* Retrospective evaluation of a prospective manual database. *Measurements and main results:* VAP isolates in a multidisciplinary ICU documented by quantitative respiratory cultures and recorded in a 42-month database were compared, based on the presence or absence of trauma. Causative microorganisms were classified in four groups, based on mechanical ventilation duration (> 5 days), and previous antibiotic exposure. One hundred eighty-three patients developed 196 episodes of VAP (98 trauma). Methicillin-sensitive *Staphylococcus aureus* (MSSA) was more frequent (34.5% vs. 11.5%, $p < 0.01$) in trauma, whereas methicillin-resistant *Staphylococcus aureus* (MRSA) was more frequent (2% vs. 11.5%, $p < 0.01$) in non-trauma. No significant differences were found between trauma and non-trauma patients regarding prevalence of other microorganisms. In trauma patients, MSSA episodes were equally distributed between early- and late-onset VAP (51% vs. 49%), but no MRSA episode occurred in the early-onset group. *Conclusions:* Trauma influences the microbiology of pneumonia and it should be considered in the initial antibiotic regimen choice. Our data demonstrate that patients with trauma had a higher prevalence of MSSA, but the overall prevalence was sufficiently high to warrant *S. aureus* coverage for both groups. On the other hand, since no MRSA was isolated during the first 10 days of mechanical ventilation on trauma patients, MRSA coverage in these patients becomes necessary only 10 days after admission.

Keywords Ventilator-associated pneumonia · Trauma · Antibiotics · Methicillin resistance · *Staphylococcus aureus*

Introduction

Ventilator-associated pneumonia (VAP) is the leading infection encountered in intensive care units (ICU) [1], prolonging hospital stay and contributing to mortality [2, 3]. Prompt initiation of appropriate therapy is a cornerstone in management, and even short delays in administering adequate antibiotic regimen are associated with worsened

outcomes [4, 5]. Therefore, current management strategies recommend an early start of broad-spectrum antibiotic regimen, followed by de-escalation [6, 7].

Several factors are associated with the presence of multiresistant pathogens in VAP, but duration of mechanical ventilation (or hospitalization, in patients not admitted from the emergency department) and prior antibiotic exposure appear to be the most important [8–10]. Indeed, MRSA and non-fermentative Gram-negative bacilli are usually considered in episodes with these factors. The descriptive findings from the Assessment of Local Antimicrobial Resistance Measures (ALARM) study [11] found that combination therapy with three antibiotics to cover these organisms in late-onset pneumonia is a usual initial choice. However, three antibiotics may not always be needed, and the contribution of other risk factors—such as the reason for mechanical ventilation—has not been sufficiently investigated. Prior reports suggested that trauma patients may have different causative organisms and outcomes.

The first goal of this study was to evaluate whether trauma influences the prevalence of microorganisms. Considering that trauma patients now account for a substantial portion of all admissions to our multidisciplinary ICU, we compared episodes of VAP in the presence or absence of trauma. Our hypothesis was that trauma patients have different prevalence of microorganisms in VAP, independently of antibiotic exposure and pneumonia onset, and that this information may help to guide the choice of initial antibiotic therapy.

Methods

Study population and design

A retrospective observational cohort study was conducted in a multidisciplinary (medical, surgical and trauma) ICU, at the Joan XXIII University Hospital, Tarragona. The prospectively recorded database for nosocomial infection surveillance from January 2003 to June 2006 was reviewed and all consecutive episodes of VAP with identified isolates were documented. All patients were managed following a standardized protocol if VAP was suspected. Management was guided by 'The Tarragona Strategy', described elsewhere [6, 12, 13]. Selective decontamination of digestive tract and antibiotic prophylaxis for pneumonia are not performed in this ICU. Fiberoptic bronchoscopic examination using a protected specimen brush (PSB) or bronchoalveolar lavage (BAL) was performed in all patients within 6 h of the onset of a new pulmonary infiltrate on weekdays from 8 a.m. to 5 p.m. Samples in episodes that developed after 5 p.m. or at the weekend were always collected using quantitative tracheal aspirates. The etiological diagnosis of VAP was upheld only when PSB yielded $\geq$ 1,000 colony-forming units (cfu)/ml, BAL $\geq$ 10,000 cfu/ml, or quantitative tracheal aspirate $\geq$ 100,000 cfu/ml of at least one microorganism. Episodes with microorganisms under these thresholds were excluded because of low specificity [14].

Isolates were classified in six groups: (1) Non-fermentative Gram-negative bacteria (including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*); (2) methicillin-resistant *Staphylococcus aureus* (MRSA); (3) Enterobacteriaceae (including *Escherichia coli, Klebsiella pneumoniae*, *Klebsiella oxytoca, Proteus vulgaris, Enterobacter aerogenes*, *Enterobacter cloacae, Morganella morgagni*, and *Serratia marcescens*); (4) methicillin-sensitive *Staphylococcus aureus* (MSSA); (5) *Streptococcus* species (including *S. pneumoniae*, *S. viridans*, and *S. pyogenes*); (6) *Haemophilus influenzae* and *Moraxella catarrhalis.*

The patient's underlying disease and its severity, presence of shock, acute respiratory distress syndrome (ARDS), coma on admission, chronic obstructive pulmonary disease (COPD), immunodepression status, diabetes mellitus and recent steroid use were recorded. Duration of mechanical ventilation prior to the development of VAP and recent antibiotic exposure status were also recorded for each episode.

Definitions

Trauma was defined as presence of injury to more than one body area or system or the presence of major cranial trauma alone. The non-trauma group included postoperative states and all medical conditions. *Pneumonia* was diagnosed when new, persistent pulmonary infiltrates, not otherwise explained appeared on chest X-rays plus the presence of local (purulent respiratory secretions) and systemic signs of inflammatory response (WBC count $> 10{,}000/mm^3$, rise in WBC count $> 20\%$ or fever). Patients with documented massive gastric aspiration were excluded. Pneumonia was considered *early-onset* when it occurred within 5 days (episodes within the first 48 h—very early-onset pneumonia—were included if related to intubation) and defined as *late-onset* if it started at least 5 days after admission, in accordance with the guidelines of the Centers for Disease Control [15]. Moreover, we decided to evaluate late-onset episodes with an additional breakpoint of 10 days, as suggested elsewhere [16]. *Fever* was defined as two or more consecutive measurements of temperature $> 38\,^{\circ}C$. *Underlying diseases* were aggregated as trauma or absence of trauma. *Severity of underlying disease* was evaluated with APACHE II score for each patient in the first 24 h after ICU admission. *Recent antibiotic therapy* was considered when a patient received antimicrobial agents for more than 48 h during the 15 days preceding the episode of VAP [17]. *COPD* was diagnosed using criteria consistent with those recommended by the American Thoracic

Society (ATS). *Coma* was diagnosed when the Glasgow Coma Scale (GCS) score was lower than 9 (both sedation and non-sedation) for more than 24 h [18]. *ARDS* was diagnosed according to the criteria of the American–European Consensus Conference Committee [19]. *Shock* was described as systolic blood pressure < 90 mmHg despite adequate fluid resuscitation and need for vasopressor agents. *Polytransfusion* was described as the need for > 10 units of packed red cell within 24 h. *Immunocompromise*, *recent steroid use* and *diabetes mellitus* have been defined elsewhere [20] as have our bacteriologic processing and identification methods [21].

Definition of the four groups of episodes

Four groups were created on the basis of days of mechanical ventilation (> 5 days) before pneumonia onset and recent antibiotic exposure. Group 1: early-onset episodes without recent antibiotic exposure; group 2: early-onset episodes with recent antibiotic exposure; group 3: late-onset episodes without recent antibiotic exposure; group 4: late-onset episodes with recent antibiotic exposure. Isolates were compared in each of these four groups based on presence or absence of trauma. Late-onset episodes were also evaluated with a breakpoint of 10 days.

Statistical analysis

Continuous variables were described as median values (interquartile ranges 25 to 75) and compared using Student's *t*-test (when not appropriate, the Mann–Whitney U-test was used). Categorical variables were compared with Pearson χ^2 and, if appropriate, Fisher's exact test. Multiple logistic regression was used to assess variables associated with trauma and non-trauma groups. The dependent variable was trauma. Variables which were significant in the univariate analysis were entered in the multivariate model, as were variables which have been previously reported in the literature. Differences between the groups were significant for variables yielding a *p*-value ≤ 0.05. SPSS software (version 11.0; Chicago, IL, USA) was used for all the calculations.

Results

One hundred ninety-six episodes of VAP were documented in 183 patients. Ninety-one patients were admitted for trauma (T) and 92 for non-trauma reasons (AT). Demographic characteristics of patients and outcomes are compared in Table 1. Although trauma patients were younger, disease severity was similar. ICU mortality was higher (34.8% vs. 15.4%, $p < 0.01$) in the AT group, but in survivors median length of stay was similar (13 vs. 11.5

Table 1 Demographic characteristics and outcomes in trauma (*T*) and absence of trauma (*AT*) patients

Variable	Overall			Group 1 (early onset, no prior antibiotic) ($n = 70$)			Group 2 (early onset, with prior antibiotic) ($n = 19$)		
	T ($n = 91$)	AT ($n = 92$)	*p*-value	T ($n = 38$)	AT ($n = 32$)	*p*-value	T ($n = 10$)	AT ($n = 9$)	*p*-value
Age (years)	36 (26–55)	62 (47–51)	< 0.01	35.5 (25.8–50.8)	57 (45–67.8)	0.01	34.5 (20.8–49.8)	50 (43–58)	0.05
Male gender	76 (83.5)	67 (72.8)	0.11	30 (78.9)	24 (75.0)	> 0.20	9 (90.0)	7 (77.8)	> 0.20
APACHE II score, on admission	16 (10–21)	18 (13–23)	0.11	15.5 (10–20)	17 (13.3–22.3)	0.17	16 (15–22.5)	12 (9.5–22)	> 0.20
Mortality	14 (15.4)	32 (34.8)	< 0.01	5 (13.2)	11 (34.4)	0.05	0	3 (33.3)	0.09
Length of ICU stay after diagnosis¶(days)	11.5 (4.8–15.8)	13 (4.3–35)	> 0.20	26.4	29.3	> 0.20	7	> 0.20	
Episode per patient	1.08	1.07	> 0.20	1	1	> 0.20	1	1	> 0.20

Variable	Group 3 (late onset, no prior antibiotic) ($n = 55$)			Group 4 (late onset, with prior antibiotic) ($n = 39$)		
	T ($n = 28$)	AT ($n = 27$)	*p*-value	T ($n = 15$)	AT ($n = 24$)	*p*-value
Age (years)	39 (29.3–62.8)	68 (53–74)	< 0.01	40.5 (26.3–58.5)	64 (41–76)	< 0.01
Male gender	24 (85.7)	22 (81.5)	> 0.20	13 (86.7)	14 (58.3)	0.08
APACHE II score, on admission	13 (9–16.8)	18 (13–24)	< 0.01	21 (15–25)	18 (15–23)	> 0.20
Mortality	6 (21.4)	8 (29.6)	> 0.20	3 (20.0)	10 (41.7)	> 0.20
Length of ICU stay after diagnosis¶(days)	20.4	21.7	> 0.20	17.6	10	0.01
Episode per patient	1	1.04	> 0.20	1,47	1.21	0.18

Values given as number of patients in that group (%), age, APACHE II score, length of stay are given as median (IQR 25–75); *APACHE II*, Acute Physiology and Chronic Health Evaluation II score; Thirteen patients developed two episodes [1 in group 3 (*AT*), 12 in group 4 (7 *T*, 5 *AT*)]; ¶For survived patients

Table 2 Differences in some characteristics between trauma (*T*) and absence of trauma (*AT*) patients

Variable	Group T ($n=91$)	Group AT ($n=92$)	*p*-value (univariate analysis)	OR (95 % CI) (multivariate analysis)
Age, years	36 (26–55)	62 (47–71)	< 0.01	0.95 (0.93–0.97)
APACHE II score, on admission	16 (10–21)	18 (13–23)	0.11	
Vasopressors, on admission	7 (7.7)	19 (20.7)	0.02	0.32 (0.11–0.95)
Coma, on admission	72 (79.1)	38 (41.3)	< 0.01	2.85 (1.32–6.19)
Immunocompromise	1 (1.1)	6 (6.5)	0.12	
Diabetes mellitus	1 (1.1)	7 (7.6)	0.03	
COPD	1 (1.1)	14 (15.2)	< 0.01	0.10 (0.01–1.01)
Abdominal surgery	2 (2.2)	14 (15.2)	< 0.01	
ARDS	22 (24.1)	21 (22.8)	> 0.20	
Multiple Transfusion	4 (4.4)	4 (4.3)	> 0.20	
Cirrhosis	3 (3.3)	6 (6.5)	> 0.20	
Chronic dialysis	0	1 (1.1)	> 0.20	
Transfer from nursing home	0	0	> 0.20	
Recent steroid use	0	5 (5.4)	0.02	

Values given as number of isolates in that group (%); age and APACHE II score are given as median (IQR 25–75); *APACHE II*, Acute Physiology and Chronic Health Evaluation II score; *COPD*, chronic obstructive pulmonary disease; *ARDS*, acute respiratory distress syndrome

days). Significant differences between these cohorts are detailed in Table 2. In addition, no significant differences were associated with polytransfusion, ARDS, or prior antibiotic exposure. The independent variables included in the model were: APACHE II score on admission, age, coma, COPD, steroid use, immunosuppression, diabetes mellitus, ARDS, cirrhosis, vasopressor use, multiple transfusion, previous antibiotic exposure and surgery. The multivariate analysis revealed that coma was associated with the trauma group (OR 5.4, 95% CI 2.8–10.4), while vasopressor use (OR 3.1, 95% CI 1.2–7.8), age > 40 years (OR 10.4, 95% CI 4.7–23.2) and COPD (OR 16.1, 95% CI 2.1–125.6) were associated with the non-trauma group. Indications for mechanical ventilation in non-trauma patients are shown in Table 3.

In both groups there were 98 episodes of VAP, with 1.08 vs. 1.07 episodes per patient in the T and AT groups respectively. Thirty-two episodes in the T group (32.7%) and 38 (38.8%) in the AT group occurred in patients with recent antibiotic exposure ($p > 0.20$), whereas 50 (51.0%) in the T group and 57 (58.2%) in the AT group were late-onset VAP ($p > 0.20$). Eighty-four polymicrobial episodes were recorded, more frequently in trauma than in non-trauma patients. Overall, 278 microorganisms were isolated: 148 in the T group and 130 in the AT group. MSSA was the most frequent pathogen with 66 (23.7%) isolates, followed by Enterobacteriaceae with 59 (21.2%), *H. influenzae* 50 (18.0%), non-fermentative Gram-negative bacilli 48 (17.3%), *Streptococcus* species 37 (13.3%) and MRSA 18 (6.5%). The distribution of pathogens is detailed in Table 4.

In patients with trauma and early-onset infection, MSSA was the most frequently isolated pathogen. MSSA distribution in trauma and non-trauma patients at different periods of mechanical ventilation is shown on Fig. 1. Pathogens occurring more frequently in late-onset pneumonia included MSSA and non-fermentative Gram-negative bacilli. The non-fermentative Gram-negative bacilli were significantly more frequent in late-onset than in early-onset episodes. No difference in prevalence between early- and late-onset episodes was found

Table 3 Indications for mechanical ventilation in 92 patients with absence of trauma

Variable	Number of patients (%)
Abdominal surgery	14 (15.2)
Otorhinolaryngologic surgery	6 (6.5)
Neurologic emergencies	33 (35.9)
Intracranial hemorrhage	24
Guillain–Barré syndrome	3
Coma	3
Convulsion	2
Meningitis	1
Respiratory emergencies	18 (19.6)
COPD exacerbation	2
Severe CAP	5
Severe asthma attack	1
Respiratory insufficiency	10
Cardiac emergencies	6 (6.5)
Heart failure decompensation	4
Tamponade	1
Acute myocardial infarction	2
Sepsis/septic shock	7 (7.6)
Intoxication	2 (2.2)
Others	6 (6.5)
Hemorrhagic shock due to gastrointestinal bleeding	3
Near-drowning	1
Goodpasture syndrome	1
Malign neuroleptic syndrome	1

COPD, Chronic obstructive pulmonary disease;*CAP*, community-acquired pneumonia

Table 4 Isolates in episodes of trauma (*T*) and non-trauma (*AT*) admissions*

Variable	Overall			Group 1 (early onset, no prior antibiotic)			Group 2 (early onset, with prior antibiotic)		
	T ($n=148$)	AT ($n=130$)	*p*-value	T ($n=59$)	AT ($n=47$)	*p*-value	T ($n=12$)	AT ($n=11$)	*p*-value
Multiresistant bacteria									
Non-fermentative Gram-negative bacilli	21 (14.2)	27 (20.8)	0.16	4 (6.8)	3 (6.4)	> 0.20	1 (8.3)	2 (18.2)	> 0.20
P. aeruginosa	14	24		3	3		1	2	
A. baumannii	7	3		1	0		0	0	
MRSA	3 (2.0)	15 (11.5)	< 0.01	0	0		0	3 (27.3)	0.09
Non-multiresistant bacteria									
Enterobacteriaceae¶	28 (18.8)	31 (23.9)	> 0.20	10 (16.9)	5 (10.6)	> 0.20	4 (33.3)	4 (36.4)	> 0.20
MSSA	51 (34.5)	15 (11.5)	< 0.01	22 (37.3)	9 (19.1)	0.05	4 (33.3)	1 (9.1)	> 0.20
Streptococcus species¶¶	19 (12.9)	18 (13.8)	> 0.20	11 (18.7)	16 (34.0)	0.11	1 (8.3)	0	> 0.20
Haemophilus influenzae¶¶¶	26 (17.6)	24 (18.5)	> 0.20	12 (20.3)	14 (29.8)	> 0.20	2 (16.7)	1 (9.1)	> 0.20
Isolates (number per episode)	1.51	1.33	< 0.01	1.55	1.47	> 0.20	1.20	1.22	> 0.20

Variable	Group 3 (late onset, no prior antibiotic)			Group 4 (late onset, with prior antibiotic)		
	T ($n=48$)	AT ($n=40$)	*p*-value	T ($n=29$)	AT ($n=32$)	*p*-value
Multiresistant bacteria						
Non-fermentative Gram-negative bacilli	7 (14.6)	9 (22.5)	> 0.20	9 (31.0)	13 (40.6)	> 0.20
P. aeruginosa	5	8		5	11	
A. baumannii	2	1		4	2	
MRSA	0	6 (15)	< 0.01	3 (10.3)	6 (18.8)	> 0.20
Non-multiresistant bacteria						
Enterobacteriaceae¶	8 (16.7)	10 (25)	> 0.20	6 (20.7)	12 (37.5)	0.17
MSSA	16 (33.3)	4 (10)	0.01	9 (31)	1 (3.1)	< 0.01
Streptococcus species¶¶	7 (14.9)	2 (4.8)	0.17	0	0	
Haemophilus influenzae¶¶¶	10 (20.8)	9 (22.5)	> 0.20	2 (6.9)	0	> 0.20
Isolates (number per episode)	1.71	1.43	0.06	1.32	1.10	0.05

Values given as number of isolates (%); *MSSA*, Methicillin-sensitive *Staphylococcus aureus*; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *Patients may be infected by multiple pathogens; ¶Includes *E. coli, Klebsiella* species, *Proteus vulgaris, Enterobacter* species, *Morganella morgagni*, *Serratia marcescens* ¶¶Includes *S. pneumoniae*, *S. pyogenes*, *S. viridans*; ¶¶¶Includes *Haemophilus influenzae* and *Moraxella catarrhalis*

for Enterobacteriaceae, *Haemophilus* or *Streptococcus* species.

In patients without trauma, *Streptococcus* species were the most frequent pathogen and significantly associated with early-onset infection. *Haemophilus influenzae* and MSSA tended to occur more frequently in early-onset episodes. Pathogens occurring more frequently in late-onset pneumonia were non-fermentative Gram-negative bacilli and Enterobacteriaceae.

In group 1 (early onset, no antibiotic) MSSA was significantly more frequent in trauma than in non-trauma patients (37.3% vs. 19.1%, $p < 0.05$). In these two subgroups, non-fermentative Gram-negative bacilli were rare. Among the four subgroups with early-onset pneumonia, MRSA was isolated (27.3%) only in non-trauma group 2 patients (early onset with antibiotic exposure). Although not statistically significant, an association was found between MRSA presence and non-trauma (OR = 5.2, 95% CI 0.8–41.8). In fact, all MRSA isolates were in non-trauma subgroups, except for a 10.3% prevalence in trauma group 4 (late onset with recent antibiotic exposure). Prevalence of other isolates was similar in the different subgroups. No MRSA isolates were documented in trauma patients within the first 10 days of ventilation.

The distribution of MRSA and MSSA prevalence in VAP episodes differed depending on the presence of trauma, recent antibiotic exposure, and time of pneumonia onset. MSSA was the most frequent isolate in all trauma subgroups. MSSA was associated with trauma (52.0% vs. 15.3%, $p < 0.01$), early onset (40.4% vs. 28.0%, $p = 0.07$) and absence of recent antibiotic exposure (40.5% vs. 21.4%, $p < 0.01$) whereas MRSA was associated with absence of trauma (15.3% vs. 3.1%, $p < 0.01$), late onset (14.0% vs. 3.4%, $p = 0.01$) and recent antibiotic exposure (17.1% vs. 4.8%, $p < 0.01$).

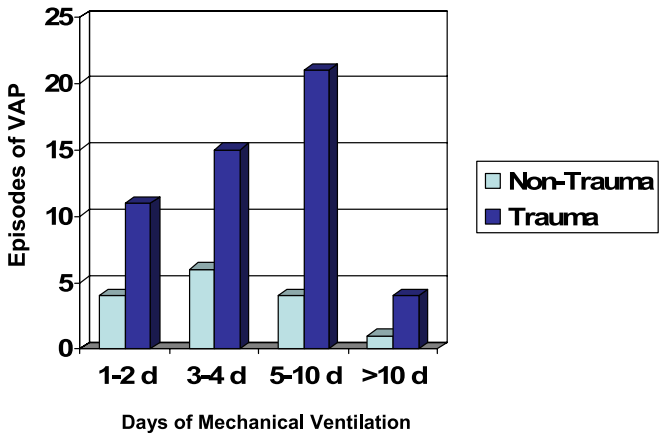

Fig. 1 Distribution of MSSA in *trauma* and *non-trauma* patients in different periods of mechanical ventilation

Discussion

This study demonstrates that trauma is a major determinant of the prevalence of microorganisms, epidemiology and outcomes in VAP. This suggest that the underlying disease should be considered in the initial decision on antibiotic choice in VAP. A unique feature of this study is that it analyzed pathogens in VAP comparing trauma with non-trauma in a multidisciplinary unit. MSSA was a major pathogen in VAP, with a notably higher occurrence in trauma patients, even in the presence of predisposing factors for multiresistant bacteria, whereas MRSA was found only rarely. Moreover, no episodes of early-onset VAP were caused by MRSA.

Our data demonstrated that different subsets of trauma and non-trauma patients were more likely to be infected by MSSA. However, the overall incidence of these pathogens was sufficiently high to warrant the use of empiric therapy likely to be active against these pathogens. Therefore, our data support the use of the currently recommended empiric therapy [7] for both trauma and non-trauma VAP.

Several studies have demonstrated an association between inadequate antibiotic therapy and mortality [4, 5]. Indeed, prompt initiation effective antibiotic regimen is the cornerstone of management and the role for combination therapy is to increase the likelihood that potential multiresistant pathogens will be adequately treated. Current guidelines [7] suggest that initial therapy for late onset pneumonia will usually require three antibiotics: two drugs of different classes active against non-fermentative Gram-negative bacilli, and a third for MRSA. In our institution, we found no MRSA in VAP episodes during the first 10 days in trauma patients, even in those episodes with recent antibiotic exposure. The addition of an antibiotic active against MRSA was unnecessary, and therapy without vancomycin or linezolid would have been adequate.

In trauma patients, most reports regarding microorganisms indicate that *H. influenzae* and MSSA are the most prevalent [22, 23]. These studies also report MSSA as a frequent isolate in late-onset episodes. In the current study, trauma patients were younger and 79.1% had coma; this condition significantly increased the risk of VAP due to MSSA. Other studies reported that comatose patients were more susceptible to early-onset pneumonia, particularly due to MSSA [24–28]. On the other hand, MRSA VAP has been associated with previous antibiotic exposure, COPD [29], or older age [30]. Our findings were consistent with these observations.

In our cohort, MSSA was the most frequent pathogen in trauma patients, but this did not involve a difference in therapy. The association between MSSA and trauma was described by Rello et al. [25] in 1992. Head trauma and coma are associated with MSSA VAP episodes. Nasal carriage and tracheal colonization of *S. aureus* on admission and within 24 h of intubation are known risk factors for early-onset pneumonia [31, 32]. Several studies have con-

firmed this finding, and in these patients antibiotic coverage for MSSA is mandatory [33, 34].

Pseudomonas aeruginosa and *Acinetobacter baumannii* were isolated in episodes with risk factors (late onset and prior antibiotics), whereas Enterobacteriaceae were isolated in all subsets. As expected, late-onset episodes have different rates of pathogens in T and AT groups, but this difference does not affect empirical antibiotic therapy because the same pathogens should be covered.

Some limitations should be noted in this study. First, this was a retrospective observational analysis. However, the data were collected prospectively by specialists trained in nosocomial infection surveillance. Second, the distribution of other potentially important predisposing factors, such as COPD, recent steroid use, coma, age, diabetes, surgery and vasopressor use, differed between trauma and non-trauma patients, and this may be partly responsible for the differences found between the two groups. Third, the influence of specific classes of prior antibiotics administered and particular resistance phenotypes was not analyzed. Information on exposure to specific antibiotic classes would also help the choice of specific empiric therapy, by avoiding the repetition of the same antimicrobial [35, 36]. Fourth, some reports regarding trauma patients suggest that some non-fermentative Gram-negative bacilli, such as *Acinetobacter baumannii*, may be more frequent in late-onset episodes [22, 37, 38]. We recognize that the relatively small size of this cohort may not have sufficient statistical power to identify differences regarding certain isolates with low prevalence, particularly in groups 2 and 4, or to perform a multi-variate analysis identifying potential confusion biases in the association between trauma and MSSA. Further studies in larger cohorts should clarify whether the documented association was due to trauma by itself or associated with the different comorbidities founded. Fifth, the study is from a single center and therefore institution-specific variables may have influenced the findings. Our results may not be generalizable to settings with a high MRSA prevalence. We used the duration of mechanical ventilation as a clinical parameter to categorize timing of pneumonia, because most of our patients (88% of trauma and 78% of non-trauma patients, $p = 0.1$) are admitted directly from the emergency department. We were unable to analyze our patients with VAP according to duration of hospitalization, as the ATS guidelines suggest [7]. We were also unable to analyze antibiotic treatment and prior hospitalization in the previous 3 months. The high number of patients admitted directly from the emergency department may reduce the potential impact of this limitation. Finally, some epidemics/outbreaks of colonization pressure by exogenous organisms (*S. maltophilia*, MRSA, etc.) and antibiotic exposure vary from institution to institution and this may limit the generalizability of our findings to other settings [39, 40]. We are aware that the specificity of BAL/PSB specimens is higher than that of quantitative tracheal aspirates, and specificity could be improved if only bronchoscopic studies were performed. However, recent studies [41, 42] did not find better results for mortality or de-escalation rates in patients with bronchoscopic studies.

In summary, the findings of this study indicate that trauma influences prevalence of pathogens in VAP. The differences in the microbiologic findings in early-onset VAP episodes between trauma and non-trauma patients—that is, the absence of MRSA in our trauma group—has clear implications for therapy. Restriction of glycopeptides or linezolid in empiric therapy to only those trauma patients with late-onset pneumonia and prior antibiotic exposure would mean avoiding the use of these antibiotics in 80% of episodes of VAP in trauma patients. In addition to reducing antibiotic-associated costs, this may help to reduce selection pressures for the emergence of antimicrobial resistance in the hospital.

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