


# *Staphylococcus aureus* carriage at admission predicts early-onset pneumonia after burn trauma

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**Abstract** Early-onset pneumonia (EOP) is frequent after burn trauma, increasing morbidity in the critical resuscitation phase, which may preclude early aggressive management of burn wounds. Currently, however, preemptive treatment is not recommended. The aim of this study was to identify predictive factors for EOP that may justify early empirical antibiotic treatment. Data for all burn patients requiring  $\geq 4$  h mechanical ventilation (MV) who were admitted between January 2001 and October 2012 were extracted from the hospital's computerized information system. We reviewed EOP episodes ( $\leq 7$  days) among patients who underwent endotracheal aspiration (ETA) within

5 days after admission. Univariate and multivariate analyses were performed to identify independent factors associated with EOP. Logistic regression was used to identify factors predicting EOP development. During the study period, 396 burn patients were admitted. ETA was performed within 5 days in 204/290 patients receiving  $\geq 4$  h MV. One hundred and eight patients developed EOP; 47 cases were caused by *Staphylococcus aureus*, 37 by *Haemophilus influenzae*, and 23 by *Streptococcus pneumoniae*. Among the 33 patients showing *S. aureus* positivity on ETA samples, 16 (48.5 %) developed *S. aureus* EOP. Among the 156 *S. aureus* non-carriers, 16 (10.2 %) developed EOP. *Staphylococcus aureus* carriage independently predicted EOP ( $p < 0.0001$ ). We identified *S. aureus* carriage as an independent and strong predictor of EOP. As rapid point-of-care testing for *S. aureus* is readily available, we recommend testing of all patients at admission for burn trauma and the consideration of early preemptive treatment in all positive patients. Further studies are needed to evaluate this new strategy.

**Highlights** • *Staphylococcus aureus* carriage at admission was identified as an independent and strong predictor of EOP

- Rapid point-of-care testing for *S. aureus* is readily available
- All burn patients should be tested at admission, and early preemptive treatment should be considered in all positive patients

The contributions of Philippe Eggimann and Yok Ai Que are equivalent.

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## Abbreviations

ABA	American Burn Association
ARDS	Acute respiratory distress syndrome
AUC	Area under the curve
BICU	Burn intensive care unit
EOP	Early-onset pneumonia
ETA	Endotracheal aspiration
ICU	Intensive care unit
IQR	Interquartile range
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MV	Mechanical ventilation
SAPS II	Simplified Acute Physiology Score
TBSA	Total body surface area
VAP	Ventilator-associated pneumonia

## Introduction

Although advances in hemodynamic and respiratory support have reduced the rate of early death from burn trauma, sepsis remains the predominant cause of morbidity and mortality in burn units. Among the most common and devastating infections in burn patients, respiratory tract infections (including ventilator-associated pneumonia, VAP) are predominant [1–4].

Burn patients' vulnerability to pneumonia is multifactorial. Inhalation injury damages the mucosa of the upper and lower airways, impairs mucociliary clearance, activates neutrophils, releases oxygen free radicals, increases microvascular permeability, and reduces the quantity of surfactant [5]. The reported incidence of nosocomial pneumonia among critically ill patients is up to 48% [6, 7], and mechanical ventilation (MV) is the single greatest risk factor for pneumonia after burn trauma [4, 8].

Pneumonia after a burn injury drastically increases morbidity and mortality [4, 9]. According to Shirani et al. [4], the age- and burn size-specific mortality of patients with severe burn injuries increases by 20% when inhalation injury is present at admission, by 40% when pneumonia develops, and by 60% when both of these conditions are diagnosed. Pneumonia increases not only mortality among burn patients, but also the length of hospital stay and associated costs [9]. Moreover, early-onset pneumonia (EOP) may delay surgical debridement and early grafting, and antibiotic exposure may rapidly result in selection for resistant flora responsible for further nosocomial infection, which is particularly difficult to avoid in these patients with lengthy hospital stays. *Staphylococcus aureus* is among the leading endogenous microorganisms responsible for EOP and for which rapid detection and focused preemptive treatment are available. In this context, we aimed to analyze the epidemiology, characteristics, and risk factors associated with *S. aureus* EOP to identify predictive factors that could be used to target it with early preemptive treatment, such as that using focused antibiotics or specific monoclonal antibodies.

## Materials and methods

### Study population and setting

This retrospective analysis examined the occurrence of EOP in a prospective cohort of burn patients hospitalized at the five-bed reference Lausanne burn intensive care unit (BICU) between January 2001 and October 2012. All included patients required  $\geq 4$  h MV and underwent endotracheal aspiration (ETA) via endotracheal tube according to our local written standard operating procedures. The BICU is part of a tertiary care hospital and 32-bed medico-surgical adult intensive care unit (ICU) [10, 11]. The Institutional Review Board of the Centre Hospitalier Universitaire Vaudois approved this study.

### Baseline data collection

Demographic data collected prospectively were patient age, sex, and the following specific burn characteristics: total body surface area (TBSA) affected, presence of burn inhalation injury, Ryan score, and Simplified Acute Physiology Score (SAPS II) [12, 13]. Data on all patients included in the retrospective analysis were extracted from computerized patient records (MetaVision®; iMDsoft, Tel Aviv, Israel).

### Staging of inhalation injury

Inhalation injury was first documented based on classical physical findings as singed facial hair, carbonaceous deposits (oropharynx or sputum), facial burns, and changes in voice/phonation. The diagnosis of inhalation injury was then standardized since 2006 in our institution using a systematic ear–nose–throat (ENT) examination and bronchoscopy within the first 24 hours in all intubated patients [14]. Of note, this inhalation score integrates separate scoring of the upper and lower airways.

### Characterization of pneumonia episodes

Two experts from the BICU reviewed episodes of respiratory tract infection and scored them according to predefined criteria [11]. Briefly, infection severity (sepsis, severe sepsis, septic shock) was diagnosed according to the proposed criteria of the 2001 Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians/American Thoracic Society/Surgical Infection Society (SCCM/ESICM/ACCP/ATS/SIS) International Sepsis Definitions Conference [15] and adapted for burn patients according to the 2007 American Burn Association (ABA) criteria [16]. Pneumonia was defined according to criteria published by Garner et al. [17] and Calandra et al. [18]. We defined EOP as an episode of pneumonia occurring within 7 days after BICU admission. Upper respiratory tract *S. aureus* carriage was defined as *S. aureus* culture positivity for ETA samples obtained within 5 days after admission and before EOP diagnosis.

### Statistical analysis

Continuous variables are reported as medians and interquartile ranges (IQRs; 25th–75th percentile), and categorical variables are reported as frequencies and percentages. Group differences were tested using the Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. Associations between the development of *S. aureus* EOP and age, TBSA affected, SAPS II, presence of inhalation lesions, and *S. aureus* positivity of ETA samples were assessed using a logistic regression model. The predictive performance of the model was measured using the area under the receiver operating characteristic curve (AUC). Two-sided *p*-values  $< 0.05$

were considered to be statistically significant. All statistical analyses were performed using R software (version 3.3.1) [19].

## Results

### Patient characteristics

Between January 2001 and October 2012, 396 burn patients were admitted to the Lausanne BICU. Among the 290 (73.2 %) patients who received  $\geq 4$  h MV, ETA was performed within 5 days in 204 (51.5 %) patients (Fig. 1). Table 1 describes the characteristics of the study population. Patients had a median age of 40.0 (IQR, 28.0–54.0) years and a median TBSA affected of 22.0% (IQR, 13.0–40.0%). More men (67.0%) than women were included in the study, and most (64.0%) patients had inhalation injuries.

### Characteristics of EOP and *S. aureus* EOP

Of the 108 patients who developed EOP, ETA was performed before EOP diagnosis in 93 patients and on the day of diagnosis in 15 patients (Fig. 1). In total, 176 microorganisms were identified. The three most prevalent microorganisms isolated were *S. aureus* ( $n = 47$ , 26.7%), *Haemophilus influenzae* ( $n = 37$ , 21.0%), and *Streptococcus pneumoniae* ( $n = 23$ , 13.1%; Fig. 2). All but one ( $n = 46$ , 97.9%) case of *S. aureus* EOP were caused by methicillin-sensitive *S. aureus*.

Only 16.2% (33/204) of patients in whom ETA was performed within 5 days after admission showed *S. aureus* positivity. However, almost half ( $n = 16$ , 48.5%) of these patients

developed EOP, and all of these cases were caused by *S. aureus*. In contrast, the proportion of *S. aureus* EOP cases among the 77/156 (49.4%) *S. aureus* non-carriers who developed EOP was small ( $n = 16$ , 20.8%; Fig. 1). The association between *S. aureus* positivity of ETA samples and *S. aureus* EOP development was highly significant ( $p < 0.0001$ ).

Patients with *S. aureus* EOP were younger than those with non-*S. aureus* EOP (31 [IQR, 23–50] vs. 42 [IQR, 30–58] years,  $p = 0.046$ ; Table 1). They tended to be more severely burned (29% [IQR, 15–40%] vs. 25% [16–46%] TBSA) and less likely to have inhalation lesions (59% vs. 67%) compared to patients with non-*S. aureus* EOP, but these differences were not significant ( $p = 0.65$  and  $p = 0.50$ , respectively).

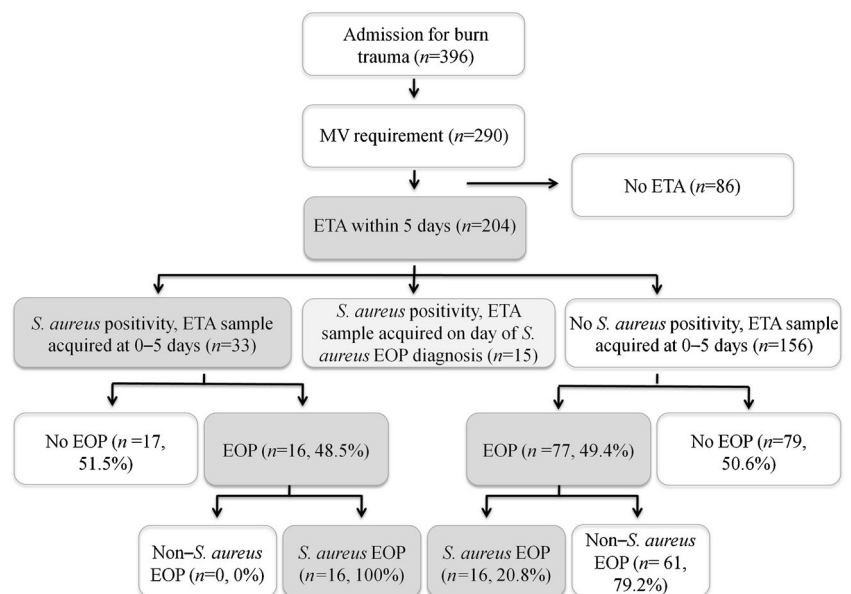
### Risk factors for *S. aureus* EOP development

Multivariate analysis showed that *S. aureus* carriage was the only factor that independently predicted *S. aureus* EOP (odds ratio = 7.64, 95 % confidence interval [3.23–18.45],  $p < 0.0001$ ). In the logistic regression model, the AUC for *S. aureus* presence + age + TBSA affected + inhalation syndrome + SAPS II was 0.758. The AUC for the presence of *S. aureus* alone was 0.696. The use of *S. aureus* carriage as a unique criterion for the initiation of early empirical treatment would result in 17 unnecessary antibiotic treatments (17/[17 + 16], 51.5%; Fig. 1).

## Discussion

This study describes the epidemiology and characteristics of EOP in a population of burn patients admitted over an 11-year period. The characteristics of our burn population are

**Fig. 1** Study flow chart. MV mechanical ventilation; ETA endotracheal intubation; EOP early-onset pneumonia



**Table 1** Characteristics of burn patients requiring >4 h MV and undergoing ETA

Characteristics	All patients	Patients without EOP	Patients with EOP	Patients with <i>S. aureus</i> EOP	Patients with non- <i>S. aureus</i> EOP
Number of patients	204	96	93	32	61
Age (years), median (IQR)	40 (28–54)	43 (28–55)	39 (28–53)	31 (23–50)	42 (30–58)
Male, <i>n</i> (%)	137 (67%)	64 (67%)	61 (68%)	22 (69%)	39 (64%)
TBSA affected (%), median (IQR)	22 (13–40)	16 (10–33)	25 (16–43)	29 (15–40)	25 (16–46)
Inhalation lesions, <i>n</i> (%)	130 (64%)	61 (64%)	60 (65%)	19 (59%)	41 (67%)
Ryan score, median (IQR)	1 (1–1)	1 (1–1)	1 (1–2)	1 (1–1)	1 (1–2)
SAPS II, median (IQR)	31 (24–39)	29 (21–36)	33 (26–40)	29 (24–38)	35 (27–41)
ETA <i>S. aureus</i> positivity, <i>n</i> (%)	33 (17%)	17 (18%)	16 (17%)	16 (50%)	0 (0%)
Mortality in the BICU, <i>n</i> (%)	21 (10%)	13 (14%)	7 (8%)	2 (6%)	5 (8%)

MV mechanical ventilation; ETA endotracheal aspiration; IQR interquartile range; TBSA total body surface area; SAPS II Simplified Acute Physiology Score; BICU burn intensive care unit

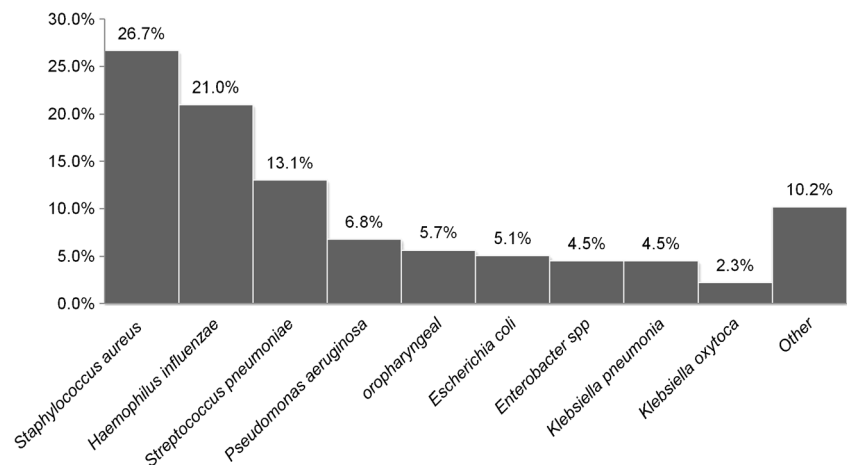
comparable to those reported previously. We found the same associations with age, inhalation injury, burn severity (defined by %TBSA), and mortality as first described by Ryan et al. [12] and subsequently confirmed by others [20–23].

EOP occurs frequently after burn trauma. In our study population, it affected 37.2% of burn patients who required MV, and 43.5% of episodes were caused by *S. aureus*. These results are not surprising, as approximately 20% of the healthy population are permanent *S. aureus* carriers, 30% are intermittent carriers, and 50% are non-carriers [24]. After burn injury (and probably enhanced by intubation and MV), *S. aureus* may be inoculated from the upper airways, where it usually resides, to the lower airways. There, favorable conditions may lead it to grow and to cause pneumonia.

In our burn population, EOP was not associated with increased attributable mortality; in contrast, pneumonia, particularly VAP, is a recognized risk factor for mortality in ICU burn patients [25, 26]. This difference may be due to early aggressive treatment of pneumonia and an overall low mortality rate in our cohort. In addition, the attributable mortality of VAP (10 %) may be due largely to late onset. The major

pathogens recognized in our patients were *S. aureus*, *H. influenzae*, and *S. pneumoniae* (together comprising 60.8% of pathogens), and not more virulent nosocomial pathogens, such as *Pseudomonas aeruginosa* (6.8% of all pathogens). The small proportions of *P. aeruginosa*, *Escherichia coli*, *Klebsiella* sp., and *Acinetobacter*, as well as methicillin-resistant *S. aureus* (MRSA; *n* = 1) can be explained by the fact that these aerobic Gram-negative bacilli are most commonly responsible for late-onset VAP [27]. Other researchers have made similar observations in Belgium and the USA [27–29], and reported mortality rates are highest for pneumonia caused by nosocomial pathogens, such as *P. aeruginosa*.

According to the ABA guidelines [27], VAP is common in burn patients who require MV, and inhalation injury is a unique risk factor for VAP in this patient population. Inhalation injury greatly increases the incidence of respiratory failure and acute respiratory distress syndrome (ARDS). It is also the cause of most early deaths among burn victims [30]. Interestingly, the only independent predictor of *S. aureus* EOP was *S. aureus* carriage at admission in our cohort.

**Fig. 2** Microorganisms causing early-onset pneumonia

Other authors have found a positive correlation between culture positivity and the occurrence of VAP. Among patients who were endotracheally intubated for >72 h, Matsushima et al. [31] found that early treatment of respiratory infection with appropriate antibiotics according to Gram staining findings contributed to the prevention not only of VAP, but also of ARDS. Carter et al. [32] confirmed this finding in burn patients. In their retrospective review, they found that MRSA surveillance culture positivity predicted the occurrence of MRSA VAP. They also showed that all patients who developed multidrug-resistant VAP did so after 7 days of MV.

Preemptive therapy is based upon screening with a sensitive assay in the attempt to detect early infection and avoid progression to invasive disease. Actual recommendations for VAP among burn patients, however, focus on prophylactic antibiotic use, not on preemptive therapy [27]. They specify that “although prophylactic antibiotics reduce early-onset VAP, routine prophylactic use of antibiotics should be discouraged in hospital settings where there are high levels of antibiotic resistance (recommendation grade: A)” [27].

However, rapid point-of-care testing exists for *S. aureus* detection. It is readily available, easy to use, and inexpensive. The use of this strategy for MRSA detection in intensive care settings is well documented [33, 34], and it has been practiced in our hospital since 2012. As such testing also exists for some other microorganisms, our approach could be expanded to detect these microorganisms and further evaluate their implication in the occurrence of pneumonia.

Our study has several strengths. First, it consisted of the review and analysis of EOP episodes in a cohort of almost 300 burn patients over an 11-year period. Second, two experts reviewed and recoded all pneumonia episodes based on available clinical data and microbiology reports. However, this study also has some limitations. It was retrospective and monocentric. In addition, the population may not be representative of the majority of populations affected by burn trauma, which are located mainly in developing countries. Indeed, risk factors for burn trauma are associated strongly with socioeconomic status, environmental factors, and race and ethnicity, as well as region of residence and patient comorbidities [29]. We focused on *S. aureus* EOP, which was the most common cause of EOP; we did not have sufficient data to explore EOP caused by other microorganisms. Finally, clinical practices in our BICU have changed over the years, which may have affected outcome profiles.

In this study, we identified *S. aureus* carriage as an independent and strong predictor of EOP; it was the only significant predictor in our burn population. As rapid point-of-care testing for *S. aureus* is readily available, we recommend testing of all patients at the time of admission for burn trauma, and the consideration of early preemptive treatment in all positive patients. Further studies are needed to evaluate whether this

new strategy improves outcomes and/or decreases MV duration and length of hospital stay.

**Authors' contributions** PE, YAQ, PV, and FS designed the study. MK, C-LB, CF, OP, and AF collected the data. AF, PE, YAQ J-LP, and J-PR analyzed the data. AF, PE, YAQ, and PV wrote the manuscript. All authors contributed to and approved the final version of the manuscript.

#### Compliance with ethical standards

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**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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