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Early Onset Pneumonia

Risk Factors and Consequences in Head Trauma Patients

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Background: **Early onset pneumonia occurs frequently in head trauma patients, but the potential consequences and the risk factors of this event have been poorly studied.**

Methods: **This prospective observational study was undertaken in the surgical intensive care unit of a university teaching hospital in Clichy, France. Head trauma patients requiring tracheal intubation for neurologic reasons and ventilation for at least 2 days were studied to assess the risk factors and the consequences of early onset pneumonia.**

Results: **During a 2-yr period, 109 head trauma patients were studied. The authors found an incidence of early onset pneumonia of 41.3%. *Staphylococcus aureus* was the most common bacteria involved in early onset pneumonia. Patients with early onset pneumonia had a lower worst arterial oxygen tension: fraction of inspired oxygen ratio, more fever, more arterial hypotension, and more intracranial hypertension, factors known to worsen the neurologic prognosis of head trauma patients. Nasal carriage of *S. aureus* on admission (odds ratio, 5.1; 95% confidence interval, 1.9–14.0), aspiration before intubation (odds ratio, 5.5; 95% confidence interval, 1.9–16.4) and barbiturate use (odds ratio, 3.9; 95% confidence interval, 1.2–12.8) were found to be independent risk factors of early onset pneumonia.**

Conclusions: **The results suggest that early onset pneumonia leads to secondary injuries in head-injured patients. Nasal carriage of *S. aureus*, aspiration before intubation, and use of barbiturates are specific independent risk factors for early onset pneumonia and must be assessed to find and evaluate strategies to prevent early onset pneumonia.**

PNEUMONIA is a frequent occurrence in head trauma patients,[1–4] with specific patterns such as delay of occurrence and microbiology. It differs from usually studied ventilator-associated pneumonia because it is not related to duration of ventilation and is frequently associated with specific germs in the first week.[1,3–6] Few studies have evaluated factors associated with early onset pneumonia after head trauma. Carriage of *Staphylococcus aureus*[6–9] and pulmonary aspiration[10–12] are suspected to participate to the genesis of early onset pneumonia. Several other risk factors have not been studied, particularly sedation. Moreover, early onset pneumonia is associated with events (fever, arterial hypotension, hypoxemia, hypocapnia, or hypercapnia) known to participate in the occurrence of secondary cerebral injuries. Hence, identifying risk factors for early onset pneumonia and the potential consequences of this event is critical in the management of head trauma. The aim of our study was to find the risk factors of early onset pneumonia and to identify potential consequences of early onset pneumonia as secondary brain injuries in a cohort of head trauma patients requiring mechanical ventilation.

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Materials and Methods

According to French legislation, no informed consent is needed to use data for an epidemiologic study. We performed a prospective, monocentric, observational cohort study in Beaujon Hospital (a university teaching hospital in Clichy, France, with 682 beds) in a 17-bed surgical intensive care unit (ICU) over a 2-yr period (1999 and 2000). All head trauma patients who needed tracheal intubation for neurologic reasons and ventilation for at least 2 days were included. The exclusion criteria were transfer from another hospital more than 2 days after trauma and early death (within the first 2 days).

Patients had nasogastric or orogastric tubes and were started within 2 days after admission on enteral feeding. Treatment with sucralfate was used routinely. Selective oropharyngeal decontamination was never performed during the study. Routine oral care was performed three times per day with use of a mixture of 1.4% bicarbonate with a solution for mouthwash containing hexetidine, choline salicylate, and chlorobutanol. Antibiotic prophylaxis was only administered for surgery or during 48 h in case of open fractures. Patient care was given according to French recommendations for initial treatment of severely head-injured patients.[13] According to these recommendations, all of the patients included underwent orotracheal intubation. There was no tracheostomy performed during the first week after trauma. Intentional sedation was used for all of the patients with severe head trauma and was managed with use of an intracranial pressure catheter for maintenance of cerebral perfusion pressure above 70 mmHg. When needed, sedation was

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obtained with midazolam and fentanyl. Barbiturates were administered in case of refractory intracranial hypertension. The decision to withdraw sedation and to extubate a patient was left to the patient's physician.

Several parameters were prospectively collected:

- Glasgow coma score (reported by attending physicians at arrival on the scene), time between trauma and tracheal intubation, clinical aspiration before intubation (if noted by the initial caregivers), seizure (charted by the physician on the scene)
- age, sex, associated injuries, Simplified Acute Physiology Score 2 and Injury Severity score, presence of thoracic trauma at admission (seen on thoracic tomodensitometric imaging performed in all patients at arrival)
- carriage of *S. aureus*, occurrence of pneumonia
- use of barbiturates, hyperthermia ($\geq$ 38.5°C), worst arterial oxygen tension:fraction of inspired oxygen (Pao_2:Fio_2) ratio, occurrence of hypotension (any systolic arterial pressure $<$ 90 mmHg), intracranial hypertension (sustained intracranial pressure $\geq$ 25 mmHg), antibiotic prophylaxis (during surgery) or administration of antibiotics during the first 2 days (reported as "first 48-h antibiotics"), duration of sedation and ventilation, ICU length of stay, death, Glasgow coma score on discharge from ICU

Nasal carriage of *S. aureus* was assessed by using nasal swabs at arrival, which is a routine procedure performed early and then weekly in our ICU. Nasal swabs were cultured on mannitol–salt agars and incubated at 37°C for 24–48 h. *S. aureus* was identified by means of standard microbiologic methods.[14] Methicillin susceptibility was tested by means of a disk diffusion method on Mueller-Hinton with 5 μg oxacillin–containing disks (Biorad, Marnes la Coquette, France). Plates were incubated at 30°C for 18 h.

Ventilator-associated pneumonia was diagnosed when several criteria were present: new and/or progressive pulmonary infiltrates on chest x-ray and two of the following criteria: fever (temperature $\geq$ 38.5°C) or hypothermia (temperature $\leq$ 36°C), leukocytosis ($\geq$ 12,000 cells/mm^3) or leukopenia ($\leq$ 4,000 cells/mm^3), and purulent tracheobronchial secretions. Ventilator-associated pneumonia was then confirmed with an invasive method[15] using a fiberoptic bronchoscope by a protected specimen brush growing 10^3 colony forming units/ml or more. *Early onset pneumonia* was defined as pneumonia occurring during the first 7 days after trauma, and *late-onset pneumonia* was defined as occurring after day 7.

Statistical Analysis

All results are expressed as mean $\pm$ SD or as a ratio of total patients. Qualitative variables were compared with use of the chi-square test or the Fisher exact test (two-sided) when needed. Continuous variables were compared with use of the Student *t* test. A multivariate analysis was performed to determine risk factors of early onset pneumonia with use of a logistic regression taking variables with $P \leq 0.1$ into account. Data are presented in table 3, which includes the coefficient of the explanatory variable and the associated SE, odds ratio, 95% confidence interval of the odds ratio, and *P* value (calculated with the Wald chi-square test). Explanatory variables were assessed for colinearity and tested for interaction. Statistical analysis was performed with use of Statview 5.0 software (SAS Institute, Cary, NC) and JMP 3.0 software (SAS Institute Inc.).

Table 1. Organisms Associated with 45 Early Onset Pneumonias in Study Patients

	Patients	
Organism	No.	%
Staphylococcus aureus*	26	57.8
Haemophilus influenzae	24	53.3
Streptococcus pneumoniae	7	15.6
Entrobacteriacae	8	17.8
Other†	4	8.9

Organisms shown are those isolated at a significant level from protected brush. The total number of organisms is more than 45 because 24 patients had two isolates.

* One case of *S. aureus* was methicillin resistant. † *Streptococcus* species (3), *Neisseria meningitidis* (1).

Results

One hundred fourteen head trauma patients were admitted during the 2-yr study period. Five patients were not included because four died in the first 2 days and the last one was transferred from another hospital on the third day. The remaining 109 patients formed the study group and had a mean Glasgow coma score on admission of 7.2 $\pm$ 2.6, a mean age of 34 $\pm$ 15 yr, and a mean Simplified Acute Physiology Score 2 of 36.2 $\pm$ 11.8; 70.6% were multiple trauma patients. Death occurred in 20 patients (18.3%). Forty-one patients were found to carry *S. aureus* on admission (37.6%). All strains of *S. aureus* were methicillin-susceptible except two (one patient was living with his mother, who was a nurse in a hospital, and no risk factor was found for the other patient).

Fifty-five patients had ventilator-associated pneumonia (50.5%), with 45 having early onset pneumonia (overall incidence, 41.3%; 26.7/1,000 days of ventilation) and 10 having late-onset pneumonia. In the 45 cases of early onset pneumonia, culture retrieved a single bacteria in 21 cases and two organisms in the remaining 24 (53.3%). *S. aureus* was the first bacteria involved in early onset pneumonia (table 1). Twenty-three of the 26 patients with early onset pneumonia with *S. aureus* were carrying *S. aureus* on admission; the 3 others were found to carry *S. aureus* on the fourth day and had early onset pneumonia on the seventh day. In 3 of the 26 patients

Table 2. Univariate Analysis of Risk Factors of Early Onset Pneumonia in Study Patients

Characteristic	Patients with Early Pneumonia (n = 45)	Patients without Early Pneumonia (n = 64)	*P* Value
Mean age, yr	37 ± 14.9	31.2 ± 15.4	0.05
Female, %	22.2	14.1	NS
Multiple trauma patients, %	68.9	71.9	NS
Lung trauma, %	53.3	51.6	NS
Mean Glasgow score on scene	7.2 ± 2.6	7.2 ± 2.6	NS
Glasgow score < 9 on scene, %	80	71.9	NS
Mean SAPS 2 score on admission	36.9 ± 12	35.8 ± 11.8	NS
Mean ISS score on admission	33 ± 8	36 ± 11	NS
Delay between trauma and intubation, min	165 ± 216	109 ± 159	0.12
Aspiration before intubation, %	48.9	12.5	< 0.0001
Nasal carriage of *Staphylococcus aureus* on admission, %	57.8	23.4	0.0006
Intentional sedation > 48 h, %	82.2	62.5	0.03
Barbiturate use, %	42.2	12.5	0.0004
Antibiotic prophylaxis, %	35.6	37.5	NS
First 48 h antibiotics, %	15.6	32.8	0.04

ISS = Injury Severity Score; NS = not significant; SAPS = Simplified Acute Physiology Score.

with early onset pneumonia who had *S. aureus* on admission, *S. aureus* was not found to be the bacteria involved in the pneumonia.

On univariate analysis, early onset pneumonia was significantly associated with an older age, aspiration before intubation, nasal carriage of *S. aureus* on admission, barbiturate infusion, intentional sedation, and absence of antibiotic use in the first 48 h (table 2). On multivariate analysis, aspiration before intubation, use of barbiturates, and nasal carriage of *S. aureus* on admission remained independent risk factors of early onset pneumonia (table 3). We found no colinearity and no interaction between independent variables.

Early onset pneumonia was significantly associated with a lower Pa_{O_2}:F_{IO_2} ratio, more episodes of arterial hypotension, a greater incidence of fever, more episodes of intracranial hypertension, a longer duration of mechanical ventilation, a lower Glasgow score on ICU discharge, and a higher duration of stay in the ICU (table 4).

Discussion

As described in previous studies,[2,5,8] early onset pneumonia was frequent in our study, probably because of the inclusion criteria (only head trauma necessitating at least 2 days of artificial ventilation, and mainly severe head trauma). We also found that early onset pneumonia results in deleterious early secondary brain injuries such as fever, arterial hypotension, and hypoxemia. Patients with early onset pneumonia showed more intracranial hypertension, a poorer Glasgow coma score on ICU discharge, and a longer mechanical ventilation duration and ICU stay. There was a trend toward a higher mortality rate (24.4 *vs.* 14.1%; $P = 0.17$).

The main result of this study is that aspiration before intubation, use of barbiturates, and nasal carriage of *S. aureus* on admission were independent risk factors of early onset pneumonia. Forty patients (37.6%) had nasal carriage of *S. aureus* at admission, which is similar to the rate usually reported in the general population or in patients at admission.[16] The incidence of early onset pneumonia was significantly higher in patients carrying *S. aureus* at admission (63.4 *vs.* 27.9% for patients without carriage of *S. aureus*; $P = 0.0003$). Campbell *et al.*[7] found a similar result; however, they did not report *S. aureus* carriage as an independent risk factor for pneumonia. In comatose patients and mostly before tracheal intubation, high inoculum aspiration of oropharyngeal secretions probably always occurs. Several publications suggested that, in conjunction with artificial ventilation, the presence of *S. aureus* and probably other pathogens such as *Haemophilus influenzae* and *Streptococcus*

Table 3. Multivariate Logistic Regression Analysis of Risk Factors of Early Onset Pneumonia*

Variable	Coefficient†	SE	Odds Ratio	95% CI	*P* Value‡
Age > 40 yr	0.829	0.548	2.3	0.8–6.7	0.13
Intentional sedation > 48 h	0.251	0.592	1.3	0.4–4.1	0.67
First 48 h antibiotics	−0.336	0.632	0.7	0.2–2.5	0.59
Aspiration before intubation	1.697	0.553	5.5	1.9–16.4	0.002
Barbiturate use	1.376	0.596	3.9	1.2–12.8	0.02
Nasal carriage of *Staphylococcus aureus* on admission	1.642	0.510	5.1	1.9–14.0	0.001

* *Early onset pneumonia* was defined as the dependent variable coded as "present or absent" with 45 early onset pneumonias in 109 observations. † Coefficient of the explanatory variable. ‡ *P* values were calculated with the Wald chi-square test.

Table 4. Univariate Analysis of Events in Intensive Care Unit and Crude Outcomes in Study Patients

Characteristic	Patients with Early Onset Pneumonia (n = 45)	Patients without Early Pneumonia (n = 64)	*P* Value
Arterial hypotension, %	80	56.2	0.009
Fever, %	84.4	46.9	< 0.0001
Mean worst Pao_2/Fio_2 ratio, mmHg	132 ± 55	232 ± 82	< 0.0001
Intracranial hypertension, %*	62.2	32.8	0.002
Mean sedation duration, days	8.8 ± 4.3	5.8 ± 4.8	0.004
Mean ventilation duration, days	20.8 ± 12	13.8 ± 9.7	0.004
Mean ICU duration of stay, days	26.8 ± 13.2	20.4 ± 12.1	0.02
Mean Glasgow score on ICU discharge	12.7 ± 2.4	13.8 ± 1.7	0.01
Death in ICU, %	24.4	14.1	0.17

* Defined as the occurrence of sustained intracranial pressure ≥ 25 mmHg.

Fio_2 = fraction of inspired oxygen; ICU = intensive care unit; Pao_2 = arterial oxygen tension.

pneumoniae in this aspiration lead to early onset pneumonia.[4,9,10] This fact is also supported by Ewig *et al.*,[9] who showed that bacterial colonization with *S. aureus*, *H. influenzae*, or *S. pneumoniae* was frequent in head-injured patients and was associated with early onset pneumonia. Unfortunately, Ewig *et al.*[9] did not find carriage of these pathogens to be an independent risk factor of early onset pneumonia because only 48 patients were included in their study. We also found, like Akça *et al.*,[11] that aspiration before tracheal intubation was an independent risk factor of early onset pneumonia, and this result explains a major part of the pathophysiology of early onset pneumonia in head trauma. Finally, regarding barbiturates as a risk factor, this finding has been reported previously.[17–20] Ewig *et al.*[9] also found that barbiturate use was a risk factor for bacterial colonization of upper airway (odds ratio of 8.0) for different reasons, including inhibition of mucociliary clearance and alteration of immunologic functions.

The question of using a different cutoff to define early onset pneumonia is a major issue. The cutoff of 5 days considered by the American Thoracic Society guidelines is mainly based on two points, the causative pathogens and the different prognosis in early onset *versus* late-onset ventilator associated pneumonia.[15,21] A cutoff of 7 days to define early onset *versus* late-onset pneumonia was chosen *a priori* in our ICU on the basis of annual reviews of microorganisms' antibiotic susceptibility (retrieved in bronchoscopic samples) in head trauma patients. Considering microorganisms, we observed that causative pathogens were similar in the first 7 days and found no evident change between day 4 and day 7, particularly in multidrug-resistant bacteria and the *Enterobacteriaceae* family. Except for one patient carrying methicillin-resistant *S. aureus* on admission, no multidrug-resistant bacteria was found. Regarding the role of *Enterobacteriaceae*, we found that enteric gram-negative bacterias were involved in 5 of 25 cases of pneumonia occurring before day 5 and in 3 of the remaining 20 cases of pneumonia if we use a cutoff of 7 days. Ewig *et al.*[9] did not show such a result regarding the *Enterobacteriaceae* family, but they excluded patients with gross aspiration before admission and showed that enteric gram-negative bacterias were mainly located in gastric juice at admission. We did not exclude patients with aspiration before or at admission because it is a rather frequent event in comatose patients with deleterious consequences, as shown in our study. Therefore, this could explain why we found such a result regarding enteric gram-negative bacterias. Considering the influence of delay of pneumonia on the outcome, we considered that it was better to include 20 pneumonias occurring between day 4 and day 7 because consequences on cerebral lesions as secondary injuries are particularly important in the first week. Moreover, several authors emphasized the fact that pneumonia occurs particularly frequently in comatose patients between day 4 and day 7.[2–4] Analyzing the whole group of data by using a cutoff of 4 days (data not shown), the incidence of early pneumonia was 22.9% with a similar distribution of causative pathogens. On univariate analysis, aspiration before admission, nasal carriage of *S. aureus* on admission, and age are significantly associated with early pneumonia, whereas use of antibiotics during the first 48 h is associated with a lower rate of early pneumonia. Consequences of early pneumonia (worst Pao_2:Fio_2 ratio, arterial hypotension, hyperthermia) remain significant except for the occurrence of intracranial hypertension and duration of stay in the ICU, which do not reach statistical significance. On multivariate analysis, carriage of *S. aureus* (odds ratio, 5.9; 95% confidence interval, 2.0–17.2) and aspiration (odds ratio, 3.1; 95% confidence interval, 1.1–9.2) are still independent predictors of early pneumonia. Barbiturate use is not significant in the analysis because there are fewer events (25 *vs.* 45) within the first 4 days and because administration of barbiturates results in pneumonias occurring after day 3. Considering *S. aureus* carriage leading to *S. aureus* pneumonias, no typing was performed to confirm that the same strains of *S. aureus* were involved in both carriage and pneumonia. However, it has been shown in studies regarding various infections that, using typing by pulsed-field gel electrophoresis, the *S. aureus* causing infection and that isolated from the nares on admission were the

same.[7,22–24] The main matter of our study is not whether it is the same strain but that nasal colonization of *S. aureus* is a major risk factor of early onset pneumonia. Whether early onset pneumonia itself is responsible for a lower Glasgow score on discharge from the ICU is not shown in our study, but the fact is that early onset pneumonia is significantly associated with fever, arterial hypotension, and hypoxemia, which are known to be major factors resulting in secondary cerebral injury.

What are the solutions to avoid early onset pneumonia, and first of all, is it necessary to avoid it? In head trauma patients, the consequences of early onset pneumonia, as shown in our study, are particularly deleterious because they occur in the first days, known to be the most important days of care of severe head injury, and early onset pneumonia must be prevented then. How can we achieve this goal? A few ways are possible. First, subglottic suctioning has proved its efficiency in reducing ventilator-associated pneumonia by reducing aspiration of orotracheal secretions,[25–27] especially for early onset pneumonia. However, because the major part of aspiration probably occurs before tracheal intubation, subglottic suctioning is probably ineffective. Second, selective digestive decontamination, despite the controversy regarding this technique, could be a good means[28–30]; however, Korinek *et al.*[30] showed that it was effective to reduce gram-negative bacilli infections (especially bronchopneumonia) but that *S. aureus* remained the main cause of pneumonia due to failure to control *S. aureus* in the lower airways. Third, early administration of antibiotics seems to be a reasonable choice, regarding the supposed physiopathology of early onset pneumonia. Sirvent *et al.*[31] have shown that the incidence of early onset pneumonia can be reduced by half with two single high doses of cefuroxime. This solution must be weighed with the risk of selecting resistant bacterias. Ewig *et al.*[9] reported that antibiotics significantly reduced bacterial colonization with pathogens responsible for early onset pneumonia but were associated with a greater risk of late-onset pneumonia. This risk may be less important than the benefits of avoiding early secondary cerebral injuries due to early onset pneumonia with early administration of antibiotics, especially in patients carrying *S. aureus* or with aspiration before intubation, because of the particularly great risk of occurrence of early onset pneumonia. To support this fact, we found, despite the fact that antibiotics were not used to prevent early onset pneumonia, that early administration of antibiotics during 48 h for open fracture resulted in a significant difference in the incidence of early onset pneumonia (25% of early onset pneumonia with antibiotics *vs.* 47% without).

In summary, we found that early onset pneumonia is a frequent event in head trauma patients and leads to cerebral secondary injuries during the most important days of care of head-injured patients. Carriage of *S. aureus* is an independent risk factor of early onset pneumonia, probably by causing infection of initial and continuous aspiration of oropharynx secretions in comatose patients. Prevention strategies must be guided by the presence of major risk factors, carriage of *S. aureus* on admission, aspiration before the airway is secure, and use of barbiturates and should be evaluated to avoid cerebral consequences of early onset pneumonia.

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