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ORIGINAL ARTICLE

Early-Onset Ventilator-Associated Pneumonia in Patients with Severe Traumatic Brain Injury: Incidence, Risk Factors, and Consequences in Cerebral Oxygenation and Outcome

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Abstract

Background Early-onset ventilator-associated pneumonia (EOVAP) occurs frequently in severe traumatic brain-injured patients, but potential consequences on cerebral oxygenation and outcome have been poorly studied. The objective of this study was to describe the incidence, risk factors for, and consequences on cerebral oxygenation and outcome of EOVAP after severe traumatic brain injury (TBI).

Methods We conducted a retrospective, observational study including all intubated TBI admitted in the trauma center. An EOVAP was defined as a clinical pulmonary infection score >6, and then confirmed by an invasive method. Patient characteristics, computed tomography (CT) scan results, and outcome were extracted from a prospective register of all intubated TBI admitted in the intensive care unit (ICU). Data concerning the cerebral oxygenation monitoring by $PbtO_2$ and characteristics of EOVAP were retrieved from patient files. Multivariate logistic regression models were developed to determine the risk factors of EOVAP and to describe the factors independently associated with poor outcome at 1-year follow-up.

Results During 7 years, 175 patients with severe TBI were included. The overall incidence of EOVAP was 60.6% (47.4/1000 days of ventilation). Significant risk factors of EOVAP were: therapeutic hypothermia (OR 3.4; 95% CI [1.2–10.0]), thoracic AIS score ≥ 3 (OR 2.4; 95% CI [1.1–5.7]), and gastric aspiration (OR 5.2, 95% CI [1.7–15.9]). Prophylactic antibiotics administration was a protective factor against EOVAP (OR 0.3, 95% CI [0.1–0.8]). EOVAP had negative consequences on cerebral

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oxygenation. The $PbtO_2$ was lower during EOVAP: 23.5 versus 26.4 mmHg ($p < 0.0001$), and there were more brain hypoxia episodes: 32 versus 27% ($p = 0.03$). Finally, after adjusting for confounders, an EOVAP was an independent factor associated with unfavorable neurologic functional outcome at the 1-year follow-up (OR 2.71; 95% CI [1.01–7.25]).

Conclusions EOVAP is frequent after a severe TBI (overall rate: 61%), with therapeutic hypothermia, severe thoracic lesion, and gastric aspiration as main risk factors. EOVAP had a negative impact on cerebral oxygenation measured by $PbtO_2$ and was independently associated with unfavorable outcome at 1-year follow-up. This suggests that all precautions available should be taken to prevent EOVAP in this population.

Keywords Traumatic brain injury · Ventilator-associated pneumonia · Risk factors · Incidence · Cerebral oxygenation · $PbtO_2$ · Outcome

Abbreviations

TBI	Traumatic brain injury
GCS	Glasgow Coma Scale
EOVAP	Early-onset ventilator-associated pneumonia
CPP	Cerebral perfusion pressure
$PbtO_2$	Brain tissue oxygen tension
ICU	Intensive care unit
ICP	Intracranial pressure
CPIS	Clinical pulmonary infection score
mini-BAL	Mini-bronchoalveolar lavage
ARDS	Acute respiratory distress syndrome
FiO_2	Fraction of inspired oxygen
GOS	Glasgow Outcome Scale
ROC	Receiver operating characteristic
95% CI	95% confidence interval
MDR	Multidrug resistant

Background

Traumatic brain injury (TBI) is a leading cause of premature death and disability, with an annual incidence estimated at 500/100,000 in the USA and Europe [1–3]. TBIs are considered severe when, after initial resuscitation, they score ≤8 on the Glasgow Coma Scale (GCS) [4]. This population has a high incidence (up to 45%) of early-onset ventilator-associated pneumonia (EOVAP) [5]. EOVAP is classically caused by antibiotic-susceptible pathogens [6, 7]. It is currently well established that EOVAP has a deleterious impact on morbidity; it was associated with long mechanical ventilation times and prolonged hospital stays [6, 8]. However, apparently, EOVAP was not associated with an increased risk of hospital mortality or a poor outcome [5, 9].

EOVAP occurs soon after a neurologic injury and may have consequences on systemic oxygenation, body temperature, and cerebral perfusion pressure (CPP), which may negatively affect brain tissue oxygenation [6]. It was also demonstrated that brain hypoxia, measured by continuously monitoring brain tissue oxygen tension ($PbtO_2$), was associated with a poor functional neurologic outcome, because cerebral hypoxic events lead to secondary cerebral injuries [10]. However, few studies have investigated the consequences of EOVAP on cerebral oxygenation. The present study aimed to describe the characteristics of patients with severe TBIs that develop EOVAP and to determine the consequences of EOVAP on cerebral oxygenation and functional neurologic outcome.

Patients and Methods

Study Design and Patient Selection

This 7-year retrospective, observational, single-center study was conducted at the Sainte Anne Military Hospital of Toulon (France). Patients with TBIs were eligible when they were intubated and admitted to the intensive care unit (ICU) between January 2007 and December 2013. Inclusion criteria were: age >18 years old; TBI graded severe, with a GCS score ≤8 after initial resuscitation; and ≥2 days on mechanical ventilation. Patients were excluded when they had mild/or moderate TBIs (GCS score >8) or died within 2 days of admission.

All patients were sedated, intubated, and mechanically ventilated, in accordance with international guidelines [11–16]. The institutional therapeutic management approach is presented in Fig. 1 and remained constant throughout the study period.

Enteral feeding with a nasogastric or orogastric tube was initiated at the discretion of the physician in charge. Guidelines for preventing ventilator-associated pneumonia (VAP) were followed routinely [17]. All patients were intubated via an orotracheal course. Routine oral care was performed four times per day with a mouthwash solution containing chlorhexidine and chlorobutanol. The endotracheal tube cuff pressure was monitored four times per day, and pressure was maintained at 20–30 mmHg. EOVAP preventive strategies also included the use of a closed/in-line endotracheal suctioning system, residual gastric volume monitoring, and stress ulcer prophylaxis. In February 2012, we began using endotracheal tubes with subglottic secretion drainage ports. Antibiotic prophylaxis with amoxicillin/clavulanate was administered for 48 h at the discretion of physician in charge, mostly when open

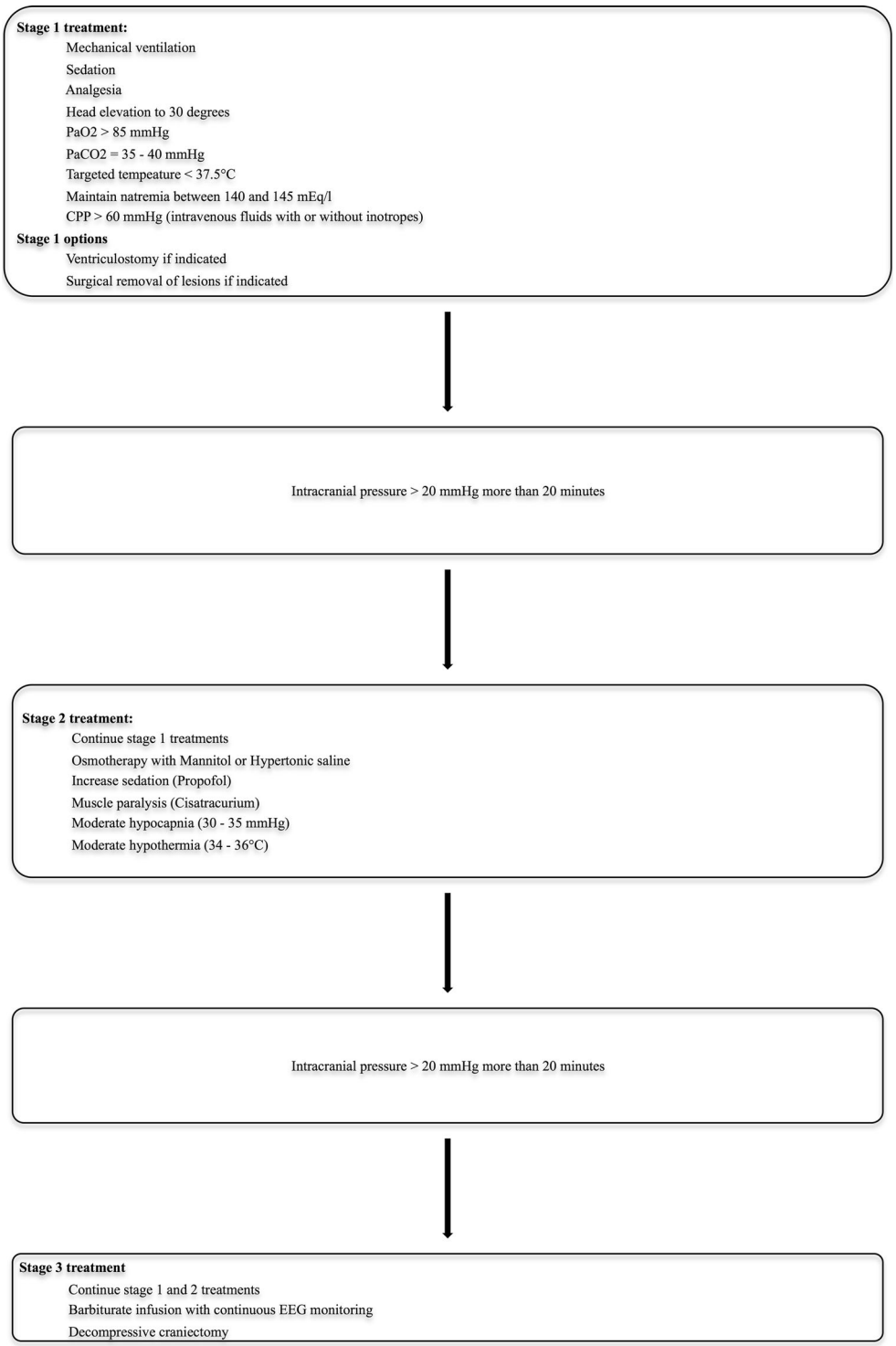

Fig. 1 Stages of therapeutic management. *CPP* Cerebral perfusion pressure, *EEG* Electroencephalogram

fractures or facial traumas required prolonged nasal packing. At admission, all patients underwent tracheobronchial aspiration, and the sample was examined for bacteria.

The Institutional Review Board approved the study and waived the requirement for informed consent from patients and their relatives, given the observational nature of the study.

Definition and Diagnosis of EOVAP

EOVAP was defined as pneumonia that occurred during the first 7 days after a trauma, consistent with the literature [6, 18–21]. The clinical pulmonary infection score (CPIS) was assessed daily for the first 7 days to screen patients for pneumonia [22, 23]. When the CPIS was $\geq$5, the

institutional protocol required a fiberoptic bronchoscopy with a mini-bronchoalveolar lavage (mini-BAL). EOVAP was diagnosed when the CPIS was >6, and the mini-BAL revealed potentially pathogenic bacteria ($\geq 10^4$ colony forming units/ml). When a quantitative analysis showed that the culture was positive, the EOVAP diagnosis was confirmed. In the absence of a positive bacteriological sample, EOVAP was diagnosed when the CPIS >6 could not be explained by pulmonary edema, atelectasia, or pulmonary embolism. EOVAP severity was classified according to the degree (none, mild, moderate, severe) of acute respiratory distress syndrome (ARDS), based on the criteria specified in the Berlin definition of ARDS [24]. During all EOVAP episodes, a lung-protective ventilation strategy was employed (tidal volume set at 6–8 mL/kg body weight). Positive End-Expiratory Pressure (PEEP) was adjusted to achieve the best PaO_2/FiO_2 ratio, without a predefined maximal limitation.

Brain Tissue Oxygen Tension Monitoring ($PbtO_2$)

Cerebral oxygenation was monitored at the discretion of the treating physician. The local protocol specifically indicated that monitoring was required in the youngest patients (age <65 years) that had no expected wake-up test in the first 48 h and an expected survival of more than 48 h. When indicated, a $PbtO_2$ probe (LICOX®, Integra Neurosciences, USA) was inserted at the bedside in the ICU through the same screw used for the intracranial pressure (ICP) probe (Bolt system, IM2, Integra Neurosciences, USA). The monitors were placed in brain white matter that appeared normal on an admission head computed tomography (CT) in the hemisphere with the most extensive injury. When the brain pathology was not asymmetrical on the CT, the probe was placed in the right frontal lobe. The correct location of the $PbtO_2$ probe was confirmed with a follow-up CT scan and by manipulating the fraction of inspired oxygen (FiO_2). Values were recorded only after an initial in vivo equilibration period of 2 h. In accordance with other clinical studies, the ischemic threshold was <20 mmHg [25, 26].

Data Collected

We accessed a registry of data prospectively collected on all patients intubated for TBIs and admitted to the ICU. The registry included data on patient characteristics, mechanisms of injury, the initial GCS score, whole-body CT scan results, evolution of the disease, inhospital mortality, and neurologic functional outcome at 6 months and 1 year, according to the Glasgow Outcome Scale (GOS). The GOS score is a five-point scale, where 1 = death, 2 = persistent vegetative state, 3 = severe disability, 4 = moderate disability, and 5 = good recovery [27]. GOS scores were used at the 1-year follow-up to define favorable (GOS = 4–5) and unfavorable (GOS = 1–3) functional neurologic outcomes.

Data on EOVAP and cerebral oxygenation monitoring were retrieved from patient files. According to the local protocol, every 4 h during the monitoring phase, the following variables were simultaneously recorded: $PbtO_2$ (mmHg), CPP (mmHg), ICP (mmHg), arterial CO_2 pressure ($PaCO_2$; mmHg), arterial O_2 pressure (PaO_2; mmHg), FiO_2, PaO_2/FiO_2 ratio, arterial oxygen saturation (SaO_2), temperature (°C), and hemoglobin level (g/dL). The values not paired were excluded from analysis.

Study Aims

This study had multiple aims. The first was to characterize patients with severe TBI that developed EOVAP. The second was to identify risk factors for EOVAP. The third was to evaluate the effects of EOVAP on cerebral oxygenation and on patient outcome.

Statistical Analysis

All statistical analyses were performed with XLSTAT, version 2015.3.01 (Addinsoft). Continuous data are reported as the mean ± SD. Data that were not normally distributed are expressed as the median and interquartile range (IQR; 25th–75th percentile). Nominal variables are reported as numbers and proportions (%).

In the univariate analysis, the χ^2 test or Fisher's exact test was used to compare categorical variables (medians), and the Mann–Whitney test or Student t test was used to compare groups of continuous variables (means). The Kruskal–Wallis test was used to compare values measured at baseline and during EOVAP, including $PbtO_2$ values and values of multiple variables that influenced cerebral oxygenation,.

Independent factors associated with EOVAP were identified with a logistic regression model. A second model was constructed to identify independent factors associated with an unfavorable functional neurologic outcome. For both models, all clinically relevant parameters with p values <0.1 in the univariate analysis were included in the multivariate regression model. The Hosmer–Lemeshow goodness-of-fit test and the area under the receiver operating characteristic (ROC) curve were used to evaluate the overall fits of the final models. Final model results were expressed as the odds ratio (OR) and 95% confidence intervals (95% CI). For all tests, p <0.05 was considered statistically significant.

Results

Study Population

During the study period, 243 patients with TBIs were intubated and admitted to the ICU. Sixty-eight patients were excluded, due to mild or moderate TBIs ($n = 10$), early death in the first 48 h after admission ($n = 30$), and mechanical ventilation for less than 2 days ($n = 28$). Among the 175 patients included (139 males, 79.4%; 36 females, 20.6%), the most common mechanism of injury was a motorcycle crash (31.4%). These patients had a median age of 37 (IQR: 23–55) years, a median injury severity score (ISS) score of 22 (IQR: 16–34), a median abbreviated injury scale (AIS) score for head injury of 5 (IQR: 4–5), and a median initial GCS score of 6 (IQR: 4–8).

Early-onset Ventilator-Associated Pneumonia

EOVAP was diagnosed in 106 patients with severe TBIs (overall incidence, 60.6%, 95% CI 53–68.1; 47.4/1000 days of ventilation). According to the Berlin definition, among patients with EOVAP, eight patients (7.5%) had no ARDS, 20 patients (18.9%) had mild ARDS, 62 patients (58.5%) had moderate ARDS, and 13 patients (12.3%) had severe ARDS. At the time of EOVAP, patients received volume-limited assist-control ventilation with a median tidal volume of 6.8 (IQR: 6.2–7.5) mL/kg body weight, and a median PEEP of 8 (IQR: 7–12) cm H_2O. The most common strain of bacteria was *Hemophilus influenza* (25.2%) and methicillin-susceptible, *Staphylococcus aureus* (24.4%; Fig. 2).

In comparisons of patients with and without EOVAP, the most notable difference was that patients with EOVAP were more severely injured (Table 1). The median ISS scores were 25 (IQR: 16–34) for those with EOVAP, and 18 (IQR: 14–32) for those without EOVAP ($p = 0.009$). The gravity of brain injuries was comparable between the groups, in terms of the median head AIS (5, IQR: 4–5 vs. 5, IQR: 4–5; $p = 0.09$), the median Marshall score (2.5, IQR: 2–5 vs. 2, IQR: 2–5; $p = 0.10$), and the median minimal GCS score before sedation (6, IQR: 4–7 vs. 6, IQR: 4–8; $p = 0.46$). Compared to patients without EOVAP, those with EOVAP more frequently received therapeutic hypothermia (54.7 vs. 21.7%, $p < 0.0001$), barbiturate infusion (37.7 vs. 11.6%, $p = 0.0002$), and/or decompressive craniectomy (32.1 vs. 13%, $p = 0.004$).

The multivariate logistic regression analysis identified four major significant parameters associated with EOVAP: therapeutic hypothermia (OR 3.4; 95% CI 1.2–10.0, $p = 0.02$), thoracic AIS score ≥ 3 (OR 2.4; 95% CI 1.1–5.7, $p = 0.04$), a positive quantitative culture of the endotracheal aspiration acquired at admission (OR 4.2, 95% CI 1.7–10.6, $p = 0.002$), and gastric aspiration (OR 5.2, 95% CI 1.7–15.9, $p = 0.004$). Prophylactic antibiotics administered during the first 48 h remained a protective factor against EOVAP (OR 0.3, 95% CI 0.1–0.8, $p = 0.01$). Other variables included in the model are shown in Table 2. The area under the ROC curve was 0.85. The Hosmer–Lemeshow test demonstrated a good model fit ($\chi^2 = 11.6$, $df = 8$, $p = 0.17$).

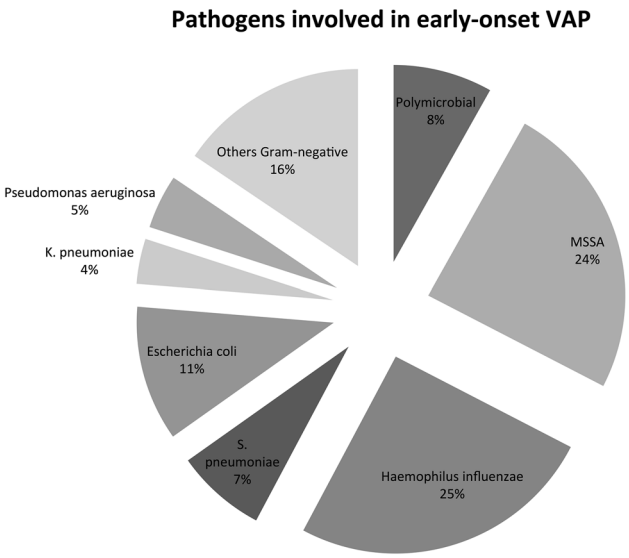

Fig. 2 Pie chart shows pathogens involved in early-onset ventilator-associated pneumonia (VAP). *MSSA* methicillin-susceptible Staphylococcus aureus

Effects on Cerebral Oxygenation

Cerebral oxygenation was monitored in 72 patients (41%) with $PbtO_2$ measurements. We identified a total of 2046 paired measurements. We excluded 604 measurements from the analysis, because the PaO_2/FiO_2 ratio was <300, with no indication of pneumonia. The remaining 1442 measurements were collected in the following conditions: 854 epochs without EOVAP and 588 epochs during EOVAP episodes; the latter epochs included 142 without ARDS, 211 with mild ARDS, 228 with moderate ARDS, and 7 with severe ARDS. The $PbtO_2$ was significantly lower during EOVAP (median 23.5, IQR: 18.6–30.1) compared to epochs without EOVAP (median 26.4, IQR: 19.4–34.9; $p < 0.0001$). Cerebral hypoxia (defined as a $PbtO_2$ <20 mmHg) occurred significantly more frequently during EOVAP (188/588 epochs, 32%) compared to epochs without EOVAP (228/854 epochs, 27%; $p = 0.03$). $PbtO_2$ was significantly lower when EOVAP occurred with moderate or severe ARDS (Table 3). Other variables related to cerebral oxygenation (CPP, ICP, PaO_2, or

Table 1 Characteristics of patients with and without early-onset ventilator-associated pneumonia

Variable	Patients with EOVAP ($n = 106$)	Patients without EOVAP ($n = 69$)	p value
Age (years)	36 [23–53]	39 [23–59]	0.42
Male sex	90 (85%)	49 (71%)	0.03
SAPS II	44 [37–52]	41 [32–52]	0.24
ISS	25 [16–34]	18 [14–32]	0.009
Head AIS ≥ 3	105 (99%)	69 (100%)	0.42
Head AIS ≥ 5	71 (67%)	37 (54%)	0.08
Thorax AIS ≥ 3	58 (55%)	28 (41%)	0.07
Abdomen AIS ≥ 3	15 (14%)	5 (7%)	0.16
Spine AIS ≥ 3	16 (15%)	3 (4%)	0.03
Initial GCS score	6 [4–9]	7 [4–8]	0.69
Bilat mydriasis	8 (8%)	5 (7%)	0.94
Pre-hospital intubation	80 (75%)	52 (75%)	0.99
Gastric aspiration	30 (28%)	8 (12%)	0.009
Total of RBC units transfused	3 [0–7]	2 [0–5]	0.12
Positive culture of admission ETA	42 (40%)	10 (14%)	0.0004
Early enteral feeding (>2000 kcal/j before day 2)	81 (76%)	47 (68%)	0.23
Antibiotic prophylaxis	41 (39%)	38 (55%)	0.03
Therapeutic hypothermia use	58 (55%)	15 (22%)	<0.0001
Barbiturate use	40 (38%)	8 (12%)	0.0002
Decompressive craniectomy use	34 (32%)	9 (13%)	0.004

Data are presented as the number (%) or the median [25th–75th]

AIS abbreviated injury scale, *EOVAP* early-onset ventilator-associated pneumonia, *ETA* endotracheal aspiration, *GCS* Glasgow Coma Scale, *ISS* injury severity score, *RBC* red blood cell, *SAPS II*, simplified acute physiology score

Table 2 Multivariate logistic regression model results show the risk factors for early-onset ventilator-associated pneumonia

Variable	Odds ratio	95% CI	p value
Sex male	1.7	0.6–4.4	0.29
ISS > 15	2.1	0.7–5.9	0.16
Head AIS ≥ 5	1.3	0.6–2.9	0.54
Thorax AIS ≥ 3	2.4	1.1–5.7	0.04
Spine AIS ≥ 3	3.8	0.9–16.2	0.07
Gastric aspiration	5.2	1.7–15.9	0.004
Antibiotic prophylaxis	0.3	0.1–0.8	0.01
Positive culture of admission ETA	4.2	1.7–10.6	0.002
Therapeutic hypothermia use	3.4	1.2–10.0	0.02
Barbiturate use	2.2	0.7–6.8	0.18
Decompressive craniectomy use	1.2	0.4–3.8	0.80

AIS abbreviated injury scale, *CI* confidence interval, *ETA* endotracheal aspiration, *ISS* injury severity score

Area under the ROC curve: 0.85; Hosmer–Lemeshow test: $\chi^2 = 11.6$; $df = 8$, $p = 0.17$

$PaCO_2$) were also significantly altered according to EOVAP severity (Table 3). Additionally, more brain hypoxia episodes occurred in epochs of EOVAP with moderate to severe ARDS (98/235 epochs, 42%) compared to all other epochs (318/1207 epochs, 26%; $p < 0.0001$). The $PbtO_2/FiO_2$ ratio was significantly dependent on EOVAP severity ($p < 0.0001$; Fig. 3).

Effects on Morbidity and Outcome

Patients that developed EOVAP exhibited elevated morbidity during the ICU stay. In particular, compared to patients without EOVAP, those with EOVAP had significantly longer mechanical ventilation durations (12.5 IQR: 9–19 days vs. 5 IQR: 3–11 days, $p < 0.0001$), and significantly longer ICU lengths of stay (16 IQR: 11–26 days vs. 7 IQR: 4–16 days, $p < 0.0001$; Table 4). Inhospital mortality was comparable between groups: 19 (18%) versus 12 (17%) deaths, $p = 0.93$.

Nineteen patients were lost to follow-up at 1 year: 14 (13%) in the EOVAP group, and 5 (7%) in the non-EOVAP group. At 1 year, the GOS score distribution was more favorable among patients without EOVAP than among those that developed EOVAP (Fig. 4). A greater proportion of patients without EOVAP showed good recovery ($p = 0.038$), and a smaller proportion assumed a vegetative state ($p = 0.058$). Based on our

Table 3 Comparisons of $PbtO_2$ and others variables that influence cerebral oxygenation among epochs without and with early-onset ventilator-associated pneumonia of different severities

Variable	No EOVAP	EOVAP without ARDS criteria	EOVAP with mild ARDS	EOVAP with moderate ARDS	EOVAP with severe ARDS	*p* value
$PbtO_2$ (mmHg)	26.4 [19.4–34.9]	24.4 [19.8–32.4]	25.1 [20.1–31.3]	22 [17.5–27.1]	17.1 [13.7–19.4]	<0.0001
CPP (mmHg)	74 [67–82]	76 [69–83]	78 [70–86]	72 [65–81]	68 [58–71]	<0.0001
ICP (mmHg)	13 [9–18]	10 [7–14]	13 [10–18]	16 [11–20]	16 [14–26]	<0.0001
PaO_2 (mmHg)	152 [132–175]	141 [126–157]	106 [95–119]	84 [77–91]	71 [67–73]	<0.0001
PaO_2/FiO_2 ratio	388 [340–452]	375 [339–432]	241 [221–272]	168 [150–183]	93 [89–94]	<0.0001
Hb (g/dl)	9.7 [8.7–10.8]	9.7 [8.5–10.9]	9.7 [8.7–11.1]	9.5 [8.8–10.3]	10.3 [10.2–10.6]	0.15
$PaCO_2$ (mmHg)	37 [35–41]	36 [33–39]	38 [35–41]	40 [36–43]	46 [39–52]	<0.0001
Temperature (°C)	36 [34.7–37.1]	36.1 [34.9–37]	36.5 [35.5–37.2]	36.5 [35.5–37.3]	36 [34.5–37.4]	0.0001
Number of measures with brain hypoxia	228 (27%)	37 (26%)	53 (25%)	93 (41%)	5 (71%)	<0.0001

Data are presented as the number (%) or the median [25th–75th]

ARDS acute respiratory distress syndrome, *CPP* cerebral perfusion pressure, *EOVAP* early-onset ventilator-associated pneumonia, *Hb* hemoglobin levels, *ICP* intracranial pressure

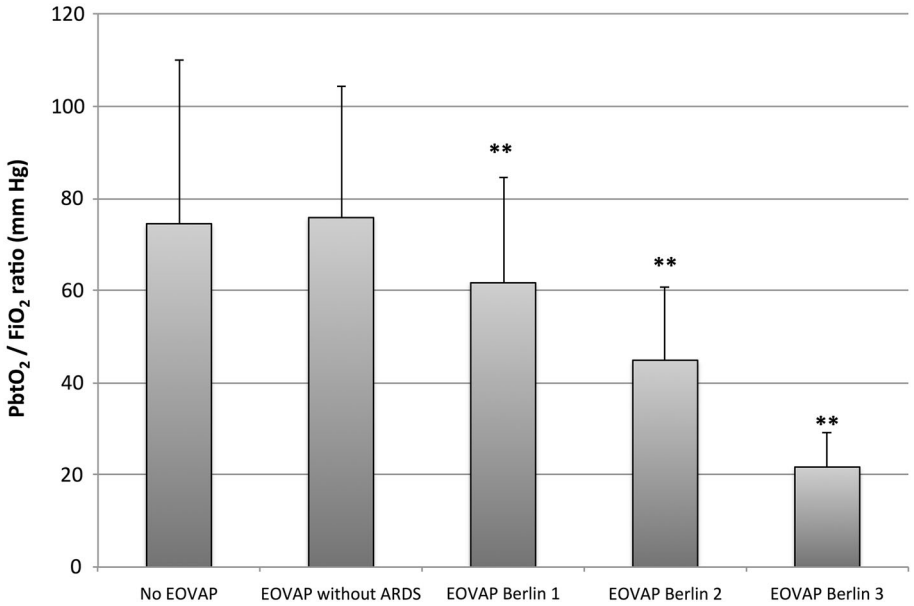

Fig. 3 Evolution of the $PbtO_2/FiO_2$ ratio according to the severity of early-onset ventilator-associated pneumonia; *bars* represent means and standard deviations (**$p < 0.0001$); ARDS: acute respiratory distress syndrome; Berlin 1–3: classification for the severity of ARDS, where *1* mild, *2* moderate, *3* severe

dichotomization, the proportion of patients with an unfavorable functional neurologic outcome was higher in the EOVAP than in the non-EOVAP group: $n = 41$ (45%) versus $n = 18$ (28%), $p = 0.037$. Characteristics of patients that presented favorable or unfavorable outcomes are shown in Table 5. In the multivariate analysis, EOVAP remained an independent factor associated with unfavorable functional neurologic outcome at the 1-year follow-up (OR 2.71; 95% CI 1.01–7.25, $p = 0.047$). Age, initial GCS score, hypernatremia (>155 mEq/L), and at least one intracranial hypertension episode during the ICU stay were also factors independently associated with an unfavorable outcome (Table 6). The area under the ROC curve was 0.86. The Hosmer–Lemeshow test demonstrated a good model fit ($\chi^2 = 3.9$, $df = 9$, $p = 0.92$).

Table 4 Clinical follow-up variables and outcomes among individuals with and without early-onset ventilator-associated pneumonia

Variable	EOVAP $n = 106$	No EOVAP $n = 69$	p value
Intracranial hypertension frequency	62 (58%)	21 (30%)	0.0003
Day of sedation interruption	8 [3–13]	3 [2–6]	<0.0001
Duration of MV (days)	13 [9–19]	5 [3–11]	<0.0001
Tracheostomy	65 (61%)	20 (29%)	<0.0001
ICU length of stay (days)	16 [11–26]	7 [4–16]	<0.0001
Hospital length of stay (days)	30 [17–42]	16 [7–30]	<0.0001
Inhospital mortality	19 (18%)	12 (17%)	0.93
GOS score at 6 months	4 [2–5]	5 [3–5]	0.03
GOS score at 1 year	4 [2–5]	5 [3–5]	0.05

Data are presented as the number (%) or the median [25th–75th]

EOVAP early-onset ventilator-associated pneumonia, *GOS* Glasgow Outcome Scale, *ICU* intensive care unit, *MV* mechanical ventilation

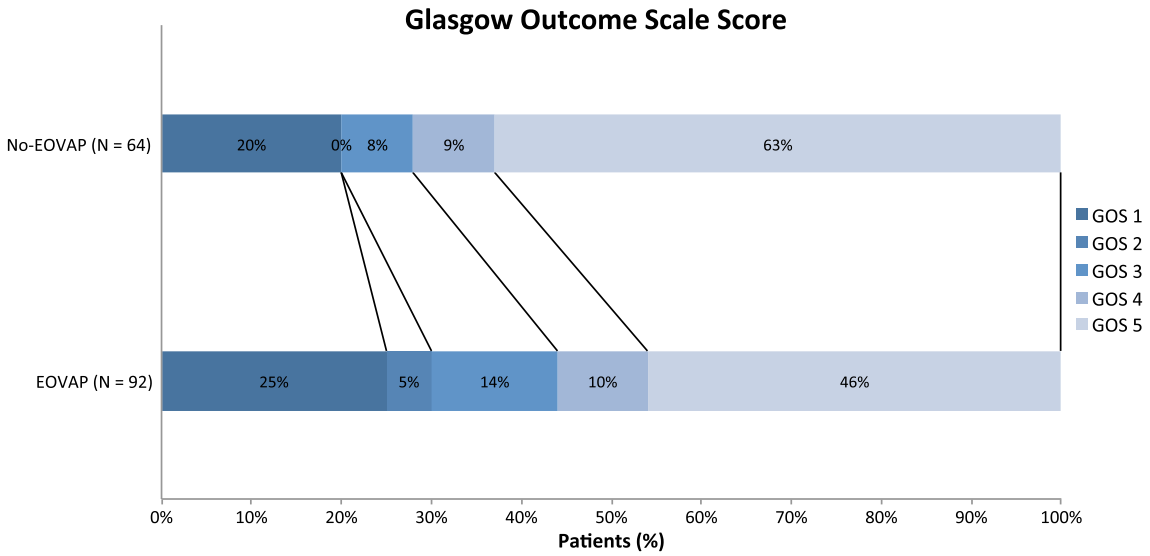

Fig. 4 Functional neurologic outcomes at 1 year after a traumatic brain injury. *EOVAP* early-onset ventilator-associated pneumonia, *GOS* Glasgow Outcome Scale

Discussion

This retrospective analysis of a prospective observational cohort of 175 patients with severe TBIs showed a very high occurrence of EOVAP (approximately of 60%). This incidence was greater than typically observed in the medical literature. Indeed, others series showed an EOVAP incidence of 20–45% in patients with TBIs admitted to the ICU [5, 6, 8, 28, 29]. One potential explanation for this discrepancy might be related to the patients included in our study: we analyzed only patients with severe TBIs. Another explanation might be linked to our area of recruitment (department of Var, France). In this rugged region, the time between a trauma and pre-hospital care is typically prolonged, due to difficult access. Delays in care can lead to more frequent gastric aspirations, a well-known risk factor of VAP [6]. This hypothesis was supported by the fact that gastric aspiration was confirmed in 22% of our patients. Additionally, many of our patients (49%) had serious associated thoracic lesions (thoracic AIS score ≥3), which are known to be associated with pulmonary infections [30, 31]. Indeed, Bronchard et al. [6] reported that, among patients with severe TBIs and high rates of associated thoracic trauma, the EOVAP incidence was approximately 41%, closer to the incidence found in our study. Finally, our definition of EOVAP included all VAP onsets within 7 days, which was a longer time window than typically applied; this longer time frame led to an increased incidence. Indeed, based on the risk of inducing multidrug-resistant (MDR) pathogens, the cutoff between early and late-onset VAP was set at day 5 by the American Thoracic Society guidelines, published in 2005 [32]. However,

Table 5 Patient characteristics according to outcome at 1 year after a traumatic brain injury

Variable	Unfavorable outcome (GOS score 1–3) $n = 59$	Favorable outcome (GOS score 4–5) $n = 97$	p value
Age (years)	48 [30–66]	31 [21–48]	0.0002
Male sex	41 (69%)	81 (84%)	0.04
Initial GCS	5 [3–8]	7 [6–9]	0.001
Bilat mydriasis	8 (14%)	3 (3%)	0.01
Pre-hospital hemodynamic shock	18 (31%)	22 (23%)	0.28
Pre-hospital hypoxia	8 (14%)	17 (18%)	0.51
Head AIS ≥ 3	59 (100%)	96 (99%)	0.99
Marshall category	3 [2–5]	2 [2–5]	0.006
Total RBC unit transfused	3 [1–8]	1 [0–6]	0.03
Natremia max (mEq/l)	153 [148–159]	147 [142–153]	<0.0001
EOVAP	41 (69%)	51 (53%)	0.04
Intracranial hypertension frequency	37 (63%)	36 (37%)	0.002

Data are presented as the number (%) or the median [25th–75th]

AIS abbreviated injury scale, *EOVAP* early-onset ventilator-associated pneumonia, *GCS* Glasgow Coma Scale, *GOS* Glasgow Outcome Score, *RBC* red blood cell

A pre-hospital hemodynamic shock was defined as a systolic arterial pressure less than 90 mmHg

A pre-hospital hypoxia was defined as a SpO_2 $<90\%$ more than 5 min

Table 6 Multivariate logistic regression model results show independent factors associated with an unfavorable functional neurologic outcome at 1 year after a traumatic brain injury

Variable	Odds ratio	95% CI	p value
Age (each year)	1.06	1.04–1.09	<0.0001
Male sex	0.37	0.13–1.04	0.06
Initial GCS score (each point)	0.75	0.64–0.87	0.0003
Bilat mydriasis	5.07	0.78–33.15	0.09
Marshall category (each point)	0.94	0.69–1.29	0.69
Intracranial hypertension during stay	3.08	1.17–8.14	0.02
EOVAP during stay	2.71	1.01–7.25	0.047
Natremia $>$ 155 mEq/l	2.99	1.10–8.16	0.03
Total number of RBC unit transfused (each unit)	0.94	0.92–1.06	0.69

CI confidence interval, *EOVAP* early-onset ventilator-associated pneumonia, *GCS*, Glasgow Coma Scale, *RBC*, Red Blood Cell

Area under the ROC curve: 0.86; Hosmer–Lemeshow test: $\chi^2 = 3.9$; $df = 9$, $p = 0.92$

numerous authors have demonstrated that causative pathogen levels are similar between days 4 and 7, particularly among MDR bacteria [6, 33]. Our results were consistent with that time window. MDR pathogen levels were 9%, when EOVAP occurred before day 5, and 14% when EOVAP occurred between days 5 to 7 ($p = 0.4$; Additional Table). Thus, like many previous studies, we chose to extend the cutoff to 7 days, because we believed that brain lesions due to an additional secondary insult occurred particularly frequently within the first week following a trauma [6, 20, 21, 34]. When we analyzed our data based on a 5-day cutoff, the incidence of EOVAP was 29.7%.

In the present study, the use of therapeutic hypothermia for treating intracranial hypertension was one of the leading factors associated with EOVAP occurrence. This association was previously demonstrated in patients that received therapeutic hypothermia after successful resuscitation from a cardiac arrest [35, 36]. Perbet et al. [35] showed that approximately 65% of this population developed EOVAP. In their multivariate analysis, hypothermia was identified as the single independent factor associated with EOVAP occurrence (OR 1.90; 95% CI 1.28–2.80). In fact, it is widely recognized that hypothermia impairs immune functions by inhibiting the secretion of proinflammatory cytokines and suppressing leukocyte migration

and phagocytosis [37]. However, among patients with severe TBIs, reported findings have been controversial. In a meta-analysis that included 12 trials (involving 689 patients), therapeutic hypothermia appeared to have no effect on the onset of new pneumonia (RR 0.81, 95% CI 0.62–1.05). However, those trials showed substantial statistical heterogeneity [38]. More recently, O'Phelan et al. conducted a retrospective study involving 114 patients with severe TBIs. They demonstrated that therapeutic temperature modulation was significantly associated with pneumonia [36]. We found other factors associated with EOVAP, including gastric aspiration, positive culture of an endotracheal aspiration sample acquired at admission, and associated thoracic injury (AIS score $\geq$3). These findings were consistent with the literature [6, 29]. Finally, unlike numerous studies, we found no association between the use of barbiturate infusions and EOVAP occurrence [6, 8]. This finding was most likely due to the fact that, in our center, barbiturates are applied in weak doses (0.5–2 mg/kg/h) and for short periods (median, 2 days).

The impact of EOVAP on morbidity has been well described; it increases the mechanical ventilation time, it prolongs the stays in the ICU and hospital, and it increases the need for a tracheostomy [5, 6, 9]. However, previous studies failed to find an association between EOVAP and increased mortality or unfavorable outcomes, probably due to a lack of statistical power. In contrast, the main finding in our study was the association between EOVAP and an unfavorable functional neurologic outcome, which remained significant even after adjusting for confounders. We demonstrated that, in patients with severe TBIs, EOVAP was associated with an approximately three-fold increase in the odds of receiving a low GOS score at 1 year. These results were consistent with those recently presented by Kesinger and colleagues [39]. Indeed, in their study, which included 141 individuals with severe TBIs, the authors showed that hospital-acquired pneumonia (early- or late-onset pneumonia) was independently associated with a poor 1-year outcome, based on the GOS-Extended score (adjusted OR 6.39; 95% CI 1.76–23.14) [39].

This study raised questions about the potential physiopathological mechanisms that underlie the negative impact of EOVAP on prognosis, which persisted for one year after a TBI. One of strengths of the present work was our analysis of cerebral oxygenation monitoring, both at baseline and during an episode of EOVAP. Thus, we showed that pneumonia had a negative impact on cerebral oxygenation, based on $PbtO_2$ measurements. In fact, brain hypoxia frequently occurred during EOVAP periods, and even more frequently when EOVAP was associated with moderate or severe ARDS. Indeed, many observational clinical studies have demonstrated a significant, independent association between brain hypoxia and unfavorable outcomes [10, 25]. In most studies, The $PbtO_2$ cutoff for defining brain hypoxia varied between 15 and 20 mmHg; moreover, Chang et al. [25] showed an exponential improvement in outcome when $PbtO_2$ exceeded 20 mmHg. As part of the classical array of secondary insults to a brain injury, EOVAP can alter many variables that influence cerebral oxygenation. First, as shown in our work, EOVAP can negatively impact systemic arterial oxygenation, due to lung infiltrates, which cause a significant drop in PaO_2. Second, as previously demonstrated, pneumonia can be associated with frequent episodes of arterial hypotension, which leads to a decrease in cerebral blood flow [6]. Third, EOVAP was associated with an increased incidence of fever [6]. This is important, because fever is known to increase the incidence of poor outcomes, probably due to aggravation of ischemic cerebral lesions [40, 41]. Finally, EOVAP may contribute to a deleterious systemic inflammatory state, which generates secondary insults to the brain that might, in turn, aggravate ischemic damage [42, 43].

Study Limitations

Our study had several limitations. First, it was a single-center study; therefore, the results are not generalizable to all ICUs or trauma centers. Second, our local protocol restricted cerebral oxygenation monitoring with $PbtO_2$ to patients with the most severe injuries. This restriction might have affected our results. Notably, EOVAP can have a greater impact on cerebral oxygenation when severe brain lesions involve already an alteration in regional cerebral blood flow. However, this potential bias was probably limited, because we analyzed outcome data for the entire cohort (patients with and without $PbtO_2$ measurements). Third, we used the CPIS to diagnose EOVAP. A recent meta-analysis demonstrated that the CPIS had poor sensitivity (65%) and specificity (64%) [44]. However, currently, there is no gold standard definition for VAP. Finally, this study raised the question of how to avoid EOVAP, but it was not designed to address this problem. The standard guidelines for preventing VAP were followed in all cases (semi-recumbent position, on a 30° incline; intubation via an orotracheal route; monitoring the endotracheal tube cuff; endotracheal aspiration with a closed system, etc.) [17]. Moreover, during the last period of the study (starting in 2012), due to their proven efficacy in reducing VAP, we used endotracheal tubes with subglottic secretion suctioning in comatose patients admitted to the ICU [45]. This change in protocol could have biased our results by modifying the incidence of pneumonia during the study period. However, as shown in the Additional Figure, the proportion of patients that developed EOVAP

remained constant throughout the study. Our results also suggested that another potential factor that reduced the occurrence of EOVAP might be the systematic use of prophylactic antibiotics and selective digestive decontamination in patients with severe TBI. Numerous previous studies have supported this theory. Indeed, they showed that prophylactics and decontamination practices reduced the occurrence of early-onset pneumonia, and even mortality, in critically ill, comatose patients that received mechanical ventilation [46, 47]. The drawback of this practice is that it increases the risk of inducing multiresistant bacteria. However, the fact that only some patients received prophylactic antibiotics at the discretion of the provider represents another limitation of our study.

Conclusions

The present work confirmed that patients with severe TBIs had a high incidence of EOVAP. We found that the main risk factors associated with EOVAP were the use of therapeutic hypothermia, serious thoracic trauma, and gastric aspiration before intubation. In addition, our results suggested that EOVAP was associated with an unfavorable functional neurologic outcome. This effect was probably due to a deleterious effect on cerebral oxygenation, based on $PbtO_2$ measurements. These results emphasized the importance of preventing EOVAP with all means available.

Authors' Contributions PE, JB, and HB contributed to the study concept and design. PE, CN, CC, ED, AM, CJ, and JC contributed to the acquisition of data. PE, HB, AD, and JB contributed to the analysis and interpretation of data. PE, HB, PG, and EM contributed to drafting the manuscript and critically revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflicts of interest.

Ethical Approval The Institutional Review Board of the Sainte Anne Military Hospital, Toulon (France), approved the study and waived the requirement for informed consent from the patients or patient relatives, given the observational nature of the study.

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