Incidence, Risk Factors, and Effects on Outcome of Ventilator-Associated Pneumonia in Patients With Traumatic Brain Injury: Analysis of a Large, Multicenter, Prospective, Observational Longitudinal Study

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BACKGROUND: No large prospective data, to our knowledge, are available on ventilator-associated pneumonia (VAP) in patients with traumatic brain injury (TBI).

RESEARCH QUESTION: To evaluate the incidence, timing, and risk factors of VAP after TBI and its effect on patient outcome.

STUDY DESIGN AND METHODS: This analysis is of the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury data set, from a large, multicenter, prospective, observational study including patients with TBI admitted to European ICUs, receiving mechanical ventilation for ≥ 48 hours and with an ICU length of stay (LOS) ≥ 72 hours. Characteristics of patients with VAP vs characteristics of patients without VAP were compared, and outcome was assessed at 6 months after injury by using the Glasgow Outcome Scale Extended.

RESULTS: The study included 962 patients: 196 (20.4%) developed a VAP at a median interval of 5 days (interquartile range [IQR], 3-7 days) after intubation. Patients who developed VAP were younger (median age, 39.5 [IQR, 25-55] years vs 51 [IQR, 30-66] years; P < .001), with a higher incidence of alcohol abuse (36.6% vs 27.6%; P = .026) and drug abuse (10.1% vs 4.2%; P = .009), more frequent thoracic trauma (53% vs 43%; P = .014), and more episodes of respiratory failure during ICU stay (69.9% vs 28.1%; P < .001). Age (hazard ratio [HR], 0.99; 95% CI, 0.98-0.99; P = .001), chest trauma (HR, 1.4; 95% CI, 1.03-1.90; P = .033), histamine-receptor antagonist intake (HR, 2.16; 95% CI, 1.37-3.39; P = .001), and antibiotic prophylaxis (HR, 0.69; 95% CI, 0.50-0.96; P = .026) were associated with the risk of VAP. Patients with VAP had a longer duration of mechanical ventilation (median, 15 [IQR, 10-22] days vs 8 [IQR, 5-14] days; P < .001) and ICU LOS (median, 20 [IQR, 14-29] days vs 13 [IQR, 8-21] days; P < .001). However, VAP was not associated with increased mortality or worse neurological outcome. Overall mortality at 6 months was 22%.

INTERPRETATION: VAP occurs less often than previously described in patients after TBI and has a detrimental effect on ICU LOS but not on mortality and neurological outcome.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov; No: NCT02210221; URL: www.clinicaltrials.gov; CHEST 2020; ■(■):■-■

KEY WORDS: mechanical ventilation; outcome; oxygenation; traumatic brain injury; ventilator-associated pneumonia

ABBREVIATIONS: CENTER-TBI = Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury; GCS = Glasgow Coma Scale; GOSE = Glasgow Outcome Scale Extended; H2 = histamine; HR = hazard ratio; IQR = interquartile range; LOS = length of stay; PPI = proton pump inhibitor; TBI = traumatic brain injury; VAP = ventilator-associated pneumonia

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Ventilator-associated pneumonia (VAP) is defined as pneumonia acquired more than 48 hours after intubation and caused by a colonization of the upper airway followed by subsequent replication of bacteria in the lower respiratory tract. It is a common iatrogenic pulmonary infection in patients who are critically ill and receiving mechanical ventilation.

Patients with traumatic brain injury (TBI), requiring intubation and mechanical ventilation mainly for posttraumatic disorders of consciousness, are at high risk of respiratory complications. The incidence, risk factors, and association with the outcome of VAP among patients with and those without TBI vary widely among studies. Some reports suggest that VAP is associated with an increased risk for mortality, poor neurological outcome, and increased hospital and ICU and length stay (LOS). However, there is substantial uncertainty regarding the incidence and risk factors for VAP development and whether they affect outcome in the specific population of patients with TBI. We therefore conducted a preplanned secondary analysis of data from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. We aimed to investigate the incidence and timing of VAP in patients with TBI, evaluate the factors associated with its development, and examine its effect on patient outcome.

Materials and Methods

The CENTER-TBI study entails a longitudinal prospective collection of TBI data in patients across 63 centers in Europe between December 19, 2014, and December 17, 2017. The CENTER-TBI study was conducted in accordance with the amended Declaration of Helsinki, and it was approved by the medical ethics committees of all participating centers. Informed consent was obtained according to local regulations.

For this study, we selected from the CENTER-TBI cohort patients with a clinical diagnosis of TBI and indication for brain CT scanning, who were admitted to the ICU within 24 hours after injury, who underwent intubation, who received mechanical ventilation for ≥ 48 hours, and who had an ICU LOS ≥ 72 hours. VAP was defined by treating physicians on the basis of the radiologic presence of pulmonary infiltration and clinical symptoms or signs (such as fever, leukocytosis, purulent secretions, or hypoxemia) during mechanical ventilation support for ≥ 48 hours. Pathogens were defined and isolated from endotracheal aspirates or BAL fluids.

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risk for the first occurrence of VAP in the ICU. Furthermore, we
described the different behavior of the PaO₂/FIO₂ ratio, PaCO₂, and
temperature variables on the day after VAP occurrence by using a
linear mixed model for longitudinal data, with a random intercept
for the subject to account for multiple measurements. In this model,
we considered as predictors of the aforementioned values the time
since intubation, the VAP diagnosis (as a time-dependent variable),
and the interaction between these two variables.

The Kaplan-Meier method was used to estimate overall mortality.
Finally, we evaluated the associations among VAP, 6-month
mortality, and GOSE, with the outcome dichotomized as favorable
or unfavorable. To adjust for covariates, we included predictors from the extended International Mission for
Prognosis and Analysis of Clinical Trials in TBI model, as defined by Lingma et al,11 which are age, GCS motor score at arrival,
pupillary reactivity, physiologic second insults (hypoxemia and
hypotension), CT scan characteristics (Marshall CT scan
classification, traumatic subarachnoid hemorrhage, and epidural
hematoma), presence of any major extracranial injury, need for
blood transfusions, hypernatremia in the first 3 days after admission,
and intracranial hypertension during the ICU stay. To evaluate the
effect of VAP on 6-month GOSE score, we performed a logistic
regression, adjusting for the same variables. Country-specific effects
have been considered in all models by adding a random effect. We
used analogous models classifying VAP as early or late27 (within and
after the sixth day after intubation, respectively) and by its severity
(PaO₂/FIO₂ < 200 and ≥ 200 on the VAP occurrence day).

To account for missing values in predictors, we used the MICE13
algorithm to multiply impute 50 sets of data with the method of
chain equations. The imputation model used all the variables that
we considered as predictors in the aforementioned models, as well as
the outcomes we targeted for analysis (ie, events indicator and the
Nelson-Aalen estimator) to avoid bias. Complete case analyses are
reported in the supplementary material. Statistical analyses were
performed using software (R version 3.6).14

Results

We included 962 patients in the final analysis. A
flowchart shows the inclusion criteria (Fig 1).

Incidence, characteristics, and timing of VAP in the
population with TBI

There were 196 patients with VAP on a total of
9,204 days at risk of VAP, resulting in an overall rate of
21 VAPs per 1,000 ventilator days. The crude
cumulative incidence at 70 days from intubation was
20.4%, and it is reported in Figure 2 as the red-shaded
area (VAP or death or discharge after VAP). The
median interval for VAP occurrence was 5 days after
ICU admission (IQR, 3-7) (e-Fig 1), with the last
occurrence observed after 35 days of mechanical
ventilation.

The probability of being in the ICU with VAP increased
in the first 10 days and then progressively decreased. This
pattern was attributable to the fact that after day 7 some
of the patients who had developed VAP had improved
and started to be discharged, mainly alive and cured, as
described in the transition probabilities plot describing
the probability over time of patients who had undergone
intubation to be in the ICU with or without VAP (Fig 2).

Among the 196 patients with VAP, the most common
pathogen isolated was Staphylococcus aureus (80 cases
[40.8%]), followed by Haemophilus influenzae (47 cases
[24.0%]), and Streptococcus pneumoniae (16 cases
[8.2%]). Lower incidence was found for Pseudomonas
aeruginosa (7.7%), Klebsiella pneumoniae (7.7%),
Escherichia coli (7.1%), Klebsiella oxytoca (5.1%), and
Candida albicans (5.1%).

Figure 1 – Flowchart for the definition of patient inclusion criteria in our study. VAP = ventilator-associated pneumonia.
Daily trends of the PaO2/FIO2 ratio and PaCO2 values in patients who developed VAP after intubation are presented in Figure 3. Longitudinal analysis showed a reduction of the PaO2/FIO2 ratio of 70.9 mm Hg (P < .001) on the day of VAP diagnosis, followed by an increase in the following days (4.2 mm Hg per day; P < .001). In e-Figure 2, we also reported the PaO2/FIO2 course in patients with and those without VAP. On the day of VAP diagnosis, seven patients (5%) presented with PaO2/FIO2 < 100, and 32 (23.4%) presented with PaO2/FIO2 < 150. However, the occurrence of VAP did not modify PaCO2 values significantly (P = .15).

Factors associated with VAP development

Baseline characteristics of the patients who developed or did not develop VAP during ICU LOS are presented in Table 1. Patients with VAP were more often male (83.7% vs 73.4%; P = .004), younger (median age, 39.5 years vs 51 years; P < .0001), and in a more neurologically severe state at arrival (GCS ≤ 8 75.1% vs 66.3%; P = .028), with a higher incidence of chest trauma (53.1% vs 43.0%; P = .014) and a more frequent history of alcohol or drug abuse (36.6% vs 27.6%; P = .026 and 10.1% vs 4.2%; P = .009, respectively). No differences were found between the two groups regarding preinjury status, comorbidities, neuroimaging features, and pupillary reactivity.

Overall, a total of 682 patients (70.9%) received antibiotic prophylaxis within the first 48 hours after admission; nearly one-half of them received cephalosporin (319 patients) (e-Table 2). Antibiotic prophylaxis was less common in the VAP group (66.3% vs 72.1%; P = .136), even though the difference did not reach statistical significance (Table 1). Patients who developed VAP compared with those who did not develop VAP more frequently received H2-receptor antagonists (41.5% vs 26.5%; P < .001) and less frequently PPI (43.6% vs 54.4%; P = .011). e-Table 3 shows the medications administrated during the ICU stay in patients with and those without VAP.

Age, chest trauma, antibiotic prophylaxis, and H2-receptor antagonist intake were associated independently with the risk of VAP occurrence (Table 2); complete cases are shown in e-Table 4. In particular, the hazard ratio (HR) of developing VAP in patients with thoracic trauma was 37% higher, and the administration of H2-receptor antagonists increased the risk of VAP by 95%. Conversely, antibiotic prophylaxis in the first 48 hours reduced the hazard of VAP by 30%. Finally, increasing age was associated inversely with the risk of developing VAP, with a decrease in incidence of 12% per decade. Results were consistent when the same model was fitted on the whole population of patients who were admitted to the ICU and underwent intubation.

Differences across countries

The incidence of VAP ranged from 40% (country 1) to 2% (country 12) among the countries that participated in the CENTER-TBI study (Fig 4). Dichotomizing countries with an incidence of VAP > or ≤ 30%, we found substantial differences in different factors, including age, Injury Severity Score, Therapy Intensity Level, fluid balance, and use of hypothermia and vasopressors (e-Table 5).

VAP effects on patient outcomes

Patients with VAP had a longer duration of mechanical ventilation (median, 15 [IQR, 10-22] days vs 8 [IQR, 5-14] days; P < .001) and ICU LOS (median, 20 [IQR, 14-29] days vs 13 [IQR, 8-21] days; P < .001). Overall mortality at 6 months was 0.22 (95% CI, 0.20-0.25).
Survival estimates of patients with and those without VAP are reported in e-Figure 3.

Mortality in the ICU was lower for patients who experienced VAP (13 [6.6%] vs 121 [15.8%] deaths) (e-Table 6), also after adjusting for possible confounding factors (HR, 0.48; 95% CI, 0.30-0.76; P = .022). During the overall 6-month follow-up, we observed 27 (16%) deaths in the VAP group and 174 (22.7%) in the other group. After adjusting for confounding factors, we found that the occurrence of VAP was not associated with an increase in mortality (HR, 0.73; 95% CI, 0.53-1.0; P = .18). We observed 89 patients (53%) with poor neurological outcome at 6 months in the VAP group and 174 (22.7%) in the other group. After adjusting for confounding factors, we found that the occurrence of VAP was not associated with an increase in mortality (HR, 0.73; 95% CI, 0.53-1.0; P = .18). We observed 89 patients (53%) with poor neurological outcome at 6 months with respect to subjects who did not experience VAP, and mild VAP with PaO2/FIO2 ≥ 200 (n = 74) had an OR of 1.29 (95% CI, 0.72-2.32; P = .398).

Discussion

VAP is a common iatrogenic pulmonary infection in patients who are critically ill and receiving mechanical ventilation. To our knowledge, the literature provides no large prospective study exploring the incidence of and risk factors for VAP development in patients with TBI. Moreover, the effect of VAP on long-term outcome still is debated. We tried to address these issues in prospectively collected data from a large cohort of patients with TBI.

The key findings from our study are that the incidence of VAP in patients with TBI admitted to ICU and receiving mechanical ventilation is less common than in previously described series and meta-analyses.15 Alcohol and drug abuse, as well as the energy of trauma, may increase VAP occurrence after trauma. The risk factors associated with VAP development include young age, chest trauma, H2-receptor antagonist intake, and no antibiotic prophylaxis. A high heterogeneity in VAP development exists among countries across Europe.

Figure 3 – Box plots of the PaO2 values, PaO2/FIO2 ratio, and PaCO2 values in patients who developed VAP after intubation. Only values regarding 1 week before and 2 weeks after the VAP diagnosis are considered. See Figure 1 legend for expansion of abbreviation.
**TABLE 1**  Baseline Characteristics of the Study Population, With VAP Diagnosis Taken Into Consideration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (n = 766)</th>
<th>Yes (n = 196)</th>
<th>P Value</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td></td>
<td></td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>562 (73.4)</td>
<td>164 (83.7)</td>
<td>.004</td>
<td>0</td>
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<td>Smoking, No. (%)</td>
<td>190 (33.9)</td>
<td>54 (33.3)</td>
<td>.963</td>
<td>240 (24.9)</td>
</tr>
<tr>
<td>Preinjury ASAPS classification, No. (%)</td>
<td>...</td>
<td>...</td>
<td>.586</td>
<td>50 (5.2)</td>
</tr>
<tr>
<td>Healthy patient</td>
<td>417 (57.5)</td>
<td>114 (61.0)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Patient with mild systemic disease</td>
<td>234 (32.3)</td>
<td>53 (28.3)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Patient with severe systemic disease</td>
<td>74 (10.2)</td>
<td>20 (10.7)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Previous TBI, No. (%)</td>
<td>46 (6.8)</td>
<td>15 (8.7)</td>
<td>.488</td>
<td>116 (12.1)</td>
</tr>
<tr>
<td>Use of anticoagulants, No. (%)</td>
<td>42 (5.9)</td>
<td>3 (1.6)</td>
<td>.030</td>
<td>61 (6.3)</td>
</tr>
<tr>
<td>Use of antiplatelets, No. (%)</td>
<td>190 (33.9)</td>
<td>54 (33.3)</td>
<td>.963</td>
<td>240 (24.9)</td>
</tr>
<tr>
<td>Alcohol involvement, No. (%)</td>
<td>66 (9.2)</td>
<td>12 (6.5)</td>
<td>.030</td>
<td>61 (6.3)</td>
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<tr>
<td>Drug involvement, No. (%)</td>
<td>184 (27.6)</td>
<td>36 (36.6)</td>
<td>.026</td>
<td>123 (12.8)</td>
</tr>
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<td>Hypoxia, No. (%)</td>
<td>129 (18.1)</td>
<td>31 (17.3)</td>
<td>.888</td>
<td>71 (7.4)</td>
</tr>
<tr>
<td>Hypotension, No. (%)</td>
<td>127 (17.6)</td>
<td>34 (19.2)</td>
<td>.694</td>
<td>63 (6.5)</td>
</tr>
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<td>Any major extracranial injury, No. (%)</td>
<td>489 (63.8)</td>
<td>133 (67.9)</td>
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</tr>
<tr>
<td>Face</td>
<td>216 (28.2)</td>
<td>53 (27.0)</td>
<td>.816</td>
<td>0</td>
</tr>
<tr>
<td>Chest</td>
<td>329 (43.0)</td>
<td>104 (53.1)</td>
<td>.014</td>
<td>0</td>
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<tr>
<td>Abdomen or pelvis</td>
<td>162 (21.1)</td>
<td>45 (23.0)</td>
<td>.651</td>
<td>0</td>
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<tr>
<td>Extremities</td>
<td>151 (19.7)</td>
<td>37 (18.9)</td>
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<tr>
<td>External</td>
<td>25 (3.3)</td>
<td>9 (4.6)</td>
<td>.495</td>
<td>0</td>
</tr>
<tr>
<td>Spine</td>
<td>171 (22.3)</td>
<td>45 (23.0)</td>
<td>.925</td>
<td>0</td>
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<tr>
<td>Intubation after ICU admission, No. (%)</td>
<td>690 (90.1)</td>
<td>181 (92.3)</td>
<td>.406</td>
<td>0</td>
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<tr>
<td>Marshall score, No. (%)</td>
<td></td>
<td></td>
<td>.615</td>
<td>145 (15.1)</td>
</tr>
<tr>
<td>I</td>
<td>40 (6.1)</td>
<td>10 (6.2)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>288 (44.0)</td>
<td>64 (39.5)</td>
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<td>III</td>
<td>70 (10.7)</td>
<td>21 (13.0)</td>
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<tr>
<td>IV</td>
<td>11 (1.7)</td>
<td>3 (1.9)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>2 (0.3)</td>
<td>2 (1.2)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>244 (37.3)</td>
<td>62 (38.3)</td>
<td>...</td>
<td></td>
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<td>GCS arrival ≤ 8, No. (%)</td>
<td>477 (66.3)</td>
<td>139 (75.1)</td>
<td>.028</td>
<td>58 (6.0)</td>
</tr>
<tr>
<td>GCS motor score at ED arrival, No. (%)</td>
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<td>...</td>
<td>.029</td>
<td>23 (2.4)</td>
</tr>
<tr>
<td>None</td>
<td>328 (43.9)</td>
<td>79 (41.1)</td>
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<td>Abnormal extension</td>
<td>37 (5.0)</td>
<td>9 (4.7)</td>
<td>...</td>
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<tr>
<td>Abnormal flexion</td>
<td>36 (4.8)</td>
<td>20 (10.4)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Normal flexion or withdrawal</td>
<td>72 (9.6)</td>
<td>19 (9.9)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Localizes to pain</td>
<td>148 (19.8)</td>
<td>44 (22.9)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Obey command</td>
<td>126 (16.9)</td>
<td>21 (10.9)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis, No. (%)</td>
<td>552 (72.1)</td>
<td>130 (66.3)</td>
<td>.136</td>
<td>0</td>
</tr>
<tr>
<td>H2-receptor antagonist,a No. (%)</td>
<td>180 (24.8)</td>
<td>77 (41)</td>
<td>&lt; .001</td>
<td>48 (5.0)</td>
</tr>
<tr>
<td>PPI,a No. (%)</td>
<td>395 (54.4)</td>
<td>82 (43.6)</td>
<td>.011</td>
<td>48 (5.0)</td>
</tr>
</tbody>
</table>

(Continued)
with a more severe neurological presentation at arrival, energy trauma and a high incidence of chest trauma, Patients with VAP were younger, probably because they criteria and treatment policies used for VAP. Our prospectively collected data show that VAP is less mechanical ventilation and are admitted to the ICU, and with large variations among studies and countries. Our association of VAP with thoracic trauma may be a ventilation, with an incidence ranging from 10% to 40%, and with large variations among studies and countries. Authors in several studies also suggest that VAP adversely affects mortality. A study attempting to control for confounding biases demonstrated a VAP-attributable mortality slightly higher than 10%. In patients with severe TBI who are receiving mechanical ventilation and are admitted to the ICU, VAP seems to occur even more frequently, reaching an incidence of up to 60%. In some studies, VAP has been associated independently with unfavorable neurological outcome. A recently published meta-analysis reported a pooled incidence of VAP of 36% (95% CI, 31%-41%) and an association with VAP occurrence and mechanical ventilation duration (OR, 5.45; 95% CI, 3.78-7.12), ICU LOS (OR, 6.85; 95% CI, 4.90-8.79), and hospital LOS (OR, 10.92; 95% CI, 9.12-12.72) but not with higher mortality. Our prospectively collected data show that VAP is less common than the previously reported incidence in patients with TBI but confirm that its occurrence can increase the duration of mechanical ventilation and ICU LOS by nearly a week. The lower incidence found in the cohort in our study and the wide variability among different centers may reflect the different diagnostic criteria and treatment policies used for VAP.

Patients with VAP were younger, probably because they are admitted after road traffic accidents with high-energy trauma and a high incidence of chest trauma, with a more severe neurological presentation at arrival, and with a higher incidence of drug and alcohol abuse. Variation in these factors may explain (at least in part) between-country differences in rates of VAP and underline the importance of preinjury and in-hospital factors. We found that countries with a higher incidence of VAP had higher use of drugs and alcohol as risk factors for low GCS scores and aspiration; a higher severity of trauma (Injury Severity Score); and more aggressive ICU treatments, such as Therapy Intensity Level, vasopressors, transfusions, and more positive fluid balance.

The association of VAP with thoracic trauma may be a marker of trauma severity and consequent poor secretion clearance, airway bleeding, and more difficult ventilator management and weaning. These findings help confirm, on a larger scale, data from previous smaller studies in TBI, which reported an increased risk of VAP with thoracic injury.

In the cohort in our study, antibiotic prophylaxis within the first 48 hours after admission was common, and it was independently associated with a reduced hazard of VAP occurrence by 30%. Although the prophylactic administration of antibiotics has been recommended by several authors, evidence for the intervention is inconsistent, and it is not currently standard of care practice because of concerns that it may induce bacterial resistance and that the risks of antibiotic prophylaxis might outweigh the benefits. The association we highlight does not conclusively show benefit but underlines the need for a better understanding of the pathogens that cause VAP in this population, as well as definition of rational antibiotic protocols that allow effective treatment while minimizing the risk of emerging resistance. On these bases, the European guidelines for the management of VAP suggest that empirical treatment with narrow-spectrum antibiotics should be based on individual cases, taking into consideration the risks, clinical status, country, and type of pathogens detected in the ICU.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VAP No (n = 766)</th>
<th>VAP Yes (n = 196)</th>
<th>P Value</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates,* No. (%)</td>
<td>189 (25.8)</td>
<td>53 (27.2)</td>
<td>.770</td>
<td>35 (3.6)</td>
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<tr>
<td>Hypothermia,* No. (%)</td>
<td>112 (15.3)</td>
<td>40 (20.5)</td>
<td>.101</td>
<td>35 (3.6)</td>
</tr>
<tr>
<td>Transfusions,* No. (%)</td>
<td>287 (37.5)</td>
<td>74 (37.8)</td>
<td>&gt; .999</td>
<td>0</td>
</tr>
</tbody>
</table>

ASAPS = American Society of Anesthesiologists Physical Status; GCS = Glasgow Coma Scale; H2 = histamine; IQR = interquartile range; PPI = proton pump inhibitor; TBI = traumatic brain injury; VAP = ventilator-associated pneumonia.

*First 3 days after admission.
We also found that H₂-receptor antagonists were administered more frequently in patients who developed VAP, thus suggesting an association between H₂-receptor antagonists and development of VAP. This association is debated even if there is some evidence suggesting that stress ulcer prophylaxis may increase VAP risk in the general ICU population. Our results in this context are in keeping with a long-standing recognition that H₂-blockers also may increase the rates of pneumonia in patients who are hospitalized, probably through increased gastric colonization in a less acid environment.36-38

Furthermore, our results suggest that VAP has an important effect on systemic oxygenation but not on CO₂ values, with a transient reduction of 70 mm Hg in the PaO₂/FIO₂ ratio once VAP has developed. However, PaO₂ values remained within an acceptable range, and the development of VAP had no effect on PaCO₂ values, which may account for a lack of effect on intracranial pressure and neurological outcome.

Finally, we found no association between VAP and mortality or neurological outcome. Our results are in agreement with those of a recent meta-analysis.15 Taken together, the severity of VAP in the cohort in our study appears to be low, with only 46% of patients with a PaO₂/FIO₂ ratio < 200 mm Hg and with no important consequences for oxygenation, CO₂, or cerebral perfusion pressure. VAP may be only a transitory

<table>
<thead>
<tr>
<th>Characteristic (n = 962)</th>
<th>VAP, No. (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>...</td>
<td>0.99 (0.98-0.99)</td>
<td>.001</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 164 (22.6)</td>
<td>1.47 (1.0-2.16)</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>Female 32 (13.6)</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td>Chest trauma</td>
<td>Yes 104 (24)</td>
<td>1.40 (1.03-1.9)</td>
<td>.033</td>
</tr>
<tr>
<td></td>
<td>No 92 (17.4)</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td>Antibiotic prophylaxis</td>
<td>Yes 130 (19.1)</td>
<td>0.69 (0.50-0.96)</td>
<td>.026</td>
</tr>
<tr>
<td></td>
<td>No 66 (23.6)</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td>H₂-receptor antagonist intake⁹</td>
<td>Yes 78 (28.8)</td>
<td>2.16 (1.37-3.39)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>No 110 (17.1)</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td>GCS at arrival ≤ 8</td>
<td>Yes 139 (22.6)</td>
<td>1.03 (0.73-1.47)</td>
<td>.858</td>
</tr>
<tr>
<td></td>
<td>No 46 (16)</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td>Alcohol involved</td>
<td>Yes 63 (25.5)</td>
<td>1.19 (0.86-1.65)</td>
<td>.285</td>
</tr>
<tr>
<td></td>
<td>No 109 (18.4)</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td>PPI intake⁹</td>
<td>Yes 82 (17.2)</td>
<td>0.87 (0.60-1.28)</td>
<td>.483</td>
</tr>
<tr>
<td></td>
<td>No 106 (24.3)</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td>Barbiturate intake⁹</td>
<td>Yes 53 (21.9)</td>
<td>1.21 (0.90-1.71)</td>
<td>.271</td>
</tr>
<tr>
<td></td>
<td>No 142 (20.7)</td>
<td>1.00</td>
<td>...</td>
</tr>
<tr>
<td>Hypothermia⁹</td>
<td>Yes 40 (26.3)</td>
<td>0.82 (0.56-1.18)</td>
<td>.286</td>
</tr>
<tr>
<td></td>
<td>No 155 (20)</td>
<td>1.00</td>
<td>...</td>
</tr>
</tbody>
</table>

The number of events, hazard ratios, and CIs are reported, along with the associated P value. The model estimation was performed after the multiple imputation procedure. See Table 1 legend for expansion of abbreviations.

⁹First 3 days after admission.
The main limitation of our study is its observational design. Our results describe associations between different factors but provide no information about causality. However, the generalizability of our results is underpinned by the size and the multicenter and multinational nature of the CENTER-TBI study, which included 52 centers across Europe. Second, the first aim of the CENTER-TBI study was to describe the neurocritical care clinical practice regarding the management of TBI. Extracranial complications, and in particular VAP, are a secondary analysis. As a consequence, several data items are missing or lack precision. In particular, data are lacking on diagnosis of VAP or unmeasured confounding variables such as selective digestive decontamination, oral decontamination, use of PPIs, type of endotracheal tubes, time of isolation of different pathogens, resistance patterns of isolated pathogens, compliance with spontaneous awakening trials and spontaneous breathing trials, as well as the occurrence of aspiration pneumonia.

To overcome all these limitations, we used a very strict statistical plan, with a multiple imputation approach, excluding in the first instance patients with missing information on the care bundles used, as well as intubation start or stop dates or early mortality. However, a sensitivity analysis in which we included all patients admitted to the ICU produced concordant results (e-Table 7). Also, our analysis includes patients with chest trauma, which is a known risk factor for VAP and could be a significant confounding factor. However, we included chest trauma in the multivariate model as a confounding factor, allowing us to explore the effect of other risk factors more effectively.

Third, the number of patients receiving an antibiotic in the first 10 days after intubation or before VAP is much greater than in other studies on the subject. This difference could explain the low incidence of VAP in the cohort in our study. Finally, in our study we studied only clinical risk factors and did not take into consideration pathophysiologic biological mechanisms, such as impaired immune function, which often occurs after brain injury.

Conclusions

VAP occurs less than previously described in patients who have undergone intubation after TBI and occurs in the first few days after ICU admission. The development of VAP did not have a detrimental effect on mortality and neurological outcome but prolonged ICU LOS and the duration of mechanical ventilation. ICU therapies appear to modulate the incidence of VAP, which is more frequent in patients given H2-blockers and less frequent in those receiving antibiotic prophylaxis. Further studies and randomized controlled trials are warranted to confirm and extend our understanding of risk factors for the development of VAP, promptly detect patients at risk of VAP, and explore the effect of early antimicrobial therapy in its prevention.
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The data supporting the findings in this study are available on reasonable request from the senior author (G. C.) and are stored at https://center-tbi.incf.org/_5cf4dbd0560bb0102b6b28c; data on vital values, at https://center-tbi.incf.org/_5cf4dcd950bb0102b6b28f; and data regarding medications, at https://center-tbi.incf.org/_5cf4d9e560bb0102b6b299.

The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.
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