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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.

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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; H_2 = 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.[1-3] It is a common iatrogenic pulmonary infection in patients who are critically ill and receiving mechanical ventilation.[4]

Patients with traumatic brain injury (TBI), requiring intubation and mechanical ventilation mainly for posttraumatic disorders of consciousness, are at high risk of respiratory complications.[1,2] The incidence, risk factors, and association with the outcome of VAP among patients with and those without TBI vary widely among studies.[1-4] 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).[5,6] 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.[7] We therefore conducted a preplanned secondary analysis of data from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study.[8] 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.[8]

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, andwho 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.

Care bundles for the prevention and treatment of VAP, as well as general clinical care, antibiotic prophylaxis, and treatment principles were based on local policies. Hypoxemia was defined as a documented PaO_2 < 8 kPa (60 mm Hg) and/or oxygen saturation < 90%; hypotension was defined as a documented systolic BP < 90 mm Hg. Details regarding data collection and extraction have been described previously.[9]

Patients' functional outcome was assessed using the Glasgow Outcome Scale Extended (GOSE)[10] at 6 months. An unfavorable outcome was defined as GOSE ≤ 4, which includes both mortality and dependent survival. We also evaluated the ICU and hospital LOS.

This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines (https://www.strobe-statement.org/index.php?id=strobe-home) (e-Table 1). The project was preregistered into the CENTER-TBI proposal platform in December 2018 and approved (e-Appendix 1) before analysis was started.

Baseline characteristics of patients are shown distinguishing between patients who developed VAP and those who did not. Continuous variables are reported as median and interquartile ranges (IQRs) and numbers and percentages for categorical variables. To assess differences between the two groups, we used the Fisher χ^2 test for categorical variables and the Kruskal-Wallis rank sum test for the continuous ones.

Multivariable Cox regression analysis was performed to model the cause-specific hazard of the first episode of VAP. Age, sex, presence of thorax or chest trauma, antibiotic prophylaxis, histamine (H_2)-receptor antagonist, barbiturate and proton pomp inhibitor (PPI) intake, hypothermia, Glasgow Coma Scale (GCS) at arrival, and alcohol involved were added to the model as predictive variables. These variables were selected according to the literature and for clinical reasons. The time of VAP occurrence was defined as the difference between the day of VAP diagnosis and the day of intubation. Patients were censored at the time of extubation, death, or ICU discharge, whichever occurred first.

To describe VAP incidence and ICU LOS, we performed a multistate analysis to account for competing risks and to obtain the transition hazards for each of the possible transitions, defined as intubation, VAP, discharge after intubation, death after intubation, discharge after VAP, and death after VAP. We also estimated the VAP rate as the number of VAPs divided by the time spent under intubation at

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risk for the first occurrence of VAP in the ICU. Furthermore, we described the different behavior of the PaO_2/FIO_2 ratio, $PaCO_2$, and body temperature values before and 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 (GOSE $\geq$ 5) or unfavorable (GOSE $\leq$ 4). We first performed a multivariable Cox regression analysis to assess the effect of VAP on ICU and 6-month mortality, treating VAP as a time-dependent variable, to avoid immortal time bias. 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 Lingsma 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 late[12] (within and after the sixth day after intubation, respectively) and by its severity ($PaO_2/FIO_2 < 200$ and ≥ 200 on the VAP occurrence day).

To account for missing values in predictors, we used the MICE[13] algorithm to multiply impute 50 sets of data with the method of chained 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%).

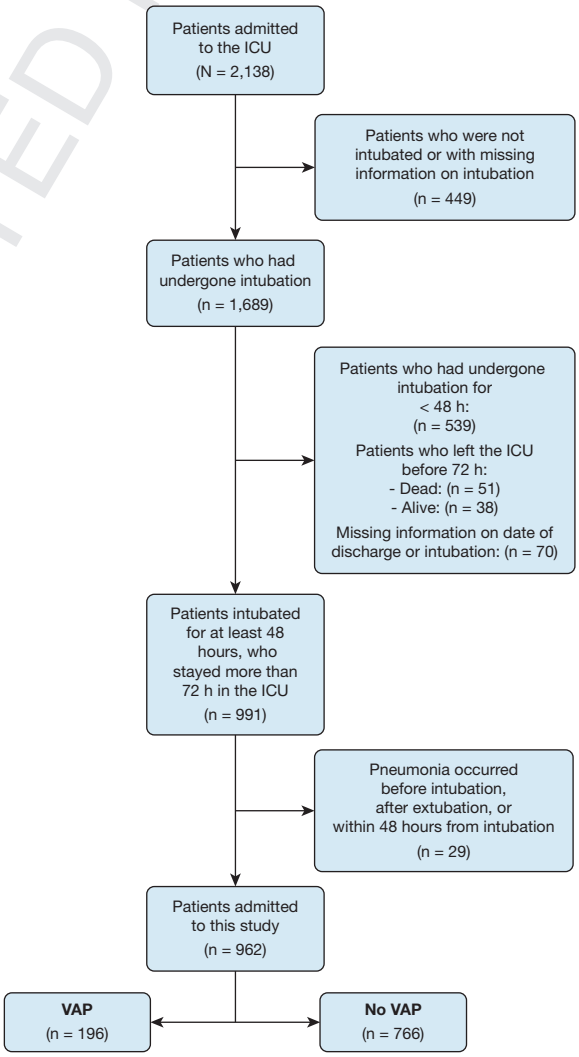

Figure 1 – *Flowchart for the definition of patient inclusion criteria in our study. VAP = ventilator-associated pneumonia.*

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Daily trends of the PaO_2/FIO_2 ratio and $PaCO_2$ values in patients who developed VAP after intubation are presented in Figure 3. Longitudinal analysis showed a reduction of the PaO_2/FIO_2 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 PaO_2/FIO_2 course in patients with and those without VAP. On the day of VAP diagnosis, seven patients (5%) presented with $PaO_2/FIO_2 < 100$, and 32 (23.4%) presented with $PaO_2/FIO_2 < 150$. However, the occurrence of VAP did not modify $PaCO_2$ 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.

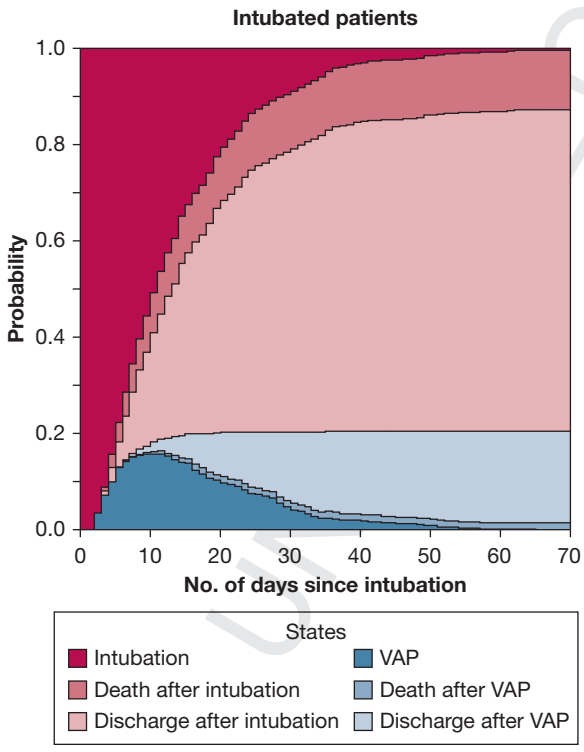

Figure 2 – *Overall transition probabilities of patients who had undergone intubation. The x-axis indicates the time since intubation, and the y-axis indicates the probability of being in one of the possible states. In particular, the red-shaded area represents the cumulative incidence of VAP. See Figure 1 legend for expansion of abbreviation.*

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 H_2-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 H_2-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 H_2-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).

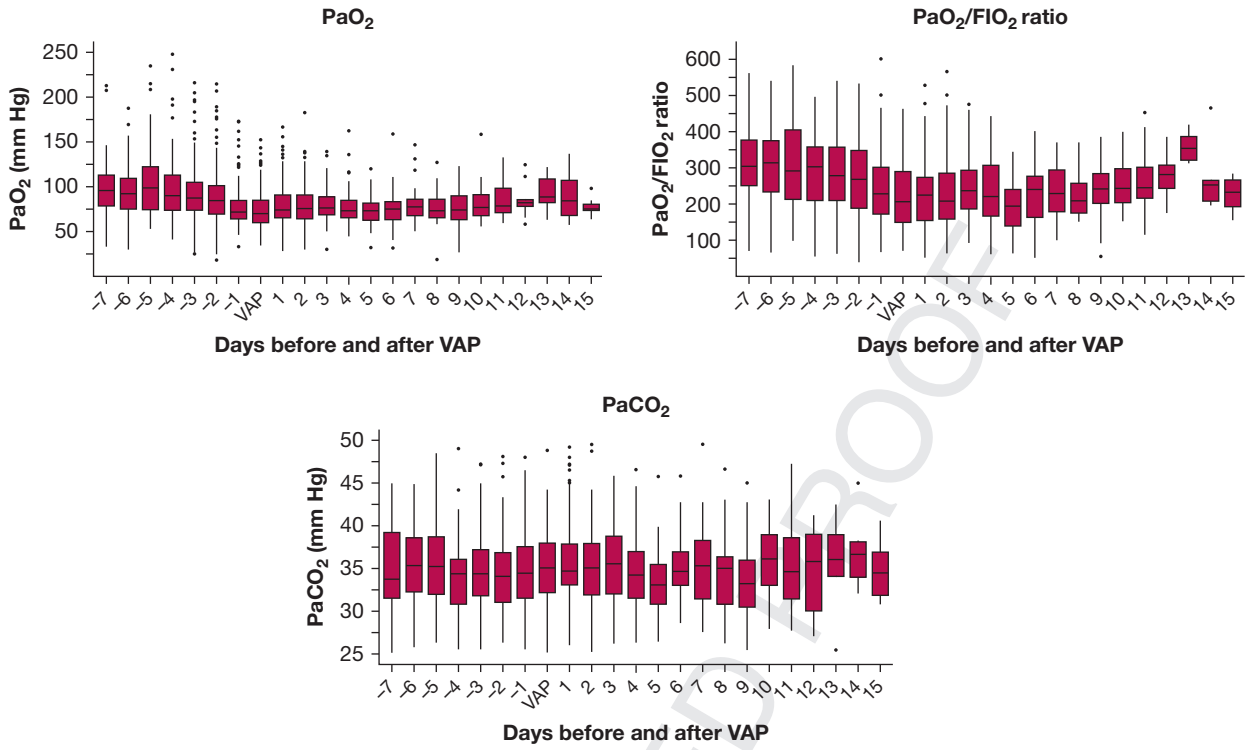

Figure 3 – *Box plots of the PaO_2 values, PaO_2/FIO_2 ratio, and $PaCO_2$ values in patients who developed VAP after intubation. Only values regarding 1 week before and 2 weeks after the VAP diagnosis are considered. See Figure 1 legend for expansion of abbreviation.*

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 377 (57%) in the other group (OR, 0.98; 95% CI, 0.66-1.46; $P = .923$ after adjusting) (e-Table 6). Results were consistent when the same model was fitted on the whole population of patients admitted to the ICU (e-Table 7). No effect on neurological outcome was detected when classifying VAP as early (n = 139 VAP from day 3 to 6; OR, 0.98; 95% CI, 0.63-1.55; $P = .94$) or late (n = 57 from day 7; OR, 0.98; 95% CI, 0.50-1.89; $P = .942$). When classifying VAP according to its severity, results were consistent: Moderate or severe VAP with $PaO_2/FIO_2 < 200$ (n = 63) had an OR of 0.83 (95% CI, 0.44-1.58; $P = .572$) of having a poor neurological outcome at 6 months with respect to subjects who did not experience VAP, and mild VAP with $PaO_2/FIO_2 \geq 200$ (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, H_2-receptor antagonist intake, and no antibiotic prophylaxis. A high heterogeneity in VAP development exists among countries across Europe.

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TABLE 1] Baseline Characteristics of the Study Population, With VAP Diagnosis Taken Into Consideration

Characteristic	VAP		*P* Value	Missing
	No (n = 766)	Yes (n = 196)		
Age, median (IQR), y	51 (30.2, 66)	39.5 (25, 55)	< .001	0
Male, No. (%)	562 (73.4)	164 (83.7)	.004	0
Smoking, No. (%)	190 (33.9)	54 (33.3)	.963	240 (24.9)
Preinjury ASAPS classification, No. (%)	…	…	.586	50 (5.2)
Healthy patient	417 (57.5)	114 (61.0)	…	…
Patient with mild systemic disease	234 (32.3)	53 (28.3)	…	…
Patient with severe systemic disease	74 (10.2)	20 (10.7)	…	…
Previous TBI, No. (%)	46 (6.8)	15 (8.7)	.488	116 (12.1)
Use of anticoagulants, No. (%)	42 (5.9)	3 (1.6)	.030	61 (6.3)
Use of antiplatelets, No. (%)	66 (9.2)	12 (6.5)	.303	61 (6.3)
Alcohol involvement, No. (%)	184 (27.6)	63 (36.6)	.026	123 (12.8)
Drug involvement, No. (%)	25 (4.2)	15 (10.1)	.009	221 (23.0)
Pupillary reactivity, No. (%)	…	…	.580	53 (5.5)
Both reacting	549 (76.2)	150 (79.4)	…	…
Both unreacting	106 (14.7)	26 (13.8)	…	…
One reacting	65 (9.0)	13 (6.9)	…	…
Hypoxia, No. (%)	129 (18.1)	31 (17.3)	.888	71 (7.4)
Hypotension, No. (%)	127 (17.6)	34 (19.2)	.694	63 (6.5)
Any major extracranial injury, No. (%)	489 (63.8)	133 (67.9)	.334	0
Face	216 (28.2)	53 (27.0)	.816	0
Chest	329 (43.0)	104 (53.1)	.014	0
Abdomen or pelvis	162 (21.1)	45 (23.0)	.651	0
Extremities	151 (19.7)	37 (18.9)	.871	0
External	25 (3.3)	9 (4.6)	.495	0
Spine	171 (22.3)	45 (23.0)	.925	0
Intubation after ICU admission, No. (%)	690 (90.1)	181 (92.3)	.406	0
Marshall score, No. (%)			.615	145 (15.1)
I	40 (6.1)	10 (6.2)	…	…
II	288 (44.0)	64 (39.5)	…	…
III	70 (10.7)	21 (13.0)	…	…
IV	11 (1.7)	3 (1.9)	…	…
V	2 (0.3)	2 (1.2)	…	…
VI	244 (37.3)	62 (38.3)	…	…
GCS arrival ≤ 8, No. (%)	477 (66.3)	139 (75.1)	.028	58 (6.0)
GCS motor score at ED arrival, No. (%)	…	…	.029	23 (2.4)
None	328 (43.9)	79 (41.1)	…	…
Abnormal extension	37 (5.0)	9 (4.7)	…	…
Abnormal flexion	36 (4.8)	20 (10.4)	…	…
Normal flexion or withdrawal	72 (9.6)	19 (9.9)	…	…
Localizes to pain	148 (19.8)	44 (22.9)	…	…
Obeys command	126 (16.9)	21 (10.9)	…	…
Antibiotic prophylaxis, No. (%)	552 (72.1)	130 (66.3)	.136	0
H_2-receptor antagonist,[a] No. (%)	180 (24.8)	77 (41)	< .001	48 (5.0)
PPI,[a] No. (%)	395 (54.4)	82 (43.6)	.011	48 (5.0)

(Continued)

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TABLE 1] *(Continued)*

Characteristic	VAP		*P* Value	Missing
	No (n = 766)	Yes (n = 196)		
Barbiturates,[a] No. (%)	189 (25.8)	53 (27.2)	.770	35 (3.6)
Hypothermia,[a] No. (%)	112 (15.3)	40 (20.5)	.101	35 (3.6)
Transfusions,[a] No. (%)	287 (37.5)	74 (37.8)	> .999	0

ASAPS = American Society of Anesthesiologists Physical Status; GCS = Glasgow Coma Scale; H_2 = histamine; IQR = interquartile range; PPI = proton pump inhibitor; TBI = traumatic brain injury; VAP = ventilator-associated pneumonia.
[a]First 3 days after admission.

VAP development is not associated with increased mortality or worse neurological outcome, but it prolongs ICU LOS and mechanical ventilation duration. These results come from large database, including patients from different countries, thus making our results representative of the current knowledge about this issue.

The literature reports VAP as a frequent ICU complication in patients receiving mechanical ventilation, with an incidence ranging from 10% to 40%, and with large variations among studies and countries.[16] Authors in several studies also suggest that VAP adversely affects mortality.[17-20] A study attempting to control for confounding biases demonstrated a VAP-attributable mortality slightly higher than 10%.[20]

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.[4] 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.[15]

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.[3] 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.[4,21]

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,[22,23] evidence for the intervention is inconsistent,[24-27] 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.[28-33] On these bases, the European guidelines[34] 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.

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We also found that H_2-receptor antagonists were administered more frequently in patients who developed VAP, thus suggesting an association between H_2-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.[35] Our results in this context are in keeping with a long-standing recognition that H_2-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 CO_2 values, with a transient reduction of 70 mm Hg in the PaO_2/FIO_2 ratio once VAP has developed. However, PaO_2 values remained within an acceptable range, and the development of VAP had no effect on $PaCO_2$ 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 PaO_2/FIO_2 ratio $<$ 200 mm Hg and with no important consequences for oxygenation, CO_2, or cerebral perfusion pressure. VAP may be only a transitory

TABLE 2] Results of the Predictive Cox Model of VAP

Characteristic (n = 962)	VAP, No. (%)	Hazard Ratio (95% CI)	*P* Value
Age	…	0.99 (0.98-0.99)	.001
Sex			
Male	164 (22.6)	1.47 (1.0-2.16)	.05
Female	32 (13.6)	1.00	…
Chest trauma			
Yes	104 (24)	1.40 (1.03-1.9)	.033
No	92 (17.4)	1.00	…
Antibiotic prophylaxis			
Yes	130 (19.1)	0.69 (0.50-0.96)	.026
No	66 (23.6)	1.00	…
H_2-receptor antagonist intake[a]			
Yes	78 (28.8)	2.16 (1.37-3.39)	.001
No	110 (17.1)	1.00	…
GCS at arrival ≤ 8			
Yes	139 (22.6)	1.03 (0.73-1.47)	.858
No	46 (16)	1.00	…
Alcohol involved			
Yes	63 (25.5)	1.19 (0.86-1.65)	.285
No	109 (18.4)	1.00	…
PPI intake[a]			
Yes	82 (17.2)	0.87 (0.60-1.28)	.483
No	106 (24.3)	1.00	…
Barbiturate intake[a]			
Yes	53 (21.9)	1.21 (0.90-1.71)	.271
No	142 (20.7)	1.00	…
Hypothermia[a]			
Yes	40 (26.3)	0.82 (0.56-1.18)	.286
No	155 (20)	1.00	…

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.
[a]First 3 days after admission.

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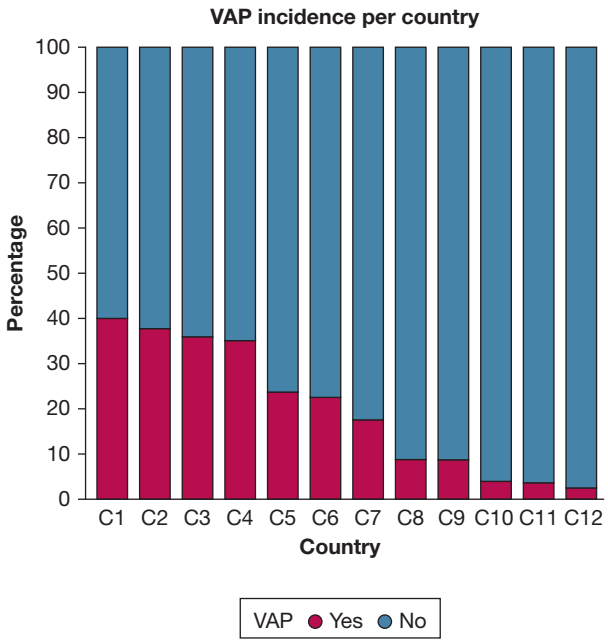

Figure 4 – *Incidence of VAP diagnosis per country. Only countries with at least 20 observations are displayed. C = country. See Figure 1 legend for expansion of abbreviation.*

phenomenon, which prolongs the acute phase of the illness (with its attendant stresses on families), but is unlikely to have an effect on outcome or mortality. Although these results might be surprising, they reflect the current state—in a nonselected population—of the occurrence of pneumonia after TBI.

Thus far, in the European setting, current antimicrobial and supportive therapies result in effective treatment in most cases, without long-term effects on patient outcome. However, the increase in LOS and mechanical ventilation duration has an effect on costs and health system resource use.[18] Therefore, better strategies aimed to prevent it are warranted, including randomized studies in the TBI cohort at higher risk with use of antibiotic prophylaxis and H_2-receptor avoidance.

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.[39-41] 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.[42]

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 H_2-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 the study are available on reasonable request from the senior author (G. C.) and are stored at https://center-tbi.incf.org/_5cf8e3d1c3b0d43708ebef42. Imaging data can be found at https://center-tbi.incf.org/_5cf4dbd0560bb01102b6b28e; data on vitals values, at https://center-tbi.incf.org/_5cf4dce9560bb01102b6b28f; and data regarding medications, at https://center-tbi.incf.org/_5cf4de0d560bb01102b6b291.

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

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