Journal of Critical Care 50 (2019) 221–226

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Effects of antibiotic prophylaxis on ventilator-associated pneumonia in severe traumatic brain injury. A post hoc analysis of two trials

Florian Reizine [a], Karim Asehnoune [b], Antoine Roquilly [b], Bruno Laviolle [c], Chloé Rousseau [c], Matthieu Arnouat [a], Claire Dahyot-Fizelier [d], Philippe Seguin [a,*]

[a] CHU Rennes, Service de Réanimation Chirurgicale, Hôpital Pontchaillou, 2 rue Henri Le Guilloux, Rennes 35000, France
[b] Département d'Anesthésie Réanimation, CHU Nantes, 1 Place Alexis-Ricordeau, Nantes 44000, France
[c] CHU de Rennes, Centre d'Investigation Clinique, 2 rue Henri Le Guilloux, Rennes 35000, France
[d] Département d'Anesthésie Réanimation, CHU Poitiers, 2 Rue de la Milétrie, Poitiers 16000, France

ARTICLE INFO

Keywords:
Ventilator-associated pneumonia
Traumatic brain injury
Antibiotic prophylaxis

ABSTRACT

Purpose: To investigate the role of antibiotic prophylaxis (AP) in the incidence of ventilator-associated pneumonia (VAP) in patients suffering from traumatic brain injury (TBI).
Materials and methods: This post hoc analysis was conducted based on data from 2 multicentre double-blind studies that aimed to prevent VAP using hydrocortisone or povidone iodine. Data from TBI patients were extracted and pooled. Patients were classified into 2 groups: those who received an AP (AP group) and those who did not (control group).
Results: 295 patients were included (AP group, n = 146; control group, n = 149). The incidence of VAP was 145 (49%). VAP incidence was lower in the AP group (39% vs 59%, Relative Risk = 0.33, 95%CI, 0.19–0.56, p = 0.001). Time to VAP occurrence was delayed (Hazard Ratio = 0.50, 95%CI 0.36–0.69, p < 0.001). The incidence of early VAP (>2 and ≤ 5 days) was lower in the AP group (10% vs 32%; p < 0.001), whereas that of late VAP (>5 days) did not differ (AP group 29% vs control group 28%; p = 0.811). Length of stay and mortality did not differ between the 2 groups.
Conclusions: Early use of AP delayed and may prevent the occurrence of VAP in severe TBI patients but did not change length of stay or mortality.

1. Introduction

Ventilator-associated pneumonia (VAP) is one of the most frequent nosocomial infections in intensive care patients, particularly in traumatic brain injury (TBI) patients, with an incidence ranging from 28 to 67% in this population [1-5]. Although its attributable mortality in trauma seems close to zero, reports have emphasized the potential deleterious effect of VAP in TBI patients [6-12]. Indeed, it has been shown that the occurrence of such an infection increases mortality, mechanical ventilation duration, intensive care and hospital length of stay [7-9]. Moreover, it was recently suggested that the occurrence of VAP may affect long-term neurologic functional outcome [10-12]. Accordingly, strategies that decrease VAP in brain trauma patients may be interesting, and antibiotic prophylaxis (AP) has been evaluated for this purpose [1,2,8,12,13]. In a study performed in 109 severe TBI patients, Bronchard et al. did not find that AP during surgery or antibiotics during the first 2 days of recovery decreased the incidence of early VAP, but a recent retrospective observational study in 175 TBI patients found that AP offered protection from early VAP [8,12]. In line with these observational studies, three trials have been published that aimed to evaluate the effect of AP in preventing VAP in comatose patients [1,2,13]. Sirvent et al. showed that cefuroxime administration was associated with a significant reduction of pneumonia in 100 comatose (Glasgow coma scale ≤12) patients [1]. In a small prospective study performed on 38 comatose patients, Acquarolo et al. investigated the effect of combined ampicillin-sulbactam delivered during the first 3 days of intensive care unit (ICU) hospitalization [13]. In the treated group, the incidence of early VAP significantly decreased, but the incidence of late VAP was not affected [13]. Similarly, Valles et al. showed that a single antibiotic dose (mainly 2 g of ceftriaxone) administered within 4 h of intubation

Abbreviations: AP, antibiotic prophylaxis; ICU, intensive care unit; TBI, traumatic brain injury; VAP, Ventilator-associated pneumonia.

* Corresponding author at: Hôpital Pontchaillou, Service d'Anesthésie Réanimation 1, Réanimation Chirurgicale, Hôpital de Pontchaillou, 2 rue Henri Le Guilloux, 35033 Rennes Cedex 9, France.
E-mail addresses: karim.asehnoune@chu-nantes.fr (K. Asehnoune), antoine.roquilly@chu-nantes.fr (A. Roquilly), bruno.laviolle@chu-rennes.fr (B. Laviolle), chloe.rousseau@chu-rennes.fr (C. Rousseau), matthieu.arnouat@chu-rennes.fr (M. Arnouat), claire.dahyot-fizelier@chu-rennes.fr (C. Dahyot-Fizelier), philippe.seguin@chu-rennes.fr (P. Seguin).

https://doi.org/10.1016/j.jcrc.2018.12.010
0883-9441/

was associated with a significant decrease in early VAP in 129 patients who had Glasgow coma scale ≤8, whereas there was no difference in late VAP incidence [2]. A recent meta-analysis including these 3 trials concluded that AP reduced the incidence of early VAP and slightly reduced ICU stay in comatose patients [14]. Nevertheless, these studies were monocentric, not blinded, and included various types of comatose patients and/or interventions aimed to prevent VAP that were not always well controlled; furthermore, one study used a historical control group [1,2,13].

Accordingly, the main objective of this study was to investigate the role of AP, administered to prevent infection at surgical sites (surgical incisions) or in cases of trauma wounds, on the incidence of VAP in patients suffering from severe TBI based on two large recent multicentre double blinded randomized studies [2,4].

2. Materials and methods

2.1. Ethics statement

The SPIRIT-ICU study (NCT00950027) protocol was approved by the Consultative Committee for the Protection of People in Biomedical Research of Rennes, and the CORTI-TC study (NCT01093261) was approved by the Consultative Committee for the Protection of People in Biomedical Research of Tours. Patients were enrolled after a next-of-kin provided written informed consent, and retrospective consent was obtained from patients when possible. As the present analysis was retrospective in nature, and according to French law, neither supplementary ethical approval nor informed consent from the patient was needed.

2.2. Subjects

We performed a retrospective analysis on 2 databases from previous trials performed in France. CORTI-TC was a multicentre double-blind, placebo-controlled trial performed in 19 ICUs evaluating the efficacy of low-dose hydrocortisone associated with fludrocortisone for the prevention of VAP in TBI patients, and the SPIRIT-ICU study was a multicentre double-blind, placebo-controlled trial performed in 6 ICUs that evaluated the efficacy and safety of oral care with povidone-iodine on the occurrence of VAP in severe brain injury patients [4,5]. The full methodology of these studies has been previously published [4,5,15]. For the present study, patients who had severe TBI in association or not with other traumatic injuries were included. The definition of severe brain injury did not differ between the 2 studies (Glasgow coma scale ≤8). The inclusion and exclusion criteria of the 2 studies are provided in supplementary file 1 (Inclusion and exclusion criteria for the SPIRIT-ICU and CORTI-TC studies). In both studies, recommended measures of prevention for VAP included semi-recumbent position and cuff pressure monitoring. The use of stress ulcer prophylaxis, selective decontamination of the digestive tract and subglottic secretion drainage was left to the discretion of the physician and reported. Patients who received curative antibiotic treatment for an infection present at admission or occurring during ICU hospitalization but before VAP occurrence were excluded from the analysis. Antibiotic prophylaxis was defined as the systemic administration of antibiotics to prevent the occurrence of an infection at surgical sites (surgical incisions) or in cases of trauma wounds. The delay between initial trauma and AP onset as well as the duration of AP were recorded (day 1 was defined as the day of trauma). No systemic antibiotic was given to prevent VAP. The AP recommendation was based on French guidelines [16].

2.3. Objectives

The main objective was to evaluate the impact of AP on the occurrence of VAP. Patients were classified into 2 groups: those who received an AP (AP group) and those who did not receive prophylaxis (control group). We chose to exclude patients who received curative antibiotic treatment for an infection present at admission or occurring during ICU hospitalization because the antibiotics used in these indications have a broad spectrum and were administered for an extended period. For patients who experienced VAP, AP was considered only when administered before the occurrence of VAP. The diagnosis of VAP did not significantly differ between the 2 studies and had to occur at least 48 h after tracheal intubation and mechanical ventilation. Two or more of the following criteria were required: body temperature > 38 °C, purulent pulmonary secretions, leucocytosis >12,000/mL or leucopaenia <4000/mL (the level of leucocytosis and leucopaenia was >10,000/mL and < 4000/mL, respectively, in the SPIRIT-ICU), and a new or persistent pulmonary infiltrate on chest radiography. In the SPIRIT-ICU trial, an independent diagnosis validation committee blindly classified each patient as positive or negative for VAP, whereas this procedure was not used in the CORTI-TC study. All VAP were microbiologically documented by quantitative culture from specimen brush (≥ 10^3 cfu/mL), bronchoalveolar lavage (≥ 10^{-4} cfu/mL) or endotracheal aspirate (≥ 10^{-6} cfu/mL). The occurrence of VAP was recorded until extubation within a maximum period of 28 days in both studies. Ventilator-associated pneumonia was differentiated between early (>2 and ≤ 5 days) and late (>5 days) VAP. The delay between ICU admission and first VAP occurrence and the number of VAP that occurred after the first episode were also recorded.

Secondary endpoints included duration of mechanical ventilation and day 28 total duration of antibiotic exposure. The microorganisms recovered from the respiratory samples, classes of antibiotics used for AP and duration of AP were reported. The impact of AP on other nosocomial infections, including ventilator-associated tracheobronchitis, urinary tract infection, surgical site infection, and catheter-related infection, was studied. The ICU length of stay and mortality in ICU and at day 28 were recorded.

2.4. Data collection

Patient information was collected and included age, sex, medical history, severity assessed by the initial Glasgow coma scale, calculation of the Injury Severity Score (ISS) at admission and of the severity acute physiologic score II within the first 24 h of hospitalization in ICU, the location(s) of trauma, need for neurosurgery and the rate of intracranial pressure monitoring. The need for orthopaedic surgery was also recorded.

2.5. Statistical analysis

For the present analysis, data from the CORTI-TC and SPIRIT-ICU studies were pooled. Statistical analysis was performed using SAS statistical software V9.4 (SAS Institute, Cary, NC). Variables are expressed as the median (interquartile range) in the case of significant non-normality for continuous variables and as a number (percentage) for qualitative variables. Continuous variables were compared between the control and AP groups using a Student's *t*-test or Wilcoxon rank sum test, as appropriate. The chi-square test or Fisher exact test was used when needed to compare qualitative variables. Cumulative event curves were estimated for the occurrence of VAP with the Kaplan-Meier procedure, and the results were compared between groups with a log-rank test. Sensitivity analysis was also performed using a multivariate cox regression model adjusted on preventive measures of VAP applied to the patients and baseline variables that were significantly different ($p < 0.05$) between the 2 groups. The relationship between AP duration and VAP occurrence was tested using the Cochran-Armitage trend test. For all analyses, a p value <0.2 was considered significant.

3. Results

The SPRIT-ICU and CORTI-TC studies included a total of 515 patients, with 146 (49%) patients in the AP group and 149 (50%) patients in the control group (Fig. 1). Antibiotic prophylaxis was initiated in the first 2 days after initial trauma in 136/146 (93%) patients, and the median delay between trauma and AP onset was 1 day (interquartile range: 1–1 day). The baseline characteristics are provided in Table 1. Patients in the AP group had a lower rate of history of alcoholism and a higher ISS, and they underwent neurosurgery and orthopaedic surgery more frequently than those in the control group. The location of trauma is provided in supplementary file 2 (locations of trauma). The global incidence of VAP was 145 (49%) (62 [43%] and 83 [57%] for early and late VAP, respectively). The means used to prevent VAP did not differ between the two groups (supplementary file 3: Preventive measures of ventilator-associated pneumonia). Stress ulcer prophylaxis was administered in 166 (56.8%) patients (77 [53%] and 89 [61%] for the AP and control groups, respectively, $p = 0.199$).

AP significantly reduced VAP occurrence (unadjusted hazard ratio = 0.50, 95% confidence interval (CI) [0.36;0.69], $p < 0.001$ (Fig. 2); adjusted hazard ratio = 0.44, 95% CI [0.31;0.63], $p < 0.001$). The incidence of early VAP was significantly lower in the AP group (relative risk 0.33, 95% CI [0.19;0.56], $p = 0.001$), whereas late onset pneumonia incidence did not differ between the 2 groups (relative risk 1.05, 95% CI [0.73;1.51], $p = 0.950$) (Table 2). The density incidence per 1000 ventilators days was reduced only for early onset pneumonia (Table 2). The incidence of second and third episodes of VAP was also lower in the AP group (9 [6%] vs 16 [11%], $p = 0.029$). Two patients developed a third episode of VAP in the control group, and none developed a third episode in the AP group.

The indications of AP are provided in supplementary file 4 (Indications for antibiotic prophylaxis), and the antimicrobial agents used as AP before the occurrence of VAP are displayed in Fig. 3. Among the agents used, 72% of the patients received penicillin (amoxicillin-clavulanate acid combination was predominant (93%)), 23% received cephalosporin (mainly first- and second-generation cephalosporins, with only 3 patients receiving third-generation cephalosporin), 4% received aminoglycosides, and only one patient received metronidazole. The median duration of AP was 1 day (interquartile range: 1–2 days). In the AP group, the incidence of VAP did not differ according to AP duration (Fig. 4). The total duration of antibiotic exposure was significantly lower in the AP group (Table 2). ICU length of stay and mortality in the ICU and at day 28 were not significantly different between the 2 groups (Table 2).

The pathogens recovered from respiratory samples are provided in supplementary file 5 (Microorganisms recovered from pulmonary samples in ventilator-associated pneumonia). The main microorganisms recovered were methicillin-susceptible *Staphylococcus aureus* and *Haemophilus influenza. Streptococcus pneumoniae* recovery from pulmonary samples was significantly lower in the AP group than in the control group.

The incidence of other nosocomial infections was similar between the two groups (supplementary file 6: Impact of antibiotic prophylaxis on nosocomial infections).

4. Discussion

The results of the present post hoc analysis from two recent randomized controlled studies suggest that AP reduces the occurrence of VAP in severe TBI patients but that this effect is only significant for early VAP.

The effect of AP on early VAP has been previously highlighted in patients who had various causes of coma with different antibiotic regimens [1,2,13]. Beyond administration as a prophylactic, it is worth noting that in the prospective randomized study of Sirvent et al., the control group of patients, who received an antibiotic for another reason, also experienced a significantly lower incidence of VAP [1]. Several reasons may explain this preventive effect. Indeed, coma induces glottic dysfunction, and the condition of emergency intubation may be difficult, favouring aspiration of oropharyngeal contents and early colonization of the upper airways; traumatic immunosuppression observed soon after trauma may also play a role, and these conditions may favour the development of secondary bacterial pneumonia [17-19].

Nevertheless, antibiotic use exposes populations to adverse events, and the emergence of multidrug resistant bacteria has had global and individual ecological impacts. In a retrospective study performed in trauma patients, Hoth et al. showed that trauma patients who received AP for >48 h had a delayed occurrence of nosocomial pneumonia but exhibited increases in methicillin-resistant *Staphylococcus aureus* and resistant gram-negative bacteria [20]. Moreover, there was a greater incidence of *Clostridium difficile* colitis [20]. Nevertheless, the duration of AP was particularly prolonged with a mean duration of 8 ± 4 days, and AP may include a combination of up to 3 antibiotics. More recently, in patients requiring mechanical ventilation for >48 h after major heart surgery, Bouza et al. detected linezolid-resistant staphylococci after VAP strategy prevention for 3 days with linezolid and meropenem [21]. In the present study, the median duration of prophylaxis was shorter (1 day) and marginally involved broad-spectrum antibiotics. The duration of antibiotic exposure is a key determinant of subsequent antibiotic

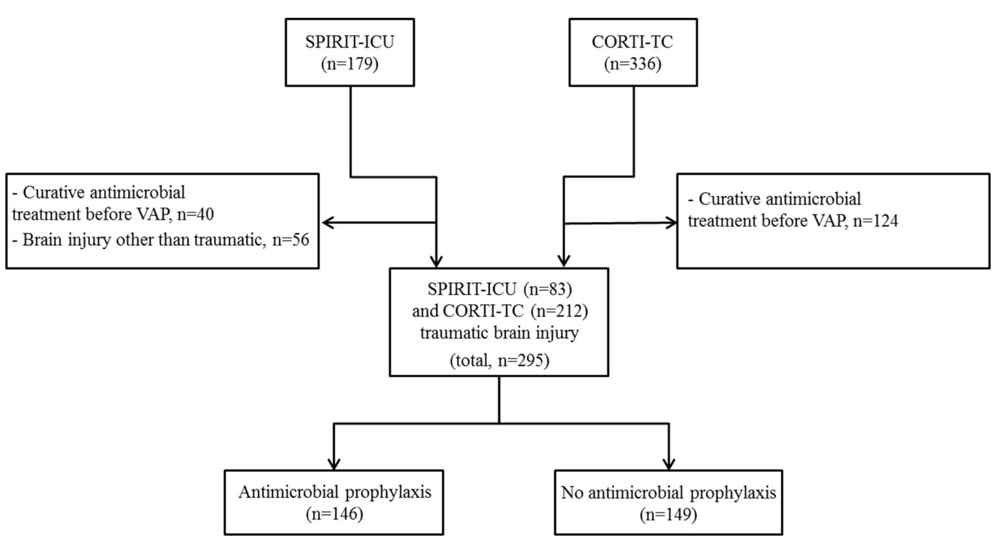

Fig. 1. Flow chart.

Table 1
Baseline characteristics.

	Total (n = 295)	Antibiotic prophylaxis (n = 146)	Control group (n = 149)	p
Age, years	37 (23–52)	36 (22–52)	39 (24–52)	0.55
Male sex	252 (85%)	124 (85%)	128 (86%)	0.81
Medical history				
Cardiac insufficiency	20 (7%)	14 (10%)	6 (4%)	0.06
Chronic pulmonary disease	7 (2%)	3 (2%)	4 (3%)	0.93
Diabetes mellitus	7 (2%)	4 (3%)	3 (2%)	0.72
Obesity	13 (4%)	8 (6%)	5 (3%)	0.38
Active smoking	98 (33%)	46 (32%)	52 (35%)	0.50
Alcoholism	69 (24%)	24 (16%)	45 (30%)	0.005
Severity				
Glasgow coma scale	6 (4–7)	6 (4–7)	6 (4–7)	0.82
Injury severity score	24 (14–29)	25 (17–30)	21 (13–26)	0.001
SAPS-II	43 (35–53)	43 (34–53)	43 (36–53)	0.63
Neurologic intervention				
Neurosurgery	91 (31%)	63 (43%)	28 (19%)	<0.001
Intracranial pressure monitoring	243 (82%)	121 (83%)	122 (82%)	0.82
Orthopaedic surgery	70 (24%)	53 (30%)	27 (18%)	0.02

Data are expressed as the median (IQR 95%) or n (%). VAP: ventilator-associated pneumonia. SAPS-II: Severity Acute Physiologic Score II.

resistance, and it has been suggested that in trauma, antibiotic resistant selection was likely to occur after 3 days of antibiotic administration and is probably irrelevant when only 2 doses are given [22]. In our study, the impact of AP on bacterial ecology could not be determined, as surveillance of colonization and/or the level of resistance of subsequently recovered bacteria were not reported in the 2 studies, except for resistance of *Staphylococcus aureus* to methicillin, which is uncommon in trauma patients. Nevertheless, AP does not seem to have a negative impact on bacterial ecology. Indeed, even in the absence of information pertaining to the colonization status of these patients, there were no significant differences when comparing the incidence of enteric gram-negative bacilli and methicillin-resistant *Staphylococcus aureus* isolations in patients with VAP in both groups. Nevertheless, a non-significant trend in the number of *Klebsiella pneumoniae* infections was observed in the AP group. Interestingly, we found that the duration of AP did not influence the incidence of VAP, suggesting that a short duration of AP may be as efficient as a longer duration for VAP prevention.

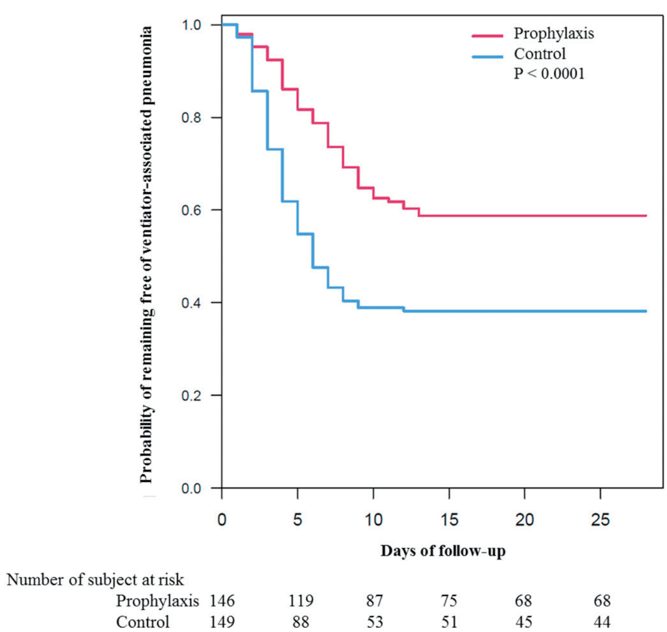

Fig. 2. Probability of remaining ventilator-associated pneumonia-free in the antibiotic prophylactic and control groups. *Adjusted for medical history of alcoholism, injury severity score, neurosurgery, semi-recumbent position (>30°), oropharyngeal decontamination, hydrocortisone, tracheal cuff monitoring, selective digestive decontamination and continuous subglottic suctioning.

Finally, the total duration of antibiotic exposure was significantly lower in the AP group than in the control group, suggesting that AP provided antibiotic savings.

Our study was probably underpowered in determining the effect of AP on mortality, intensive care length of stay and duration of mechanical ventilation, and only large randomized studies can clarify these issues. Otherwise, even without a demonstrated effect on these outcomes, VAP may influence long-term recovery. In a small retrospective study involving 40 TBI patients, a correlation was found between VAP and the Glasgow Coma Scale at 1 year [10]. In a cohort of 141 patients who had TBI, it was shown that patients who experienced hospital-acquired pneumonia had a lower Glasgow Outcome Scale-Extended at 1, 2 and 5 years. After adjustment for confounding factors, hospital-acquired pneumonia was associated with a 7-fold increase in odds of low Glasgow Outcome Scale-Extended and was the only predictor of poor outcome at all follow up times [11]. More recently, in retrospective study performed in 175 severe traumatic injury patients, the occurrence of early onset pneumonia (defined as pneumonia during the 7 first days after trauma) was associated with worse neurologic functional outcomes assessed by the Glasgow outcome scale. Indeed, patients without early onset pneumonia had better recovery and a smaller risk of being in

Table 2
Incidence of ventilator-associated pneumonia, mechanical ventilation, antibiotic use and mortality in the antimicrobial prophylaxis and control groups.

	Antimicrobial prophylaxis (n = 146)	Control group (n = 149)	p
Occurrence of ventilator-associated pneumonia	57 (39%)	88 (59%)	<0.01
Incidence density per 1000 ventilator days (95%CI)	32.0 (24.7–41.5)	42.7 (34.6–52.6)	0.09
Early onset pneumonia[a]			
Incidence	15 (10%)	47 (32%)	<0.01
Incidence density per 1000 ventilator days (95%CI)	15.7 (9.5–26.1)	39.5 (29.7–52.5)	<0.01
Late onset pneumonia[a]			
Incidence	42 (29%)	41(28%)	0.81
Incidence density per 1000 ventilator days (95%CI)	26.6 (19.7–36.1)	32.0 (23.6–43.5)	0.40
Mechanical ventilation, days	9 (5–16)	11 (6–18)	0.61
Total antibiotic duration, days	3 (1–9)	8 (7–12)	<0.01
Length of stay in ICU	13 (7–19)	14 (8–23)	0.29
Mortality in ICU	27 (18%)	32 (22%)	0.50
Mortality at day 28	26 (18%)	28 (19%)	0.83

Data are expressed as the median (IQR 95%) or n (%).
[a] Early onset pneumonia was defined as pneumonia occurring after at least 48 h and ≤ 5 days of mechanical ventilation, and late onset pneumonia was defined as pneumonia occurring >5 days of mechanical ventilation.

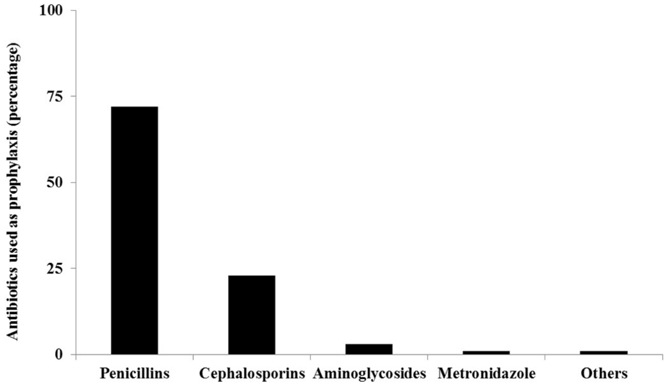

Fig. 3. Antimicrobial agents used as prophylaxis.

a vegetative state [12]. Persistent and prolonged inflammation secondary to lung infection may contribute to the deleterious effect of VAP. Moreover, it has been shown that patients who had early onset pneumonia experienced more fever, more hypotension, a lower level of arterial oxygen tension and more intracranial hypertension; these parameters are all well-known deleterious secondary insult in TBI [8]. Finally, in 72 patients who had brain tissue oxygen monitoring, the occurrence of early VAP was associated with significantly more episodes of cerebral hypoxia, which may also contribute to poorer functional outcomes [12].

This study has some limitations that must be noted. First, there is a difference between the two protocols of the previous studies. Indeed, SPIRIT-ICU assessed the effect of povidone-iodine on the occurrence of VAP, whereas CORTI-TC tested the efficacy of low-dose hydrocortisone with fludrocortisone for the prevention of hospital-acquired pneumonia. Thus, half of our population was exposed to hydrocortisone plus fludrocortisone and half to povidone-iodine, which may represent a confounding bias. Nevertheless, the treatment that the patients received was included in the multivariate analysis. Second, the lack of standardization of the preventive antimicrobial treatment limits the relevance of our study from a clinical perspective, although narrow-spectrum antibiotics were the most common choice in these studies. Third, our study was a retrospective analysis, but the data were obtained from prospective, randomized, multicentre double-blind studies; combining data from these two studies enabled analysis of a larger cohort of ventilated patients with TBI and reduced the risk of beta error. Fourth, the VAP definition did not include worsening of gas exchange or increased oxygen requirements, which is a more objective clinical criterion compared to purulence of secretions and even chest X-ray

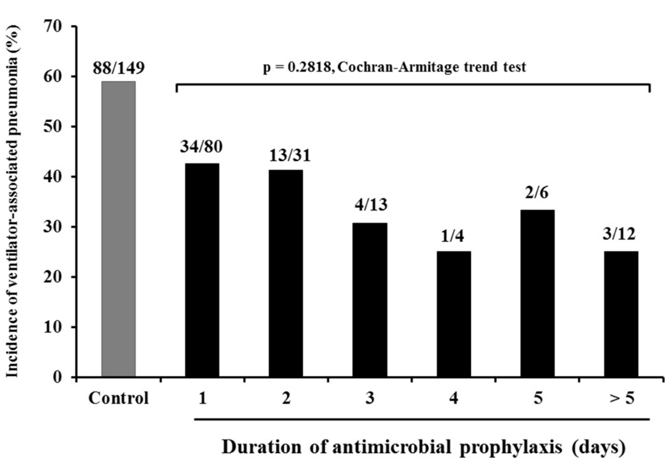

Fig. 4. Incidence of ventilator-associated pneumonia and the duration of antibiotic prophylaxis.

interpretation, the latter of which may be difficult in trauma patients. Nevertheless, the 2 studies included in the analysis were double-blind, and randomization limits the difference that would be present in one group compared to another. Finally, we studied only TBI patients, and a similar intervention could have different results in other medical settings with high rates of antibiotic resistance.

In conclusion, in a large population of severe TBI, AP delayed and may prevent the occurrence of VAP. Nevertheless, AP should not be routinely use in clinical practice to prevent VAP because it had no effect on length of stay and mortality, and it remains to be seen whether this treatment has a significant impact on bacterial ecology and late neurologic functional outcomes.

Acknowledgements

None.

Declarations of interest

None.

Financial support and potential conflicts of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.12.010.

References

[1] Sirvent JM, Torres A, El-Ebiary M, Castro P, de Batlle J, Bonet A. Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. Am J Respir Crit Care Med 1997;155:1729–34. https://doi.org/10.1164/ajrccm.155.5.9154884.

[2] Vallés J, Peredo R, Burgueño MJ, Rodrigues De Freitas AP, Millán S, Espasa M, et al. Efficacy of single-dose antibiotic against early-onset pneumonia in comatose patients who are ventilated. Chest 2013;143:1219–25. https://doi.org/10.1378/chest.12-1361.

[3] Roquilly A, Mahe PJ, Seguin P, Guitton C, Floch H, Tellier AC, et al. Hydrocortisone therapy for patients with multiple trauma: the randomized controlled HYPOLYTE study. JAMA 2011;305:1201–9. https://doi.org/10.1001/jama.2011.360.

[4] Asehnoune K, Seguin P, Allary J, Feuillet F, Lasocki S, Cook F, et al. Hydrocortisone and fludrocortisone for prevention of hospital-acquired pneumonia in patients with severe traumatic brain injury (Corti-TC): a double-blind, multicentre phase 3, randomised placebo-controlled trial. Lancet Respir Med 2014;2:706–16. https://doi.org/10.1016/S2213-2600(14)70144-4.

[5] Seguin P, Laviolle B, Dahyot-Fizelier C, Dumont R, Veber B, Gergaud S, et al. Effect of oropharyngeal povidone-iodine preventive oral care on ventilator-associated pneumonia in severely brain-injured or cerebral hemorrhage patients: a multicenter, randomized controlled trial. Crit Care Med 2014;42(1):1–8. https://doi.org/10.1097/CCM.0b013e3182a2770f.

[6] Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis 2013;13:665–71. https://doi.org/10.1016/S1473-3099(13)70081-1.

[7] Rincón-Ferrari MD, Flores-Cordero JM, Leal-Noval SR, Murillo-Cabezas F, Cayuelas A, Muñoz-Sánchez MA, et al. Impact of ventilator-associated pneumonia in patients with severe head injury. J Trauma 2004;57:1234–40.

[8] Bronchard R, Albaladejo P, Brezac G, Geffroy A, Seince PF, Morris W, et al. Early onset pneumonia: risk factors and consequences in head trauma patients. Anesthesiology 2004;100(2):234–9.

[9] Kallel H, Chelly H, Bahloul M, Ksibi H, Dammak H, Chaari A, et al. The effect of ventilator-associated pneumonia on the prognosis of head trauma patients. J Trauma 2005;9:705–10.

[10] Khajavikhan J, Vasigh A, Khani A, Jaafarpour M, Kokhazade T. Outcome and predicting factor following severe traumatic brain injury: a retrospective cross-sectional study. J Clin Diagn Res 2016;10:PC16–9. https://doi.org/10.7860/JCDR/2016/16390.7294.

[11] Kesinger MR, Kumar RG, Wagner AK, Puyana JC, Peitzman AP, Billiar TR. Hospital-acquired pneumonia is an independent predictor of poor global outcome in severe traumatic brain injury up to 5 years after discharge. J Trauma Acute Care Surg 2015;78:396–402. https://doi.org/10.1097/TA.0000000000000526.

[12] Esnault P, Nguyen C, Bordes J, D'Aranda E, Montcriol A, Contargyris C. Early-onset ventilator-associated pneumonia in patients with severe traumatic brain injury: incidence, risk factors, and consequences in cerebral oxygenation and outcome. Neurocrit Care 2017;27:187–98. https://doi.org/10.1007/s12028-017-0397-4.
[13] Acquarolo A, Urli T, Perone G, Giannotti C, Candiani A, Latronico N. Antibiotic prophylaxis of early onset pneumonia in critically ill comatose patients. A randomized study. Intensive Care Med 2005;31:510–6. https://doi.org/10.1007/s00134-005-2585-5.
[14] Righy C, do Brasil PEA, Vallés J, Bozza FA, Martin-Loeches I. Systemic antibiotics for preventing ventilator-associated pneumonia in comatose patients: a systematic review and meta-analysis. Ann Intensive Care 2017;7(1):67. https://doi.org/10.1186/s13613-017-0291-4.
[15] Asehnoune K, Roquilly A, Sebille V. The Corti-TC trial group. Corticotherapy for traumatic brain-injured patients—the Corti-TC trial: study protocol for a randomized controlled trial. Trials 2011;12:228. https://doi.org/10.1186/1745-6215-12-228.
[16] Antibioprophylaxie en chirurgie et médecine interventionnelle (patients adultes). Actualisation 2010. Ann Fr Anesth Reanim 2011;30:168–90.
[17] Sirvent JM, Torres A, Vidaur L, Armengol J, de Batlle J, Bonet A. Tracheal colonisation within 24 h of intubation in patients with head trauma: risk factor for developing early-onset ventilator-associated pneumonia. Intensive Care Med 2000;26:1369–72.
[18] Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U. Central nervous system injury-induced immune deficiency syndrome. Nat Rev Neurosci 2005;6:775–86. https://doi.org/10.1038/nrn1765.
[19] Asehnoune K, Roquilly A, Abraham E. Innate immune dysfunction in trauma patients: from pathophysiology to treatment. Anesthesiology 2012;117:411–6. https://doi.org/10.1097/ALN.0b013e31825f018d.
[20] Hoth JJ, Franklin GA, Stassen NA, Girard SM, Rodriguez RJ, Rodriguez JL. Prophylactic antibiotics adversely affect nosocomial pneumonia in trauma patients. J Trauma 2003;55:249–54. https://doi.org/10.1097/01.TA.0000083334.93868.65.
[21] Bouza E, Granda MJ, Hortal J, Barrio JM, Cercenado E, Muñoz P. Pre-emptive broad-spectrum treatment for ventilator-associated pneumonia in high-risk patients. Intensive Care Med 2013;39:1547–55. https://doi.org/10.1007/s00134-013-2997-6.
[22] Poole D, Chieregato A, Langer M, Viaggi B, Cingolani E, Malacarne P. Systematic review of the literature and evidence-based recommendations for antibiotic prophylaxis in trauma: results from an Italian consensus of experts. PLoS One 2014;9:e113676. https://doi.org/10.1371/journal.pone.0113676.