Antibiotic Prophylaxis and Ventilator-Associated Pneumonia in Traumatic Brain Injury Patients: Insights from The CREACTIVE Study

Claudia Santucci[1], Aimone Giugni[2], Greta Carrara[3], Arturo Chieregato[4], Akos Csomos[5], Joanne M. Fleming[3], Lorenzo Gamberini[2], Primoz Gradisek[6,7], Rafael Kaps[8], Theodoros Kyprianou[9,10], Isaac Lazar[11], Elisa Marchionni[12], Malgorzata Mikaszewska-Sokolewicz[13,14], Marco Madaghiele[15], Giulia Paci[16], Carlotta Rossi[3], Fabiola Signorini[3], Nektaria Xirouchaki[17], Giovanni Nattino[3], Guido Bertolini[3], for the CREACTIVE consortium

(1) Department of Clinical Sciences and Community Health, Department of Excellence 2023-2027, University of Milan, Milan, Italy
(2) UOC Rianimazione ed Emergenza Territoriale 118, Dipartimento di Emergenza, Ospedale Maggiore, AUSL di Bologna, Italy
(3) Laboratory of Clinical Epidemiology, Department of Medical Epidemiology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Ranica, Bergamo, Italy
(4) Neurointensive Care Unit, Grande Ospedale Metropolitano Niguarda, Milan, Italy
(5) Hungarian Army Medical Center, Budapest, Hungary
(6) Clinical Department of Anaesthesiology and Intensive Therapy, University Medical Centre Ljubljana, Slovenia
(7) Faculty of Medicine, University of Ljubljana, Slovenia
(8) General Hospital Novo Mesto, Novo Mesto, Slovenia
(9) University of Nicosia Medical School, Nicosia, Cyprus
(10) University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK
(11) Pediatric Intensive Care Unit, Soroka Medical Center and The Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
(12) UO Malattie Infettive, Dipartimento Interaziendale per la gestione integrata del rischio infettivo, IRCCS Policlinico S.Orsola-AUSL Bologna-IRCCS IOR Bologna-AUSL Imola, Italy
(13) Clinic of Anaesthesia and Intensive Care, Medical University of Warsaw, Warsaw, Poland
(14) The Childrens' Memorial Health Institute, Warsaw, Poland
(15) Unit of Anesthesia and Intensive Care, Department of Surgery, Santa Maria delle Croci Hospital, Ravenna, Italy
(16) UO Anestesia Rianimazione, AUSL Romagna, Maurizio Bufalini Hospital, Cesena, Italy
(17) University Hospital of Heraklion, Crete, Greece

CORRESPONDING AUTHOR: *Santucci Claudia, claudia.santucci@unimi.it*

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality worldwide [1, 2]. It is now recognized as a condition involving multiorgan dysfunction, characterized by non-neurological complications, particularly respiratory ones such as ventilator-associated pneumonia (VAP), being common and associated with worse outcomes. VAP occurs frequently in intensive care unit (ICU) patients, and the incidence among those with TBI ranges from 21% to 60% and an average of 36% [3]. Prevention strategies for VAP include daily sedation interruption, spontaneous breathing trials, oral decontamination, continuous monitoring of endotracheal tube cuff pressure, the use of an endotracheal tube with subglottic drainage ports, and, most importantly, antibiotic prophylaxis (AP) [4, 5]. However, the role of AP in preventing VAP remains unclear. While some studies suggested that AP has a protective effect, particularly against early-onset VAP [6-9], others found no association between AP and VAP occurrence, length of hospital stay, or mortality [9-12]. Moreover, prolonged AP use has been associated with an increased incidence of antibiotic-resistant Gram-negative pathogens and other complications [13].

OBJECTIVES

To investigate the effect of AP on the incidence of VAP in patients with TBI admitted to ICU. We also assessed the role of AP on secondary outcomes, including the duration of mechanical

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ventilation, ICU and hospital length of stay, ICU and hospital mortality, and the six-month Glasgow Outcome Scale-Extended (GOS-E), using data from the large, multicenter, prospective CREACTIVE cohort [14].

METHODS

We included adult TBI patients requiring mechanical ventilation for more than 48 hours. AP was defined as administration of antibiotics in the absence of documented infection within the first 7 days of ICU stay. The primary outcome was the incidence of VAP, defined according to international criteria.

To create well-balanced AP and no-AP groups for all relevant confounding factors, we used a propensity score-matched design, a robust methodology for estimating causal effects in observational studies [15]. Propensity scores were estimated for each patient using a logistic regression model based on 22 covariates, including variables that were identified to impact both the decision to administer AP and the patient outcome (i.e., demographics, TBI severity, extracranial injuries, and ICU characteristics). We used the full matching algorithm [16], which requires weighted post-matching analyses, in which the weights depend on the size and composition of the matched sets [17]. Differences between no AP and AP groups for the primary and secondary outcomes were investigated using opportune weighted tests. The probability of experiencing VAP was assessed using the weighted Kaplan-Meier analysis, and a time-to-event comparison was conducted using the log-rank test.

RESULTS

A total of 2,518 patients from 70 European ICUs were included, of whom 1,392 (54%) received AP, while 1,183 (46%) did not. Compared to patients in the no-AP group, those with AP at ICU admission were younger, had fewer comorbidities, presented lower Glasgow Coma Scale scores, higher Marshall scores, more injuries in body areas other than TBI, and were more frequently involved in high-impact or traffic-related trauma. After weighting, the groups were well balanced, with weighted standardized mean differences below 10% for all variables used in model to estimate the propensity score, except for country (11.8%) and penetrating trauma (10.4%).

After weighting, patients in the no-AP group had higher probability of experiencing early VAP than those in the AP group (18.9% vs. 14.7%, p-value<0.01), although there was no significant difference in the overall occurrence of VAP (Table 1). Time-to-event analysis confirmed a reduced risk of early VAP in the AP group, particularly during the first days of mechanical ventilation (Log-rank p-value<0.05). Compared to AP patients, those without AP had higher ICU mortality (35.0% vs. 27.1%, p-value<0.01) and higher hospital mortality (43.5% vs. 37.1%, p-value<0.01). ICU and hospital stays were significantly longer for AP patients, while no difference was detected in the duration of mechanical ventilation. There were no differences between groups in the 6-month GOS-E.

Among patients who developed VAP and had available microbiological data, those in the AP group reported a lower proportion of Gram-positive bacteria compared to the no-AP group (29.3% vs. 47.2%), and a higher proportion of Gram-negative bacteria (80.9% vs. 71.4%). Moreover, AP patients showed higher rates of MDR bacteria, both Gram-positive (17.4% vs. 11.9%) and Gram-negative (32.3% vs. 15.8%).

CONCLUSIONS

Our findings suggest that AP is effective in reducing early-onset VAP among TBI patients, consistent with previous studies [6, 8, 12, 18, 19]. The benefit is pronounced during the early phase of mechanical ventilation, when patients are especially vulnerable. Patients who received AP had more Gram-negative infections and fewer Gram-positive ones but also showed higher rates of MDR in both types. The higher MDR rates in the AP group may be attributable to longer antibiotic courses, which was also evident in our results. This finding aligns with existing literature, which indicates that greater antibiotic exposure may promote the selection of resistant strains, complicating future treatment [20-23].

These results underscore the need to balance the benefits of VAP prevention with the risks of antimicrobial resistance. In conclusion, AP appears effective in reducing the incidence of VAP in TBI patients, but its use should be carefully considered. Clinicians are encouraged to apply AP selectively in high-risk cases, aiming to prevent infection while preserving antibiotic efficacy.

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Table 1. Outcomes of the of 2,575 patients included in the analysis, according to the AP at the ICU admission before and after propensity score matching

	No AP		AP	p-valueb
	N (%)	Weighted distribution,n%a	N (%)	
N of patients	1,183	1,392	1,392	
Mechanical ventilation length, days				
Mean (SD)	8.15 (9.91)	10.33 (12.63)	11.34 (11.37)	0.1271
Median (Q1-Q3)	5 (1-12)	7 (2-15)	8 (3-16)	
ICU stay, days				
Mean (SD)	10.67 (12.13)	13.40 (15.85)	15.18 (14.68)	**0.0328**
Median (Q1-Q3)	7 (2-15)	9 (3-18)	11 (5-21)	
Hospital stay, days				
Mean (SD)	18.34 (22.29)	22.10 (26.73)	26.79 (31.18)	**0.0010**
Median (Q1-Q3)	11 (4-25)	14 (6-30)	18 (7-35)	
VAP	236 (19.95)	26.57	349 (25.07)	0.3677
Early VAP c	168 (14.20)	18.93	204 (14.66)	**0.0025**
ICU mortality				
Alive	738 (62.38)	64.96	1,012 (72.91)	**<.0001**
Dead	444 (37.53)	35.04	376 (27.09)	
Last hospital mortality				
Alive	623 (53.07)	56.52	872 (62.91)	**0.0006**
Dead	551 (46.93)	43.48	514 (37.09)	
GOS-E (6 months)				
Upper good recovery	91 (7.69)	7.09	108 (7.76)	0.1567
Lower good recovery	82 (6.93)	7.61	91 (6.54)	
Upper moderate disability	78 (6.59)	7.13	93 (6.68)	
Lower moderate disability	45 (3.80)	4.43	78 (5.60)	
Upper severe disability	66 (5.58)	7.84	117 (8.41)	
Lower severe disability	186 (15.72)	15.54	232 (16.67)	
Vegetative state	40 (3.38)	3.94	78 (5.60)	
Dead	595 (50.30)	46.41	595 (42.74)	

SD, standard deviation. [a] Data for patients in the no AP group are weighted to make them comparable with those in the AP group with respect to pretreatment covariates. Weights are defined by the matched design. [b] P-value of the weighted tests comparing the no AP and AP groups. [c] Defined as occurred <7 days from start mechanical ventilation

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