Ceftriaxone to prevent early ventilator-associated pneumonia in patients with acute brain injury: a multicentre, randomised, double-blind, placebo-controlled, assessor-masked superiority trial

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Summary

Background Patients with acute brain injury are at high risk of ventilator-associated pneumonia (VAP). The benefit of short-term antibiotic prophylaxis remains debated. We aimed to establish the effect of an early, single dose of the antibiotic ceftriaxone on the incidence of early VAP in patients with severe brain injury who required mechanical ventilation.

Methods PROPHY-VAP was a multicentre, randomised, double-blind, placebo-controlled, assessor-masked, superiority trial conducted in nine intensive care units in eight French university hospitals. We randomly assigned comatose (Glasgow Coma Scale score [GCS] ≤12) adult patients (age ≥18 years) who required mechanical ventilation for at least 48 h after acute brain injury to receive intravenous ceftriaxone 2 g or placebo once within the 12 h following tracheal intubation. Participants did not receive selective oropharyngeal and digestive tract decontamination. The primary outcome was the proportion of patients developing early VAP from the 2nd to the 7th day of mechanical ventilation, confirmed by masked assessors. The analysis was reported in the modified intention-to-treat population, which comprised all randomly assigned patients except those who withdrew or did not give consent to continue and those who did not receive the allocated treatment because they met a criterion for non-eligibility. The trial is registered with ClinicalTrials.gov, NCT02265406.

Findings From Oct 14, 2015, to May 27, 2020, 345 patients were randomly assigned (1:1) to receive ceftriaxone (n=171) or placebo (n=174); 330 received the allocated intervention and 319 were included in the analysis (162 in the ceftriaxone group and 157 in the placebo group). 166 (52%) participants in the analysis were men and 153 (48%) were women. 15 patients did not receive the allocated intervention after randomisation and 11 withdrew their consent. Adjudication confirmed 93 cases of VAP, including 74 early infections. The incidence of early VAP was lower in the ceftriaxone group than in the placebo group (23 [14%] *vs* 51 [32%]; hazard ratio 0·60 [95% CI 0·38–0·95], p=0·030), with no microbiological impact and no adverse effects attributable to ceftriaxone.

Interpretation In patients with acute brain injury, a single ceftriaxone dose decreased the risk of early VAP. On the basis of our findings, we recommend that an early, single dose of ceftriaxone be included in all bundles for the prevention of VAP in patients with brain injury who require mechanical ventilation.

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Introduction

Despite advances in prevention over the past few decades, ventilator-associated pneumonia (VAP) remains the leading cause of health-care-associated infections in critically ill patients.[1] These infections prolong mechanical ventilation and the intensive care unit (ICU) stay, increase antibiotic administration and, consequently, increase the risk of bacterial resistance to antibiotics and the heightening of hospital costs. Acute brain injury increases the risk of developing early VAP, with incidence reported in the literature ranging from 20% to 71% in severe trauma and from 28% to 76% in stroke patients.[2–6] This high risk is attributable to frequent aspiration of microorganisms from the oropharynx before tracheal intubation and occurrence of immune depression within the first week following brain injury.[7,8] In addition to usual complications, early VAP could alter neurological outcomes in patients with brain injury, although outcomes after early VAP are still poorly documented.[9,10]

Prevention is key and relies on a combination of effective measures endorsed by international guidelines. They include prolonged intravenous antibiotic prophylaxis combined with selective oropharyngeal (SOD) and digestive tract decontamination (SDD), while remaining

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Research in context

Evidence before this study

Ventilator-associated pneumonia (VAP), the leading cause of health-care-associated infections in critically ill patients, increases intensive care unit (ICU) and hospital length of stay and costs of care. Patients with acute brain injury are at risk of early VAP; the prevention of VAP is a key goal and is based on a bundle of measures. Selective oropharyngeal (SOD) and digestive tract decontamination (SDD) with or without intravenous antibiotic prophylaxis is effective, but is still rarely used owing to the emergence of bacterial resistance and to implementation difficulties. The benefit of short-term antibiotic prophylaxis remains open to debate.

We searched PubMed to identify studies in adult patients reported in English from Jan 1, 1995, to Sept 5, 2023, using the search terms ("ventilator-associated pneumonia" OR "early ventilator-associated pneumonia") AND ("brain injury" OR "traumatic brain injury" OR "stroke" OR "subarachnoid haemorrhage") AND ("prevention" OR "prophylaxis"). Three small studies reported reduced risk of early VAP in patients with brain injury after intravenous antibiotic prophylaxis following tracheal intubation, without associated SDD. Two of the studies were randomised and intravenous prophylaxis was administered for 2–5 days; the other study reported efficacy of a single administration of ceftriaxone. As no well conducted randomised controlled trials have been reported, this preventive measure alone is still not recommended by international guidelines.

Added value of this study

The PROPHY-VAP trial provides the first evidence for efficacy and safety of an early, single injection of ceftriaxone, without SOD or SDD, to prevent early VAP in patients with acute brain injury. The incidence of early VAP was lower in the ceftriaxone group (14%) than in the placebo group (32%; hazard ratio 0·60 [95% CI 0·38–0·95], p=0·030). Antibiotic prophylaxis also decreased exposure to antibiotics, decreased time in hospital and in the ICU, and increased survival at day 28, without any local or systemic side-effects during the ICU stay.

Implications of all the available evidence

By confirming in a methodologically sound study that early antibiotic prophylaxis after intubation of patients with brain injury can reduce not only the risk of VAP, but also outcomes such as exposure to antibiotics, length of hospital stay, and mortality, PROPHY-VAP provides evidence to support the modification of VAP prevention recommendations. At present, a 4-day course of intravenous antibiotic prophylaxis combined with four-times-daily SDD for the entire length of the ICU stay is recommended.

As our study population consisted of comatose patients with brain injury in the broad sense, this preventive measure could be applied in all patients with acute brain injury in the ICU, including people with stroke—a growing population over the past two decades. By reducing their risk of VAP, secondary cerebral insults that lead to worsening brain damage and outcomes could also be reduced. Moreover, by reducing the length of patients' ICU stay, we can assume that this prevention would improve patient flow and help in meeting the growing demand for ICU care.

The other issue concerns antibiotic savings, which remain the principal means of preventing the global public health problem of bacterial resistance to antibiotics. Indeed, the PROPHY-VAP trial demonstrated that a single dose of ceftriaxone reduced antibiotic consumption in patients with severe brain injury. Furthermore, it can be assumed that a single injection of antibiotics for prophylaxis would have less impact on the microbiota and reduce the emergence of bacterial resistance to antibiotics than prolonged intravenous antibiotic prophylaxis combined with SDD throughout the ICU stay. Further studies are needed to assess the impact of this new practice not only on the microbiota but also on neurological outcomes in this population of patients in intensive care.

cautious about the uncertain consequences of this practice, particularly regarding the risk of emergence of antibiotic-resistant pathogens.[8] In patients with acute brain injury, shorter antibiotic administration alone has been suggested as a means to reduce the risk of early VAP, while also reducing the risk of emergence of antibiotic-resistant pathogens. However, little scientific evidence supports this recommendation and the few available studies all have limitations, including lack of randomisation and lack of masking of caregivers or VAP assessors to the assigned intervention.[11,12] Some were conducted in a single centre or performed in specific populations such as patients with cardiac arrest, compromising the generalisability of the findings to other patients with acute brain injury.[2,13] Finally, although most of these studies showed decreased risk of early VAP, none demonstrated any other benefit on length of stay or mortality. Therefore, this practice is not currently recommended.

In this paper, we report the results of the first large, multicentre, randomised, double-blind, placebo-controlled, assessor-masked trial evaluating an early, single administration of antibiotic to patients with acute brain injury in preventing early VAP and related outcomes. Taking into consideration the most frequently isolated bacteria in early VAP after acute brain injury, and with a view to limiting the risk of development of antibiotic resistance, a single intravenous administration of ceftriaxone 2 g was chosen for the PROPHY-VAP trial.

Methods

Study design

PROPHY-VAP was a multicentre, randomised, double-blind, placebo-controlled, assessor-masked superiority

trial conducted in nine ICUs of eight French university hospitals. The research was approved by the OUEST III institutional Review Board (2014-001668-36) and is registered with ClinicalTrials.gov, NCT02265406. The trial protocol, including the statistical analysis plan, was published previously.[14]

Participants

Comatose (Glasgow Coma Scale score [GCS] ≤12) adult patients (≥18 years of age), of both sexes and any ethnic group, who were predicted to require mechanical ventilation for more than 48 h after head trauma, stroke, or subarachnoid haemorrhage were eligible for the trial. Exclusion criteria were as follows: coma due to a tumour, an infectious disease, or cardiac arrest; high risk of death within the first 48 h after admission; ongoing antibiotic treatment; previous hospitalisation within the past month; antibiotic prophylaxis expected within the first 24 h after randomisation; tracheal intubation by nasal route; subglottic secretion drainage; mechanical ventilation on tracheostomy; contraindication or allergy to β-lactam agents; participation in another research protocol that could affect infectious risk or risk of a potential drug interaction; patient or family refusal to be involved in the study; and patients with reinforced protection or deprivation of freedom subsequent to a legal or administrative decision. Patients had to undergo randomisation within 12 h after tracheal intubation and within 48 h after hospital admission to start antibiotics promptly enough to prevent early VAP.[14]

Written informed consent was obtained from a legal surrogate or through an emergency consent procedure. In the case of an emergency procedure, the subsequent consent of the patient or a legal surrogate was required to continue the study. In each participating hospital, data were collected in an electronic clinical research file. All authors vouch for the accuracy and completeness of data and for the fidelity of the trial to the protocol.

Randomisation and masking

Patients were randomly assigned (1:1) by means of a secure web-based randomisation system. Randomisation was stratified by centre and severity of unconsciousness at the time of inclusion (GCS <8 or ≥8) to account for differences in patient treatment between centres and heightened VAP risk in patients with GCS lower than 8.[15] The sequence was computer-generated by a statistician not involved in recruitment using variable block sizes. Patients, health-care providers, assessors, and the study statistician were masked to the allocation group.

Intervention

Enrolled patients received a single 30-min intravenous administration of either ceftriaxone 2 g or saline. Particular care was taken to maintain the masking of the treatment administered. Specific vials of ceftriaxone and sodium chloride labelled "PROPHY-VAP" were used for this study and stored in an area reserved for the research protocol. Infusions were prepared by a nurse from a neighbouring unit not involved in patient care. Opaque syringes and infusion lines were used, as ceftriaxone in solution is slightly coloured. The following VAP preventive measures[16] were routinely implemented in ICUs before starting the trial: hand washing before any care; head-of-bed elevation of 30° monitored every 4 h; preferential use of heat and humidity exchange filters, changed only when soiled; monitoring of cuff pressure of the tracheal tube every 8 h to maintain pressure between 25 and 30 cm H_2O; tracheal aspiration using sterile equipment and only when required; mouth care every 8 h at a minimum following local guidelines; no systematic changes of the respirator circuits; preferential oral insertion of feeding tubes; start of enteral feeding as soon as possible; blood glucose monitoring every 4 h; and ulcer disease prevention and tracheal extubation as soon as possible according to each unit's written protocol. None of the participating centres performed SOD or SDD.

Patients were assessed by ICU physicians several times a day until day 28 during the ICU stay for VAP occurrence. For each suspected VAP case, the modified clinical pulmonary infection score was calculated at the discretion of the attending physician; bedside anteroposterior chest radiography and quantitative sampling of the lower respiratory tract (by either blind protected distal sampling, bronchoalveolar lavage, or endotracheal aspiration, at the discretion of the attending physician) were performed before any new antibiotics were administered.

To confirm reported clinical VAP, the events were defined in a standardised approach using the American Thoracic Society (ATS) criteria, which rely on clinical (at least two criteria warranted), radiological, and microbiological criteria occurring at least 48 h after the start of mechanical ventilation (patients had to meet all three types of criteria).[17] Clinical criteria were documented fever (defined as a body temperature ≥38°C) or hypothermia (defined as a body temperature <36°C), hyperleukocytosis (defined as total peripheral white cell count >12 000 per mm^3 or leukopenia (defined as total peripheral white cell count <4000 per mm^3), and purulent endotracheal aspiration. Radiological criteria were the presence of new or modification of a previously existing condensation. Microbiological criteria were a positive bacterial analysis of the respiratory tract with cultures of at least 10^3 colony-forming units (cfu) per mL blind for a brush by fibroscopy or blind protected distal sampling, 10^4 cfu/mL for bronchoalveolar lavage, and 10^6 cfu/mL for endotracheal aspirate.

A central adjudication committee, composed of two senior intensivists masked to study group assignment, reviewed all declared cases of VAP using medical charts of patients rigorously anonymised by the Poitiers University Hospital Research Department staff.

The intensivists had access to all anonymised monitored data, chest radiographs, and microbiological documentation, and the modified clinical pulmonary infection score was calculated during blind reviewing. The microbiological criterion was a positive bacterial analysis of the respiratory tract within 24 h of VAP onset. In case of disagreement, a third intensivist arbitrated the case and decided whether or not the patient had developed VAP.

Patients who developed a documented pulmonary or extrapulmonary infection received curative antibiotic therapy according to local protocols, based on national guidelines. In four participating units, rectal swabs were routinely performed at admission and discharge to screen for the emergence of extended spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* during their ICU stay.

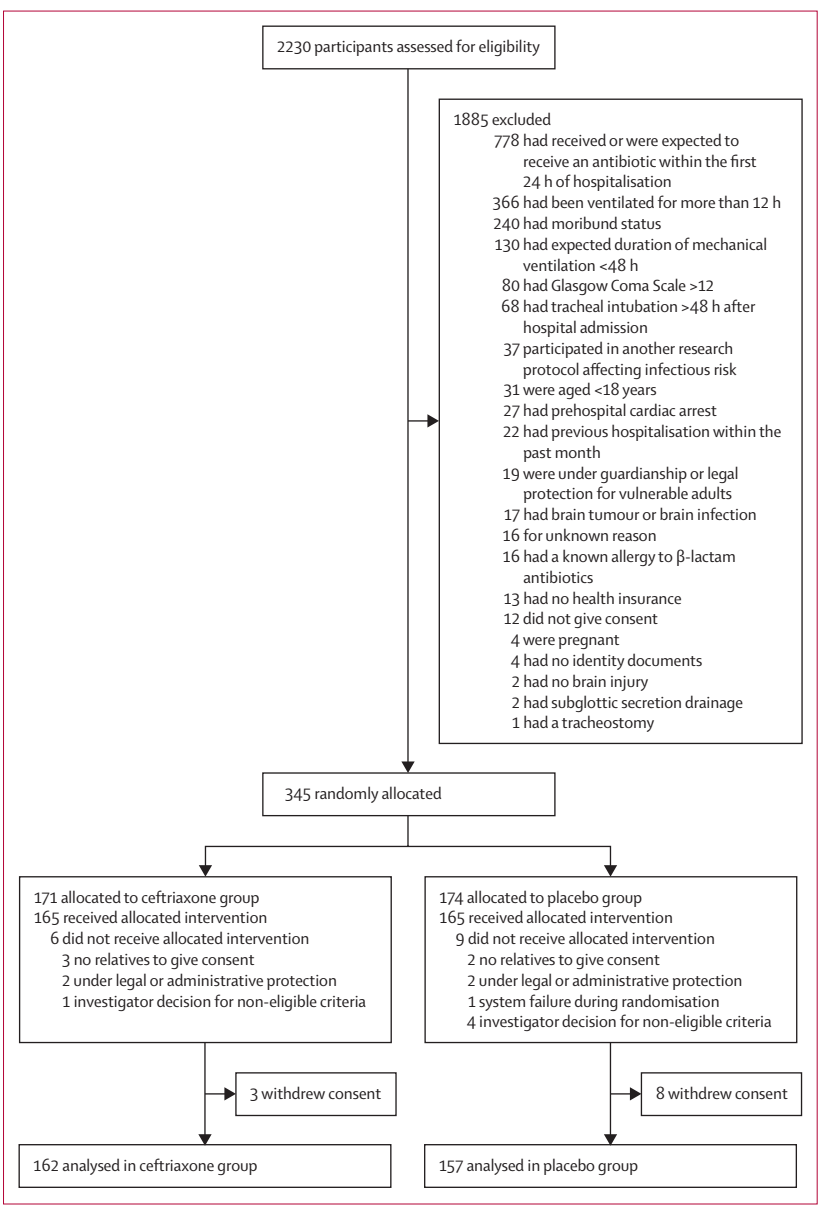

Figure 1: **Trial profile**

Outcomes

The primary outcome was the proportion of patients developing early VAP from the 2nd to the 7th day of mechanical ventilation using the ATS definition,[17] except for the time limit of occurrence. A cutoff of 7 days following tracheal intubation was chosen instead of 5 days because in patients with brain injury, the risk of developing VAP due to antibiotic-resistant microorganisms remains low until day 8.[18,19]

Secondary outcomes at discharge from ICU, or at day 28 if the patient was still in the ICU, were as follows: proportion of patients developing late VAP (>7 days after tracheal intubation) or VAP regardless of the time of occurrence; type of microorganism-induced VAP; exposure to mechanical ventilation and to antibiotics (number of ventilator-free or antibiotic-free days); proportion of patients developing ventilator-associated events according to the US Centers for Disease Control and Prevention (CDC) definition;[20] comparison with global incidences of VAP according to the ATS and CDC definitions; time between inclusion and the first spontaneous ventilation test; proportion of patients with digestive acquisition of ESBL-producing *Enterobacteriaceae*; neurological outcome according to the modified Rankin scale and Glasgow Outcome Scale; mortality; and safety.

Secondary outcomes at day 60 were as follows: exposure to ICU and hospital (number of ICU-free and hospital-free days); neurological outcome according to the modified Rankin scale and Glasgow Outcome Scale; and mortality.

Statistical analysis

The sample size was based on mean incidence of early-onset VAP of 30% in the control group, with the hypothesis that it could be reduced by half in the intervention group (15%), with a study power of 90% and a two-sided type I error of 5%. VAP incidence in the control group was based on published incidence in randomised studies of patients with brain injury. Because of wide variability in the literature, we chose low incidence. The required number of evaluable patients to be included was 354. On the basis of the expected recruitment of participating centres and protocol constraints, expected inclusion duration was initially set at 24 months.

The statistical analysis plan was based on an intention-to-treat principle. According to Fergusson and colleagues,[21] patients who withdrew consent or who did not receive the allocated treatment for a lack of consent to proceed because of a non-eligibility criterion discovered after randomisation were excluded from the analysis (figure 1).[13,21] As the risk of VAP cumulatively increases over time of mechanical ventilation, death and

ventilator weaning are competing risks for VAP occurrence. Analyses of the primary endpoint and secondary endpoints related to VAP incidence used the cumulative incidence function of the Fine-Gray model adjusted for stratification covariates, with death before VAP considered as a competing risk and ventilator weaning considered as a censoring event.[22] The initial statistical analysis plan used an adjusted Cox model but this was modified for a model of competing risk. All other categorical data were reported as number and percentage, and continuous data were reported as mean (SD) or median (IQR) for normally or non-normally distributed data. Statistical comparisons were conducted using χ^2 or Fisher's exact tests for categorical data and the *t* test or Mann-Whitney *U* test for continuous data. All data were monitored by the research monitoring officer and the quality of the data was secondarily validated by the team of data managers. For safety, all data were reviewed by the pharmacovigilance department. The statistical analysis plan is reported in the appendix (pp 14–19).

Event-free days were calculated as the number of days during which the patient was alive and free from the event of interest until day 28 (or day 60). The number of event-free days was 0 for patients who died within 28 (or 60) days.[23] The numbers of event-free days were compared between groups using the Mann-Whitney *U* test. Missing data were described and no imputation was performed for outcomes without complete data.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Oct 14, 2015, to May 27, 2020, 2230 patients were screened, 345 were randomly assigned to receive either ceftriaxone (171 patients) or placebo (174 patients), and 330 received the allocated intervention. 15 did not receive the allocated intervention and were excluded post-randomisation, six from the ceftriaxone group and nine from the placebo group, for the following reasons: lack of relatives to give consent; patients under legal or administrative protection; randomisation system failure; and after investigator decision for non-eligibility criteria discovered after randomisation (distribution between groups is detailed in figure 1).[21] 11 patients withdrew consent (three from the ceftriaxone group and eight from the placebo group). 319 patients (mean age 57 years [SD 16]; 153 [48%] women) were included in the analysis (162 assigned to receive ceftriaxone and 157 to placebo; figure 1). Patient characteristics were well balanced between the groups (table 1, appendix pp 2–3). Mouth care was performed with a 0·12% aqueous chlorhexidine solution in three centres (134 patients, 68 in the ceftriaxone group and 66 in the placebo group) and with sterile water in six centres (185 patients, 94 in the ceftriaxone group and 91 in the placebo group). Out of the 201 patients requiring surgery, only 24 required antibiotic prophylaxis, well

	Ceftriaxone group (n=162)	Placebo group (n=157)	Standardised mean difference
Age, years	56 (16)	57 (15)	0·046
Sex			
Female	82 (51%)	71 (45%)	0·108
Male	80 (49%)	86 (55%)	..
BMI	26 (5)	26 (6)	0·052
Medical history			
Chronic lung disease	4 (3%)	2 (1%)	0·088
Chronic renal failure	2 (1%)	2 (1%)	0·004
Heart failure NYHA class 3 and 4	2 (1%)	3 (2%)	0·054
Diabetes mellitus	6 (4%)	7 (5%)	0·038
Immunodepression	0 (0%)	1 (1%)	0·113
Haemopathy	2 (1%)	0 (0%)	0·158
Alcoholism	28 (17%)	23 (15%)	0·072
Smoking	34 (21%)	35 (22%)	0·032
Metastatic cancer	1 (1%)	1 (1%)	0·002
Cirrhosis	3 (2%)	0 (0%)	0·194
Main severe brain injury	..	..	0·138
Ischaemic stroke	16 (10%)	13 (8%)	..
Haemorrhagic stroke	35 (22%)	33 (21%)	..
Subarachnoid haemorrhage	62 (38%)	69 (45%)	..
Brain trauma	49 (30%)	40 (26%)	..
GCS score*	..	..	0·122
3	28 (17%)	21 (13%)	..
4–8	97 (60%)	102 (65%)	..
9–12	37 (23%)	34 (22%)	..
SAPS II score†	47 (11)	48 (13)	0·046
Time from medical care onset to tracheal intubation, h‡	1 (0–4)	1 (0–3)	0·092
PaO_2/FiO_2 ratio at randomisation	..	..	0·183
<100	3 (2%)	5 (3%)	..
100–199	28 (17%)	18 (12%)	..
≥200	131 (81%)	134 (85%)	..
Time from tracheal intubation to treatment administration, h	7 (4)	7 (3)	0·032
Temperature at ICU admission, °C	..	..	0·008
≥39	10 (6%)	10 (6%)	..
<39	152 (94%)	147 (94%)	..
Leukocytosis at ICU admission, per mm^3	..	..	0·198
<10 000	3 (2%)	0 (0%)	..
10 000–19 990	132 (82%)	128 (82%)	..
≥20 000	27 (17%)	29 (19%)	..

Data are median (IQR), mean (SD), n (%), or standardised mean difference. The following data were missing: main diagnosis for two patients receiving placebo, and time to tracheal intubation for three patients receiving ceftriaxone and one receiving placebo. GCS=Glasgow Coma Scale. NYHA=New York Heart Association. SAPS II=Simplified Acute Physiology Score II. *GCS ranges from 3 (which indicates a deep coma) to 15 (which indicates a fully awake patient). †SAPS II ranges from 0 to 163, with higher score indicating greater risk of death. ‡Time from medical care onset to tracheal intubation was the time from the beginning of prehospital care or arrival at hospital to tracheal intubation.

Table 1: **Patient characteristics at baseline**

See **Online** for appendix

balanced between groups; the remaining patients underwent radiological intervention or external ventricular derivation.

Among the 160 cases of VAP in 139 patients reported by investigators (69 in 60 patients receiving ceftriaxone and 91 in 79 patients receiving placebo; p=0·017), 93 were confirmed after adjudication (35 with ceftriaxone and 58 with placebo), with no bacteraemia. These 93 cases of VAP occurred in 90 patients (one patient developed one case of early VAP and one of late VAP; one patient developed one case of early VAP and two cases of late VAP), so 90 (28%) of 319 patients had at least one VAP episode. Among the adjudicated early VAP cases, diagnosis was based on 14 (61%) proximal and 9 (39%) distal samples of 23 in the ceftriaxone group and 32 (63%) proximal and 19 (37%) distal samples of 51 in the placebo group (p=0·878).

The median time from tracheal intubation to first VAP was 5 (IQR 3–7) days, and was significantly higher in patients receiving ceftriaxone (5 [3–9] days) compared with placebo (4 [2–6] days; p=0·048). Incidence of VAP per centre is reported in the appendix (pp 4–7).

Early VAP represented 82% of all cases of VAP and occurred less frequently in patients receiving ceftriaxone (23 [14%] of 162) than in those receiving placebo (51 [32%] of 157; hazard ratio [HR] 0·60 [95% CI 0·38–0·95], p=0·030; figure 2A, table 2).

At day 28, compared with patients receiving placebo, those receiving ceftriaxone were at lower risk of developing all types of VAP (20% *vs* 36%; HR 0·62 [0·42–0·98]); incidences of late VAP were similar between groups (figure 2B, table 2). Incidence of ventilator-associated events is detailed in the appendix (pp 8–9). Ceftriaxone administration also reduced the risk of being exposed to mechanical ventilation (median ventilator-free days 9 [IQR 0–22] *vs* 5 [0–18], p=0·023) and to antibiotics (median antibiotic-free days 21 [13–28] *vs* 15 [8–21], p<0·0001) and significantly improved the modified Rankin score (table 2). Mortality was lower in patients who received ceftriaxone than in those who received placebo (15% *vs* 25%; HR 0·62 [95% CI 0·39–0·97], p=0·036; table 2). Out of the 64 patients who were deceased at day 28, 59 deaths were reported by investigators to be related to consequences of the initial brain injury.

At day 60, exposure to ICU (median ICU-free days 34 [15–49] *vs* 26 [0–42], p=0·0033) and to hospital (median hospital-free days 23 [0–39] *vs* 8 [0–33], p=0·0057) was lower with ceftriaxone than with placebo. Neurological outcome was similar between groups, and mortality was 32 (20%) of 161 patients receiving ceftriaxone versus 46 (30%) of 157 receiving placebo (HR 0·66 [0·42–1·04], p=0·074; table 2).

Of the 93 cases of VAP, 55 (59%) were polymicrobial, with no difference between the ceftriaxone (19 [54%]) and placebo (36 [62%]) groups. The bacteria most commonly isolated in early VAP were, in order of decreasing frequency, meticillin-sensitive *Staphylococcus aureus*, *Streptococcus* spp, *Haemophilus* spp, and *Escherichia coli* (table 3). *Haemophilus influenzae* was found less often with ceftriaxone than with placebo. Overall, the incidence of resistant isolates was very low. Only one meticillin-resistant *S aureus* strain and one ESBL-producing *Enterobacteriaceae* strain were found in the placebo group. Microbiological documentation of all confirmed cases of VAP and late VAP are detailed in the appendix (pp 10–11). The antimicrobial agents prescribed in both groups are reported in the appendix (pp 12–13).

194 adverse events were reported in 152 patients, including 90 (44%) severe cases (39 with ceftriaxone and 51 with placebo). All serious events were attributed to the initial disease and not to trial intervention, except for one suspicion of anaphylaxis to study treatment in the placebo group. None of the 11 patients who withdrew consent developed any serious side-effect related to the allocated treatment.

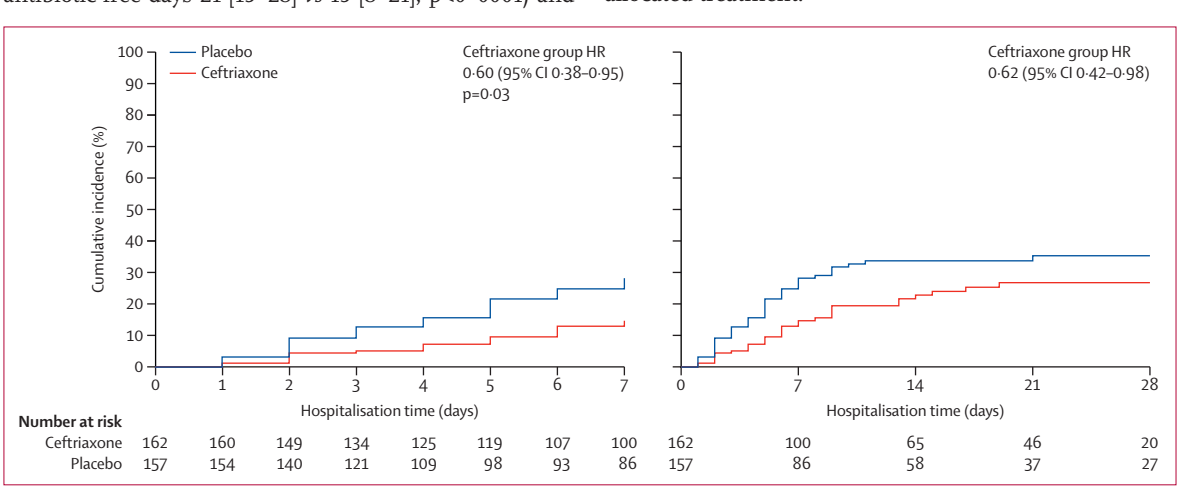

Figure 2: **Cumulative incidence of (A) early and (B) all cases of ventilator-associated pneumonia**
Cumulative incidence curves of early (from the second to the seventh day of mechanical ventilation) and all cases of ventilator-associated pneumonia were compared using the Fine-Gray approach between patients assigned to receive ceftriaxone and those assigned to receive placebo. HR=hazard ratio.

Three patients developed *Clostridium difficile* infection, one in the ceftriaxone group and two in the placebo group. Among the 115 patients with rectal swabs (59 in the ceftriaxone group and 56 in the placebo group), only two cases of ESBL-producing *Enterobacteriaceae* acquisition were observed during the ICU stay, both with ceftriaxone. No more broad-spectrum antibiotics were prescribed in the ceftriaxone group compared with the placebo group (appendix pp 12–13). Table 4 reports adverse events that occurred during the follow-up by group.

	Ceftriaxone group (n=162)	Placebo group (n=157)	HR	p value
Primary outcome				
Early VAP	23/23 (14%)	51/51 (32%)	0·60 (0·38–0·95)	0·030
Secondary outcomes on day 28				
All VAP	35/33 (20%)	58/57 (36%)	0·62 (0·42–0·98)	..
Late VAP	12/11 (7%)	7/7 (5%)	..	..
Ventilator-free days	9 (0–22)	5 (0–18)	..	0·023
Antibiotic-free days	21 (13–28)	15 (8–21)	..	<0·0001
Time between inclusion and first VAP, days	5 (3–9)	4 (2–6)	..	0·048
Modified Rankin score	..	..	..	0·032
0–1	27/145 (19%)	13/139 (9%)	..	..
2–3	30/145 (21%)	23/139 (17%)	..	..
4–5	63/145 (43%)	64/139 (46%)	..	..
6	25/145 (17%)	39/139 (28%)	..	..
Mortality	25/162 (15%)	39/157 (25%)	0·62 (0·39–0·97)	0·036
Secondary outcomes on day 60	..	..	..	..
ICU-free days	34 (15–49)	26 (0–42)	..	0·0033
Hospital-free days	23 (0–39)	8 (0–33)	..	0·005
Modified Rankin score*	..	..	..	0·17
0–1	44/158 (28%)	31/155 (20%)	..	..
2–3	32/158 (20%)	28/155 (18%)	..	..
4–5	50/158 (32%)	50/155 (32%)	..	..
6	32/158 (20%)	46/155 (30%)	..	..
Mortality	32/161 (20%)	46/157 (30%)	0·66 (0·42–1·04)	0·074

Data are median (IQR), n (%), n/N (%), mean number of events/number of patients evaluated, or HR (95% CI). HR (95% CI) are presented for qualitative variables taking account of competing risk if needed. VAP that occurred during the first 7 days of hospitalisation was defined as early, and VAP that occurred after the first 7 days of hospitalisation was defined as late. The following data were missing: antibiotic-free days for one patient receiving placebo, ICU-free days for one patient receiving placebo, modified Rankin score on day 28 for 17 patients receiving ceftriaxone and 18 receiving placebo, modified Rankin score on day 60 for four patients receiving ceftriaxone and two receiving placebo, and death at day 60 for one patient receiving ceftriaxone. HR=hazard ratio. ICU=intensive care unit. VAP=ventilator-associated pneumonia. *Modified Rankin scale ranges from 0 to 6, with 0 representing no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.

Table 2: **Primary and secondary outcomes**

Discussion

In patients with brain injury who required ICU admission and mechanical ventilation, we found that early administration of a single ceftriaxone dose decreased the risk of VAP, exposure to ventilation, exposure to antibiotics, prolonged ICU and hospital stay, and mortality, with no safety concerns.

Reported incidence of VAP among comatose patients varies widely depending on coma origin, method of VAP diagnosis, and study design, ranging from 20% in the largest European trauma brain CENTER-TBI cohort, to 28% in post-stroke patients, to 53% in the double-blind, multicentre, randomised CORTI-TC study conducted in patients with severe head trauma.[5,6,24] High risk of VAP among patients with brain injury has been linked to glottis dysfunction favouring tracheal aspiration of upper airway secretions before tracheal intubation, and prolonged need for mechanical ventilation. Indeed, upper airway colonisation was reported as an independent factor of tracheobronchial colonisation (odds ratio [OR] 9·9 [95% CI 1·8–56·3]), leading to higher risk of early VAP (OR 4·4 [0·7–23·3]),[25] a finding subsequently confirmed by other authors.[19] The progression from tracheal colonisation to infection is favoured by early impairment of immune defences secondary to brain injury.[7] In the current trial, overall incidence of patients with at least one VAP was 28%. This relatively low incidence could be attributed to the systematic implementation of bundles known to decrease VAP incidence in the ICU and to the adjudication of all suspected cases of VAP.[16] Moreover, the existence of incipient pneumonia before randomisation cannot be totally excluded, as a chest x-ray was not mandatory before randomisation. Nevertheless, the objective of antibiotic prophylaxis is the control of tracheal colonisation or incipient infection. The diagnosis of VAP remains challenging. A recent meta-analysis reported poor accuracy of classical indicators for diagnosis of VAP (physical examination, chest radiography, endotracheal aspirate, bronchoscopic sampling cultures, and clinical pulmonary infection score value over 6) compared with the reference standard (lung histopathology) even when they are used in combination,[26] and VAP is often overdiagnosed by physicians.[13] To minimise the risk of reporting bias, an adjudication committee unaware of trial group assignment confirmed all suspected cases of VAP based on predefined criteria, and 42% of cases initially reported by investigators were not subsequently confirmed after adjudication. The most frequent missing criteria were a positive bacteriological sample at the required threshold (52 of 67) and presence of a new infiltrate on chest x-ray (36 of 67). As a result, most of the suspected cases of VAP not selected by the adjudication committee met the ventilator-associated tracheobronchitis criteria. Furthermore, the significance threshold of microbiological samples at diagnosis could be challenged, because the ceftriaxone received could, theoretically, have an early impact on bacterial colonies in patients in the intervention group. However, we followed the standardised approach planned in the protocol of the trial, based on current recommended criteria for the diagnosis and confirmation of VAP.

Prevention of VAP has been widely investigated for several decades, and current recommendations suggest

	Ceftriaxone group (n=35)	Placebo group (n=85)
Gram-negative bacilli		
Enterobacter spp	4 (17%)	2 (4%)
Haemophilus influenzae	0	17 (33%)
Klebsiella spp	2 (9%)	1 (2%)
Escherichia coli	4 (18%)	3 (6%)
Proteus species	0	1 (2%)
Pseudomonas aeruginosa	1 (4%)	1 (2%)
ESBL-producing *Enterobacteriaceae*	0	1 (2%)
Others	0	2 (4%)
Anaerobes	0	1 (2%)
Gram-positive cocci		
Meticillin-sensitive *Staphylococcus aureus*	7 (30%)	25 (49%)
Meticillin-resistant *Staphylococcus aureus*	0	1 (2%)
Streptococcus pneumoniae	1 (4%)	3 (6%)
Other Streptococcus spp	8 (35%)	15 (29%)
Meticillin-resistant coagulase-negative *Staphylococcus*	0	1 (2%)
Enterococcus spp	3 (13%)	0
Anaerobes	0	1 (2%)
Oropharyngeal flora	5 (22%)	7 (14%)
Gram-positive bacilli	0	2 (4%)
Gram-negative cocci	0	1 (2%)

Data are n (%). A total of 35 pathogens were isolated in 23 samples from the ceftriaxone group, and 85 pathogens were isolated in 51 samples from the placebo group. ESBL=extended spectrum β-lactamase.

Table 3: **Microbiological documentation of confirmed early ventilator-associated pneumonia**

	Ceftriaxone group (n=95)	Placebo group (n=99)
Cutaneous abscess	1	0
Pulmonary abscess	0	1
Ischaemic stroke	7	5
Delirium	3	0
Anaemia	1	0
Pneumonia	11	13
Cardiac arrest	1	2
Atelectasis	2	0
Bacteraemia	2	2
Tracheobronchitis	3	2
Cutaneous mucosis candidosis	1	1
Cardiac failure	1	2
Anaphylactic shock	1	0
Septic shock	2	5
Hepatic cytolysis	1	1
Refractory cranial hypertension	16	23
Multiorgan failure	0	2
Acute respiratory distress syndrome	4	4
Cerebral rebleeding	4	7
Diabetes insipidus	1	0
Clostridium difficile diarrhoea	1	0
Air embolism	1	0
Pulmonary embolism	2	2
Skin rash	2	2
Erysipelas	1	0
Status epilepticus	2	0
Brain tumour	0	1
Hydrocephalus	1	0
Hyperparathyroidism	1	0
Catheter-related infection	2	2
Urinary infection	0	2
Acute kidney insufficiency	0	1
CNS infection	5	8
Myelofibrosis	1	0
Nausea or emesia	1	2
Pneumothorax	1	1
Pyelonephritis	0	1
Prostatitis	0	1
Sinusitis	1	1
Cerebral salt wasting syndrome	8	4
Thrombopenia	2	0
Thrombophlebitis	1	0
Peritonitis	0	1

Data are n.

Table 4: **Adverse events during the follow-up by group**

that systematic SOD and SDD with topical, oral, and parenteral antibiotics four times per day as long as the patient is under mechanical ventilation associated with a maximal 5-day course of intravenous antibiotic prophylaxis, to decrease mortality.[8] This recommendation is still not routinely applied worldwide due to the cumbersome nature of the selective decontamination procedures and to fear of an increased risk of antibiotic-resistant infections due to prolonged antimicrobial exposure. In a recent meta-analysis comparing mortality in trials investigating SDD with or without systemic antimicrobial therapy, in-ICU mortality was decreased only if both therapies were applied in combination, with relative risk of 0·78 (95% CI 0·69–0·89, p<0·001; I^2=33%).[27] Alternatively, early (within the first 4 days of mechanical ventilation) short-term intravenous antibiotic prophylaxis alone was investigated in comatose patients in three small-scale studies; a protective effect on early VAP was observed without any effect on mortality.[2,11,12] Moreover, all of these studies have several limitations, which raise doubts about the findings, including failure to mask the treatment received and absence of an adjudication committee for VAP diagnosis. The double-blind, randomised, placebo-controlled ANTHARTIC trial involving adult patients under mechanical ventilation after cardiac arrest confirmed the benefit of intravenous prophylactic antibiotic alone in reducing early VAP, but once again without any benefit on outcomes such as ventilator exposure or mortality.[13] As in our study,

incidence of late VAP was similar between groups, being a consequence of prolonged mechanical ventilation rather than initial tracheal colonisation.

In our study, we chose to enrol patients with acute brain injury, in part because the occurrence of VAP has the potential to worsen outcomes in this population. We chose ceftriaxone as the prophylactic antibiotic, a third-generation cephalosporin with a spectrum effective against the targeted microorganisms and a long half-life enabling efficacy for 24 h without redosing. The amoxicillin–clavulanic acid combination could have been chosen because of its greater efficacy against *S aureus*, but as previous studies had tested cephalosporins and the guidelines tended to favour cephalosporins, we chose ceftriaxone. For the first time, administration of a single dose of ceftriaxone, without associated SOD or SDD, reduced exposure to mechanical ventilation, antibiotics, hospital and ICU stay, and mortality, in addition to prevention of VAP. This could be explained by our large sample size and the target population. First, a meta-analysis that studied the attributable mortality of VAP reported an overall estimation of 13%, with the highest estimates in surgical patients (69%) and in patients with mid-range severity score (Simplified Acute Physiology Score II value of 35–58; 47%).[28] In our population, 63% of patients required surgery and the mean Simplified Acute Physiology Score II was 47 (SD 12), which might partially explain the significant effect on mortality. The other hypothesis related to a reduction in secondary insults, as our two groups were similar in terms of severity at randomisation; by decreasing VAP with ceftriaxone administration, secondary insults such as hypoxia, hypercapnia, and hypotension might have been less frequent, which could have reduced mortality in this group. Unfortunately, this hypothesis cannot be proven, as secondary insults were not followed in the study.[19] In an observational study involving 109 patients with head trauma, those with early VAP had significantly longer duration of mechanical ventilation and ICU stay and a higher mortality rate (24% *vs* 14%, p=0·17).[19] Similar results were reported in another study involving 125 patients with closed head trauma.[29] Both reported poorer neurological outcomes in patients with early VAP at ICU discharge, but assessment was based on the GCS. The absence of significant improvement in neurological outcome of our patients could be explained by a lack of power ascribable to the number of missing data. However, all these hypotheses concerning the effect of ceftriaxone prophylaxis on mortality must be treated with caution and require further investigation.

Microbiological documentation of early VAP in both study groups was broadly similar, with a predominance of *S aureus*, which is consistent with previous studies conducted in this population.[19,25] The only significant difference between study groups concerned *H influenzae*, amounting to 0% of bacteria identified in the ceftriaxone group versus 33% in the placebo group, possibly related to the high activity of ceftriaxone against *H influenzae*. No emergence of difficult-to-treat microorganisms on pulmonary samples, significant difference in ESBL-producing *Enterobacteriacae* acquisition in rectal swabs, or differences in *C difficile* infections were observed in the ceftriaxone group, although the number of events was low. This finding is in line with the ANTHARTIC trial, which compared amoxicillin–clavulanate versus placebo for 48 h in adult patients being mechanically ventilated after cardiac arrest and did not report any increase in resistance.[13] Similarly, a meta-analysis on the effects of SOD or SDD on antimicrobial resistance compared with no intervention reported a decrease in third-generation cephalosporin-resistant Gram-negative bacilli with selective decontamination (OR 0·33 [0·20–0·52]), which was associated with a decrease in antibiotic use in patients receiving selective decontamination.[30]

Our trial has some limitations. First, the implementation of recommended measures for VAP prevention was not monitored. However, the ICUs participating in the trial had extensive experience with clinical studies in the area of VAP prevention and all had a written protocol on VAP prevention. Second, the protocol was not designed to monitor modification of digestive microbiota. Only participants with routine samplings at ICU admission and discharge provided information. For these reasons, the lack of impact on the intestinal microbiota and on the risk of emergence of antibiotic-resistant bacteria require further study. Third, we did not study the impact of early administration of ceftriaxone on the occurrence of health-care-associated infections other than VAP, nor did we follow non-ventilated pneumonia and collect the type of antibiotics administered in order to determine whether the intervention modified the choice, spectrum, and duration of subsequent antibiotic treatments. Fourth, the treatment blinding procedure was not performed in the pharmacy, but infusions were prepared by a nurse from a neighbouring unit. These nurses were not involved in the care of participants and, as ceftriaxone in solution is slightly coloured, opaque syringes and infusion lines were used to avoid any information about the allocated group. Finally, the adjudication committee that reviewed all suspected cases of VAP was not independent, but medical charts of patients were rigorously anonymised and the members were strictly masked to study group assignment. In addition, the superiority of antibiotic prophylaxis in preventing early-onset pneumonia had been observed before adjudication.

Key strengths of the trial were its design (multicentre, double-blind, with placebo), inclusion of patients with a variety of traumatic and non-traumatic brain injuries, and use of a central adjudication committee masked to group assignments to diagnose VAP. Our results suggest that early administration of 2 g ceftriaxone could be

applied to all patients with brain injury who require mechanical ventilation, considering the population studied and the design of our study, in particular its multicentre nature. Further studies are needed to determine whether this strategy is safe and does not increase antibiotic resistance.

In conclusion, the study findings provide evidence of the efficacy of an early, single dose of ceftriaxone to prevent early VAP in patients with severe brain injury. This simple measure was also associated with decreased antibiotic and ventilation exposure and mortality at day 28, as well as decreased ICU and hospital exposure at day 60 without safety concerns in our study.

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Contributors

CD-F and OM conceived the study, participated in protocol development, study design, and data interpretation, and co-wrote the first draft of the report. CD-F coordinated the study. SL, TK, P-FP, TG, KA, RC, YL, VC, ML, TG, and MB participated in data collection and data interpretation, and were involved in critical appraisal and revision of the manuscript. CD-F, TK, and CG participated in the masked central adjudication committee. CD-F, OM, DF, and CA accessed and verified the data. CA and DF provided statistical expertise and review of the report. All authors had full access to all the data in the study and approved the final manuscript for submission. All collaborators for the PROPHY-VAP study group are reported in the supplementary appendix.

Declaration of interests

CD-F reports honoraria for lectures from Pulsion; and support for attending meetings or travel from Codman and Sophysa. OM reports grants from 3M and Becton Dickinson; consulting fees from 3M and Becton Dickinson; honoraria for lectures from 3M and Becton Dickinson; support for attending meetings or travel from 3M and Becton Dickinson; and payment for participation on a data safety monitoring board (DSMB) or advisory board for 3M and Becton Dickinson. KA reports consulting fees from Edwards Life Science; and honoraria for lectures from LFB, Baxter, and Edwards Life Science. SL reports consulting fees from Vifor Pharma; honoraria for lectures from Vifor Pharma and Pfizer; and support for attending meetings or travel from Pharmacosmos. MB reports grants from Becton Dickinson; honoraria for lectures from Becton Dickinson; and payment for participation on a DSMB or advisory board for Becton Dickinson and Edwards Life Science. YL reports honoraria for lectures from Integra Lifesciences. All other authors declare no competing interests.

Data sharing

Data collected for the study, including individual participant data, the data dictionary defining each field in the set, and the study protocol, will be made available to others. Data will be communicated as de-identified participant data according to French law, and will be available after publication of the manuscript. Data will be made available at the Direction de la Recherche Clinique, Poitiers University Hospital, Poitiers, France (drci@chu-poitiers.fr), with investigator support, after approval of a proposal with a signed data access agreement.

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