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Antibiotic prophylaxis of early onset pneumonia in critically ill comatose patients. A randomized study

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Abstract *Objective:* To evaluate if a 3-day ampicillin-sulbactam prophylaxis can reduce the occurrence of early-onset pneumonia (EOP) in comatose mechanically-ventilated patients. *Design:* This was a single-centre, prospective, randomised, open study. *Setting:* A 10-bed general-neurological ICU in a 2,000-bed university hospital. *Patients and participants:* Comatose mechanically-ventilated patients with traumatic, surgical or medical brain injury. *Interventions:* Patients were randomized to either ampicillin-sulbactam prophylaxis (3 g every 6 h for 3 days) plus standard treatment or standard treatment alone. *Measurements and results:* Main outcome was the occurrence of EOP. Secondary outcome measures were occurrence of late-onset pneumonia, percentage of non-pulmonary infections and of emerging multiresistant bacteria, duration of mechanical ventilation and of ICU stay and ICU mortality. Interim analysis at 1 year demonstrated a statistically significant reduction of EOP in the ampicillin-sulbactam group, and the study was interrupted. Overall, 39.5% of the patients developed EOP, 57.9% in the standard treatment group and 21.0% in the ampicillin-sulbactam group (chi-square 5.3971; P =0.022). Relative risk reduction of EOP in patients receiving ampicillin-sulbactam prophylaxis was 64%; the number of patients to be treated to avoid one episode of EOP was three. No differences in other outcome parameters were found; however, the small sample size precluded a definite analysis. *Conclusions:* Antibiotic prophylaxis with ampicillin-sulbactam significantly reduced the occurrence of EOP in critically ill comatose mechanically ventilated patients. This result should encourage a large multicenter trial to demonstrate whether ampicillin-sulbactam prophylaxis reduces patient mortality, and whether antibiotic resistance is increased in patients receiving prophylaxis.

Keywords Pneumonia · Antibiotic prophylaxis · Coma · Brain injury

Introduction

Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection in the intensive care unit (ICU), being responsible for more than half of antibiotic prescriptions in the ICU [1, 2, 3]. It is usual to distinguish early-onset VAP (EOP), which occurs during the first 4 days of mechanical ventilation, from late-onset VAP (LOP), which develops 5 or more days after initiation of mechanical ventilation [4]. This distinction is important because the causative pathogens are different, the disease is usually less severe and the prognosis is better in EOP than LOP.

Altered consciousness is a recognized risk factor for VAP [5, 6], and the occurrence of EOP in these patients is extremely high, accounting for 70% of all cases of

pneumonia [7]. In a previously published paper we showed that the occurrence of EOP in patients with an ICU stay of >48 h was 32% [8], 44% in comatose patients and 29% in non-comatose patients (unpublished data).

Colonization of the upper airways (nose, pharynx, trachea) is an independent risk factor for the development of EOP, and is already demonstrable within 24 h of ICU admission in critically ill neurological patients [6, 9]. Etiologic pathogens for EOP in these patients are the same bacteria that colonize the upper airways, namely methicillin-susceptible *Staphylococcus aureus*, *Haemophilus influenzae* and *Streptococcus pneumoniae* [6, 9].

In a randomized controlled trial (RCT), short-term antibiotic prophylaxis (two single cefuroxime doses 1,500 mg each 12 h apart after intubation) has been demonstrated to reduce significantly the occurrence of EOP in critically ill neurological patients [7]. Although this study is commonly quoted as being performed in patients with "structural coma" [7, 10], it actually enrolled patients with various degrees of consciousness alteration, either comatose [Glasgow Coma Scale (GCS) score $\leq$8] [11] and non-comatose (GCS score 9–12) patients. Coma is a powerful predictor of morbidity and mortality in several clinical conditions [11, 12, 13], and comatose patients have depressed immune function [5, 6], frequent upper airway colonisation on ICU admission [6, 9], and altered or absent airway protective reflexes with risk of aspiration [12, 14].

We hypothesized that comatose patients would mostly benefit from effective prophylactic antibiotic regimens. Therefore, we set out to evaluate if a short-term antibiotic prophylaxis can reduce the occurrence of EOP in a cohort of critically ill comatose patients.

Materials and methods

This prospective, randomized, open study was conducted at the Institute of Anesthesiology and Intensive Care of the University of Brescia, Spedali Civili, Italy, from September 2001 to October 2002. The study was approved by the local ethics committee and was unsponsored. Written informed consent was obtained by the next of kin.

Adult ($\geq$18 years), comatose mechanically ventilated patients were eligible for this study. Comatose patients were defined according to current criteria as those patients not obeying simple commands, not opening their eyes and not uttering words, with a GCS score that was $\leq$8 [11].

Patients were excluded if they: (1) had pneumonia or pulmonary contusion on admission to the ICU; (2) had received antibiotics in the previous 48 h, although single-dose perioperative antibiotic prophylaxis was allowed; (3) had multiple trauma; (4) had a clinical indication to antibiotic prophylaxis or treatment (i.e., open craniocerebral wound, or extensive soft tissue facial lesion); (5) had an estimated duration of mechanical ventilation or coma of less than 48 h; (6) had a hopeless prognosis; (7) were immunocompromised; (8) were pregnant; (9) were already included in another therapeutic trial; (10) written informed consent was not obtained.

Patients were randomly assigned to receive either ampicillin-sulbactam (3 g every 6 h for 3 days) [15] plus standard treatment or standard treatment alone. Patients in the standard treatment group did not receive a placebo. Ampicillin was chosen according to our local epidemiological data showing that 80% of micro-organisms responsible for EOP were susceptible to ampicillin-sulbactam [8]. Ampicillin-sulbactam is also active against anaerobic micro-organisms, which have been demonstrated to cause pneumonia in critically ill neurological medical patients, where aspiration is a relevant pathogenetic mechanism [16]. Finally, ampicillin-sulbactam, differently from cephalosporins, exerts a limited pressure on the emergence of gram-negative resistant bacterial strains [17].

A randomization schedule was created with computer-generated random numbers. Numbers identifying the patient's assignment were concealed in sealed opaque envelopes, which were kept in a locker, whose key was available to the attending intensivist. As soon as the patient was admitted to the ICU, and inclusion and exclusion criteria were verified, the intensivist was responsible for code disclosure and patient assignment. Ampicillin-sulbactam was started in all cases within 6 h of ICU admission. Patients in the standard treatment group did not receive antibiotics in the first 3 ICU days unless it was clinically dictated. Treating physicians and paramedics were not blinded to treatment allocation; the outcome adjudicators (TU, CG) and the data analyst (NL) were.

The primary efficacy outcome measure was the incidence of EOP. Secondary outcome measures were occurrence of LOP, percentage of non-pulmonary infections and of emerging multiresistant bacteria, duration of mechanical ventilation and of ICU stay and ICU mortality.

Data collection

At admission to the ICU all patients were intubated and mechanically ventilated. The patient's semirecumbent position was adopted whenever possible, depending on intracranial pressure and cerebral perfusion pressure management. Selective digestive tract decontamination was not used; stress ulcer prophylaxis with intravenous ranitidine (50 mg every 6 h) was instituted in all patients. Enteral feeding was used, unless gastric emptying was altered, in which case parenteral nutrition was used. We recorded each patient's age, sex, type of admission, admission diagnosis, GCS score at ICU admission, brain CT scan, APACHE II and McCabe's score (Table 1). GCS at day 7, ICU mortality, the number of days before ICU admission, and duration of mechanical ventilation and of ICU stay were also collected.

Definitions

VAP was defined as pneumonia occurring more than 48 h after endotracheal intubation and initiation of mechanical ventilation [2, 10]. EOP was defined as pneumonia occurring during the first 4 days of mechanical ventilation, whereas LOP was defined as pneumonia developing 5 or more days after the initiation of mechanical ventilation [2, 4, 10].

EOP was suspected if a new and persistent chest radiographic infiltrate was associated with one of the following criteria: (1) purulent tracheo-bronchial secretions; (2) fever $\geq$38.3°C or hypothermia; (3) leukocytosis or leucopoenia (>10,000/mm^3 and, respectively, <5,000/mm^3). EOP was confirmed by the isolation of a potentially pathogenic micro-organism from bronchoscopic BAL (>10^4 cfu/ml) or non bronchoscopic protected mini-BAL (>10^4 cfu/ml).

All patients had chest X-ray examination and pulmonary secretion sample taken with bronchoscopic BAL or non-bronchoscopic protected mini-BAL immediately after enrollment into the study, and then every 48 h or more frequently if clinically indicated for the first 5 ICU days. Thereafter, radiological and microbiological investigations were made on clinical ground and were the responsibility of the attending intensivist. The radiologist and the clinical microbiologist were not aware of the patient's treatment

Table 1 Baseline characteristics, severity and clinical outcome of the study population. *In four patients with early death, data were not available

		Standard treatment	Ampicillin-sulbactam
Number of patients		19	19
Male	Number (%)	12 (63.2)	13 (68.4)
Age	Mean (S.D.)	54.6 (17.7)	54.8 (18.0)
Admission type	Number (%)		
Urgent surgery		10 (52.6)	8 (42.1)
Elective surgery		1 (5.3)	1 (5.3)
Medical		8 (42.1)	10 (52.6)
Origin	Number (%)		
Home		15 (78.9)	16 (84.2)
Medical or surgical ward		4 (21.0)	3 (15.8)
Admission diagnosis	Number (%)		
Head trauma		7 (36.8)	6 (31.6)
Subarachnoid/cerebral haemorrhage		9 (47.4%)	8 (42.1)
Cardiac arrest		2 (10.5)	2 (10.5)
Ischaemic stroke		1 (5.3)	2 (10.5)
Carbon monoxide poisoning		–	1 (5.3)
GCS score	Median (IQR)		
At ICU admission		5 (4–7)	5 (3–7)
At 7 days*		4 (3–6)	7 (5–10)
APACHE II*	Median (IQR)	22 (18–23)	20 (17–24)
McCabe classification	Number (%)		
Nonfatal underlying disease		17 (89.5)	18 (94.7)
Ultimately fatal underlying disease		2 (10.5)	1 (5.3)
Rapidly fatal underlying disease		0	0
Days before ICU admission	Mean (S.D.)	0.9 (1.9)	0.8 (1.9)
Days of mechanical ventilation	Mean (S.D.)	10.6 (9.4)	9.9 (6.9)
ICU days	Mean (S.D.)	12.6 (9.7)	12.8 (8.7)
ICU mortality	Number (%)	8 (42.1)	7 (36.8)

assignment. Two study members (TU, CG), blind to treatment allocation, were responsible for the final diagnosis of EOP.

Other common infections (urinary tract infection, catheter-related infection, etc.) were diagnosed according to the published criteria of the Centers for Disease Control and were monitored [18].

Resistant bacteria were defined as ticarcillin-resistant *Pseudomonas aeruginosa* resistant also to ceftazidime, tobramycin, imipenem or ciprofloxacin, *Acinetobacter baumannii* , *Stenotrophomonas maltophilia* , extended-spectrum β-lactamase-producing *Enterobacteriaceae (Klebsiella, Enterobacter Aerogenes*, *Serratia*), and methicillin-resistant *Staphylococcus aureus*.

Data presentation and statistical analysis

We expressed discrete variables as counts (percentage) or median (interquartile range, IQR) and continuous variables as mean (standard deviation, SD), unless stated otherwise. The endpoints were predefined and analyzed on an intention-to-treat basis. We calculated that 142 patients randomized in equal numbers to the two groups would have an 80% power at the 5% significance level to detect a 50% EOP reduction from 44 to 22%. The 44% baseline rate was based on local epidemiological data (unpublished). The 50% reduction was based on the results of Sirvent et al. [7].

An 1-year interim analysis was planned using the Pocock stopping rule [19]. With this procedure the difference between the two groups was considered significant if the two-sided P value was <0.0294 both at the interim and final analysis. We analyzed the comparability of the standard group and ampicillin-sulbactam group by chi-square test (or Fisher's exact test), Student's t test, or Mann-Whitney U test, as appropriate. The chi-square test (or Fisher's exact test) was used to compare the occurrence of EOP in the two study arms. The risk ratio and number needed to treat were also calculated.

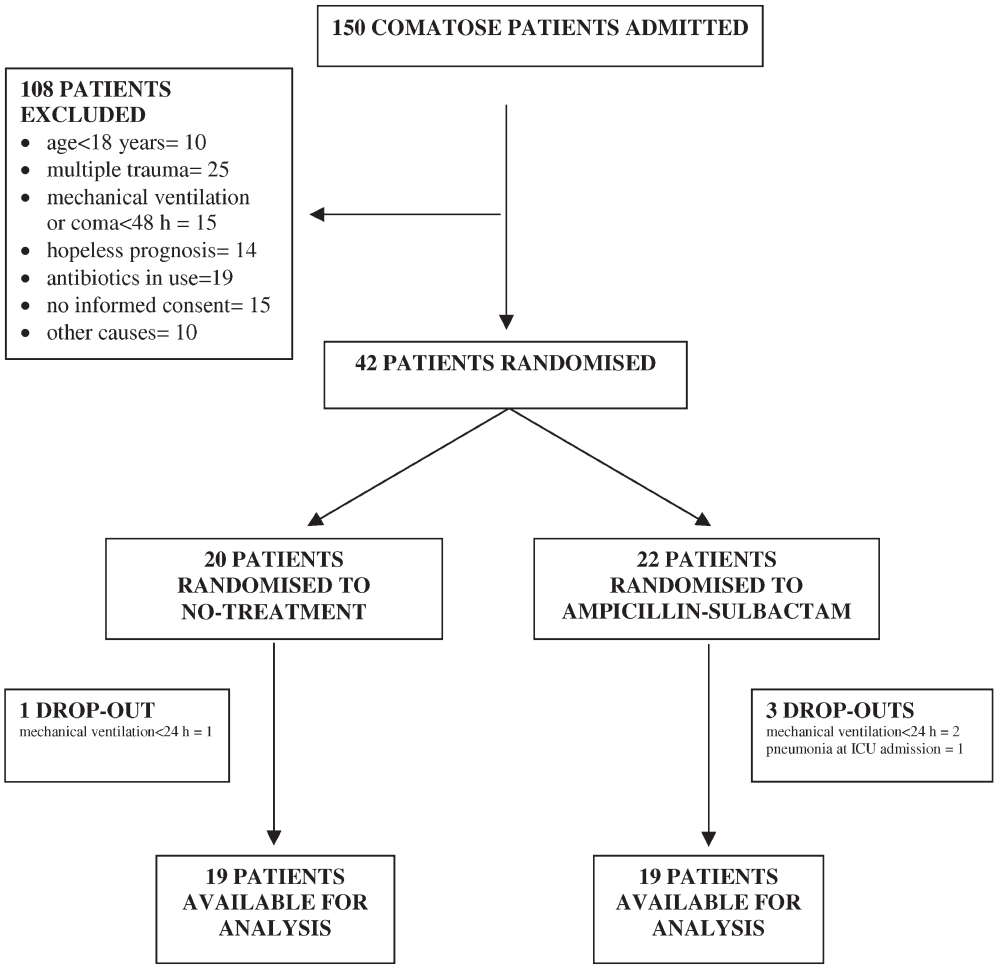
Results

The 1-year interim analysis showed that ampicillin-sulbactam significantly reduced the occurrence of EOP, and the study was stopped after 42 patients had been enrolled. Four protocol violations occurred, leaving 38 patients for the final analysis (Fig. 1). The characteristics of the study population and their main outcomes are presented in Table 1. A single 1-g dose of perioperative cefazoline was used for nine (23.7%) surgical patients, seven (36.8%) in the standard treatment group and two in the ampicillin-sulbactam group (10.5%).

Overall, 15 out of 38 patients (39.5%) developed EOP, 11 (57.9%) in the standard treatment group and 4 (21.0%) in the ampicillin-sulbactam group (chi-square 5.3971; P =0.022). The risk ratio (95% C.I.) for patients receiving ampicillin-sulbactam compared to patients receiving standard treatment was 0.36 (95% C.I. 0.14–0.94) with a relative risk reduction of 64%; the number of patients to be treated to avoid one episode of EOP was three. All 11 controls developing EOP received ampicillin-sulbactam within a mean of 3 days (range 2–5).

There were 19 LOP episodes (50.0%), 9 (47.4%) in the standard treatment group and 10 (52.6%) in the ampicillin-sulbactam group (chi-square 0.1053; P =0.746). Micro-organisms found are presented in Table 2. Multiresistant bacteria were responsible for 8 (42.1%) of 19 cases

Fig. 1 Trial profile



of LOP, 3 in the standard treatment group and 5 in the ampicillin-sulbactam group.

There were 15 episodes of non-lung infections, 8 in the standard treatment group (3 bacteraemias, 3 urinary tract infections, 1 meningitis and 1 surgical wound infection) and 7 in the ampicillin-sulbactam group (3 bacteraemias, 1 urinary tract infection, 1 meningitis, 1 surgical wound infection and 1 maxillary sinusitis). Isolates were 18, 15 bacterial and 3 fungal isolates (2 *Candida*, 1 *Aspergillus*) (Table 3). Overall, in six cases (three standard treatment, three ampicillin-sulbactam), the infections were caused by emergent multiresistant bacteria (Table 3).

The two groups were also comparable in terms of the duration of mechanical ventilation (t =0.3431, P =0.7355, duration of ICU stay (t =–0.1070, P =0.9160, and ICU mortality (chi-square 0.1101; P =0.740) (Table 1).

Discussion

In this prospective, randomized, open study we found that a 3-day ampicillin-sulbactam prophylaxis in critically ill mechanically ventilated comatose patients reduces the occurrence of EOP by 64%. No differences in other outcome parameters could be demonstrated, including the occurrence of LOP, non-lung infections and multiresistant bacteria, the duration of mechanical ventilation and ICU stay and ICU mortality. Reasons for this may be several; however, the small sample size played a major role. In fact, a much larger trial with about 3,600 patients would be needed to demonstrate a mortality reduction in the order of 5 to 6%, as in the present study, assuming an Alpha error of 5% and a power of 90%. In a recent observational study, Bronchard et al. showed a lower PaO_2:FIO_2 ratio, more episodes of arterial hypotension, a greater incidence of fever, more episodes of intracranial hypertension, a longer duration of mechanical ventilation, a lower GCS score on ICU discharge and a higher duration of stay in the ICU, together with a trend toward a higher mortality rate in head trauma patients with EOP than without (24.4 vs. 14.1%) [14]. Taken together, Bronchard's and our own results suggest that a reduction of mortality is a sensible clinical target, since development of pneumonia in the first few days of ICU admission may increase mortality in brain-

Table 2 Isolated micro-organism and resistant bacteria in lung infections

	Number (%) of isolates	Early onset pneumonia	
		Standard treatment	Ampicillin-sulbactam
		11 patients, 11 episodes, 11 isolates	4 patients, 4 episodes, 4 isolates
Staphylococcus aureus	8 (53.3%)	6[a]	2[b]
Streptococcus pneumoniae	2 (13.3%)	1	1
Pseudomonas aeruginosa	2 (13.3%)	1	1
Other bacteria	3 (20.0%)	3	0
	Number (%) of isolates	Late onset pneumonia Standard treatment 9 patients, 9 episodes, 14 isolates	 Ampicillin-sulbactam 10 patients, 10 episodes, 11 isolates
Pseudomonas Aeruginosa	4 (16.0%)	2[c]	2
Acinetobacter baumannii	0	0	0
Stenotrophomonas maltophilia	1 (4.0%)	0	1
Enterobacteriaceae			
Klebsiella	4 (16.0%)	2	2
Enterobacter aerogenes	3 (12.0%)	0	3[d]
Serratia	0	0	0
Proteus	1 (4.0%)	1	0
Haemophylus	1 (4%)	1	0
E. Coli	2 (8%)	2	0
Staphylococcus aureus	9 (36.0%)	6[e]	3[f]

[a] All *Staphylococcus aureus* methicillin sensible, [b] 1 *Staphylococcus aureus* methicillin-resistant, [c] 1 *Pseudomonas aeruginosa* imipenem-resistant, [d] 2 resistent strain *Enterobacter aerogenes*, [e] 2 *Staphylococcus aureus* methicillin-resistant, [f] all *Staphylococcus aureus* methicillin-resistant

Table 3 Isolated micro-organism and resistant bacteria in non-lung infections

	Number (%) of isolates	Gram positive isolates	
		Standard treatment	Ampicillin-sulbactam
		1 patient, 5 episodes, 5 isolates	2 patients, 3 episodes, 3 isolates
Staphylococcus aureus	6 (75.0)	4[a]	2[b]
Streptococcus pneumoniae	1 (12.5)	0	1
Other bacteria	1 (12.5)	1	0
	Number (%) of isolates	Gram negative isolates Standard treatment 2 patients, 2 episodes, 2 isolates	 Ampicillin-sulbactam 3 patients, 3 episodes, 5 isolates
Pseudomonas Aeruginosa	2 (28.6)	0	2
Acinetobacter baumannii	0	0	0
Stenotrophomonas maltophilia	0	0	0
Enterobacteriace			
Klebsiella	2 (28.6)	1	1
Enterobacter aerogenes	1 (14.3)	0	1[c]
Serratia	1 (14.3)	1	0
Proteus	0	0	0
E.Coli	1 (14.3)	0	1
Haemophylus	0	0	0
	Number of isolates	Standard treatment	Ampicillin-sulbactam
Fungi	3	1	2

[a] 3 *Staphylococcus aureus* methicillin-resistant, [b] all *Staphylococcus aureus* methicillin-resistant, [c] *Enterobacter aerogenes* resistant strain

injured comatose patients. Therefore, a large multicenter trial would be welcome in this field.

In the RCT by Sirvent et al. the occurrence of pneumonia was 50% in the control group and 24% in the cefuroxime group (EOP accounted for 70% of all pneumonia), a 52% relative risk reduction [7]. The relative risk reduction was 56% when considering only EOP (36% controls, 16% cefuroxime) [7]. Compared with these re-

sults, the occurrence of EOP in our series was higher, as was the relative risk reduction (67%). While we cannot exclude that differences are due to chance or to our local microbial epidemiology [8], the different neurological severity of the patients enrolled also played a role. According to the standard criteria [11, 12, 13], we defined as comatose those patients not obeying simple commands, not opening their eyes, and not uttering words, whose GCS score was $\leq$8, whereas Sirvent et al. simply used a GCS score of <12 to define coma [7]. There are two problems with this latter definition. First, a total GCS score can be made up by a number of different eye, motor and verbal (the three components of the GCS) profiles or permutations [20]; therefore, reporting of GCS scores in terms of profiles rather than totals is recommended [20]. Second, patients with a GCS>8 are not in coma [11]. Proper definition of coma is important since it takes account of relevant neurophysiological, neuroanatomical and neuropathological findings [13, 21]. It is also clinically relevant, since morbidity and mortality differ substantially in comatose and non-comatose patients [11, 12, 13, 22]. We therefore recommend that future studies adopt a precise definition of coma to make results comparable among different centers.

Gram-positive bacteria, particularly the *Staphylococcus aureus*, were the predominant cause of EOP in our study, a result confirming previous observations that gram-positive bacteria are the prevailing cause of pneumonia in critically ill neurological patients [5, 9]. Antibiotic prophylaxis active against gram-positive bacteria should therefore be the preferred choice in such patients.

An important question is whether the antibiotic prophylaxis may increase the emergence of multiresistant bacteria and adversely affect the outcome. We did not observe an increase of multiresistant bacteria, nor of ICU mortality, in patients receiving antibiotic prophylaxis; however, the small number of microbiological isolates and of patients enrolled precluded a definite answer. Data from the literature are controversial. Ewig et al. [6] in a prospective observational study showed that prolonged antibiotic prophylaxis independently predicts LOP; however, the mean duration of treatment was 5 days. Hoth et al. [23] in a retrospective observational study found that for patients receiving prolonged prophylactic antibiotics (mean, 8 days) the first pneumonia was diagnosed later, the causative organisms were more likely to be resistant or gram-negative bacteria, and the occurrence of antibiotic complications was two times greater than for patients who did not receive antibiotic prophylaxis. Conversely, D'Amico et al. [24] in a meta-analysis of RCTs comparing different forms of antibiotic prophylaxis (topical oral non-absorbable, systemic, combined topical and systemic) used to reduce nosocomial pneumonia and mortality found a strong reduction in respiratory tract infection and mortality when combined topical and systemic antibiotics were used, whereas a reduction in infection without a significant effect on mortality was found when only topical antibiotics were used. In the authors' view a logical next step for future trials would thus be the comparison of combined topical and systemic protocols to a regimen of a systemic antibiotic agent only to see whether the topical component can be dropped. Cook et al. in a cohort of 1,014 patients also showed that systemic antibiotic prophylaxis was an independent protective factor against pneumonia (risk ratio, 0.37; CI, 0.27 to 0.51) [1]. A recent large RCT comparing critically ill medical patients receiving topical non-absorbed antibiotics combined with an initial 4-day course of intravenous cefotaxime with controls receiving standard treatment found decreased ICU and hospital mortality in patients receiving antibiotic prophylaxis [25]. There was no evidence of increased antibiotic resistance over a 27-month observation period; however, the setting was that of low prevalence of vancomycin-resistant *Enterococcus* and meticillin-resistant *Staphylococcus aureus* [25].

In conclusion, a 3-day ampicillin-sulbactam prophylaxis was an effective measure to reduce the occurrence of EOP in critically ill comatose patients. This result should encourage a large multicentre trial to demonstrate whether antibiotic prophylaxis reduces patient mortality and whether antibiotic resistance is increased in patients receiving prophylaxis.

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