Neurocritical Care (2018) 28:362–369
https://doi.org/10.1007/s12028-017-0490-8

neurocritical care society

ORIGINAL ARTICLE

# Influence of Single-Dose Antibiotic Prophylaxis for Early-Onset Pneumonia in High-Risk Intubated Patients

Timothy D. Lewis[1,2] · Kelly A. Dehne[1,2] · Kathryn Morbitzer[1,2] · Denise H. Rhoney[2] · Casey Olm-Shipman[3] · J. Dedrick Jordan[3]

Published online: 8 January 2018


## Abstract

**Background** Early-onset pneumonia (EOP) after endotracheal intubation is common among critically ill patients with a neurologic injury and is associated with worse clinical outcomes.

**Methods** This retrospective cohort study observed outcomes pre- and post-implementation of an EOP prophylaxis protocol which involved the administration of a single dose of ceftriaxone 2 g around the time of intubation. The study included patients $\geq$ 18 years who were admitted to the University of North Carolina Medical Center (UNCMC) neuroscience intensive care unit (NSICU) between April 1, 2014, and October 26, 2016, and intubated for $\geq$ 72 h.

**Results** Among the 172 patients included, use of an EOP prophylaxis protocol resulted in a significant reduction in the rate of microbiologically confirmed EOP compared to those without prophylaxis (7.4 vs 19.8%, $p = 0.026$). However, EOP prophylaxis did not decrease the combined incidence of microbiologically confirmed or clinically suspected EOP (32.2 vs 37.4%, $p = 0.523$). No difference in the rate of late-onset pneumonia (34.6 vs 26.4%, $p = 0.25$) or virulent organism growth (19.8 vs 14.3%, $p = 0.416$) was observed. No difference was observed in the duration of intubation, duration of intensive care unit (ICU) stay, duration of hospitalization, or ICU antibiotic days within 30 days of intubation. In hospital mortality was found to be higher in those who received EOP prophylaxis compared to those who did not receive prophylaxis (45.7 vs 29.7%, $p = 0.04$).

**Conclusions** The administration of a single antibiotic dose following intubation may reduce the incidence of microbiologically confirmed EOP in patients with neurologic injury who are intubated $\geq$ 72 h. A prophylaxis strategy does not appear to increase the rate of virulent organism growth or the rate of late-onset pneumonia. However, this practice is not associated with a decrease in days of antibiotic use in the ICU or any clinical outcomes benefit.

**Keywords** Pneumonia · Mechanical ventilation · Infection · Prophylaxis · Intubation · Ceftriaxone

✉ J. Dedrick Jordan
dedrick@unc.edu

[1] University of North Carolina Medical Center, 101 Manning Drive, Chapel Hill, NC 27514, USA

[2] University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC, USA

[3] Division of Neurocritical Care, Departments of Neurology and Neurosurgery, University of North Carolina School of Medicine, 101 Manning Drive, CB #7025, Chapel Hill, NC 27599-7025, USA

## Introduction

Early-onset pneumonia (EOP), occurring within the first 4 days of mechanical ventilation, is a frequent complication of intubation in critically ill patients with a neurologic injury with a reported incidence of approximately 20–60% [1–5]. The consequences of an episode of EOP are significant and associated with a longer duration of mechanical ventilation, longer intensive care unit (ICU) length of

stay, increased incidence of cerebral hypoxia, and higher rate of poor neurologic recovery [1–5].

One of the first studies to describe early- and late-onset ventilator-associated pneumonia (VAP) suggested that patients with impaired airway reflexes who developed pneumonia within the first 4 days of hospital admission rarely cultured nosocomial bacteria. The authors proposed that EOP was likely due to aspiration of oropharyngeal flora at the time the respiratory protective reflexes were impaired, and the patient was intubated [6]. Ewig et al. reported changing microbial colonization patterns in the respiratory tract over time in patients with traumatic head injury while mechanically ventilated. These changes in colonization represented a transition from community acquired, less virulent pathogens (*Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus*, *Haemophilus influenzae*) to a pattern of more virulent, nosocomial bacteria (gram-negative aerobic bacilli, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.) approximately 3–4 days after hospital admission and intubation. In the study, prolonged antibiotic administration, but not short-course antibiotic administration led to an increased risk of late-onset pneumonia associated with gram-negative aerobic bacilli, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. [7].

In 2014 the Society for Healthcare Epidemiology of America along with the Infectious Diseases Society of America released joint updated guidelines on strategies to prevent VAP. These guidelines list selective decontamination of the oropharynx as a special approach that may be beneficial but for which insufficient data exists of the possible risks [8]. Multiple methods of selective decontamination have been proposed in clinical trials including use of a single or short course of intravenous antibiotic to prevent early-onset VAP. Sirvent, et al., Valles, et al., and Acquarolo, et al. [2, 3, 9] proposed three different pneumonia prophylaxis regimens which resulted in a decreased incidence of early VAP without increasing the rate of drug resistant bacteria. This suggests that a single dose of an antibiotic for VAP prophylaxis is not sufficient to result in a significant alteration in resistance patterns.

Based on the available evidence, a number of clinical questions require validation and remain unanswered to better understand the implications of prophylactic antibiotics on the incidence, timing, and causative organism in pneumonia. The primary aim of the study was to compare the incidence of microbiologically confirmed EOP between patients admitted to a single-center neuroscience intensive care unit (NSICU) who received a single dose of ceftriaxone or levofloxacin at the time of intubation and those who do not as part of a pre- and post-EOP prophylaxis protocol. This study also evaluated the incidence of clinically suspected EOP, incidence of late-onset pneumonia, duration of mechanical ventilation, duration of ICU stay, duration of hospitalization, incidence of pneumonia caused by virulent bacteria, and number of antibiotic days in the ICU.

## Methods

### Study Population

After obtaining institutional review board approval, a retrospective cohort study was conducted at the University of North Carolina Medical Center (UNCMC), an 803-bed academic medical center in Chapel Hill, North Carolina, that has a 16-bed NSICU. Informed consent from patients and their relatives was waived given the observational nature of the study. Data were retrieved from the Carolina Data Warehouse of all patient encounters in the NSICU during the study period. This study included adult patients aged 18 years or older who were admitted to the NSICU on the neurology or neurosurgery service at UNCMC between April 1, 2014, and October 26, 2016, and intubated for $\geq$ 72 h. Patients were excluded if intubation occurred $>$ 48 h after admission to UNCMC based on the proposed mechanism of translocation of bacteria from the upper airway and concern for more virulent bacterial colonization after 48 h as addressed by Ewing and colleagues [7]. Patients were also excluded if they were treated with systemic antibiotics for a duration of $>$ 24 h for a suspected infection that was present at the time of intubation. For patients with multiple admissions during the study period, only the first encounter with a duration of mechanical ventilation $>$ 72 h was assessed.

### EOP Protocol

An EOP prophylaxis protocol was implemented in the NSICU at UNCMC in April 2015. This protocol calls for the administration of a one-time dose of ceftriaxone 2 g intravenously to patients requiring endotracheal intubation in the NSICU or who were intubated en route or at an outside hospital immediately prior to transfer to UNCMC. In patients with a documented severe allergy to a penicillin or cephalosporin, levofloxacin 750 mg IV is administered. Patients who require systemic antibiotics for the treatment of infection at the time of intubation are excluded from this protocol. This study compared the outcomes of patients who did not receive EOP prophylaxis from April 1, 2014, to March 31, 2015, to patients who received EOP prophylaxis from April 1, 2015, to October 26, 2016. Ceftriaxone was chosen as the first-line agent in this protocol based on the results reported by Valles et al. [3]. This

antimicrobial agent is not traditionally known for having strong anaerobic bacterial coverage, but anaerobic EOP appears to be very rare based on the bacterial growth patterns presented in studies with a similar patient population [1–3, 5, 7, 9]. In addition, ceftriaxone has been shown to have possessed some anaerobic activity in vitro [10].

### Study Definitions

The primary endpoint of this study was the incidence of microbiologically confirmed EOP. For the purpose of this study, pneumonia was defined based on an adaptation of the 2016 Centers for Disease Control and Prevention (CDC) ventilator-associated event protocol for identifying possible ventilator-associated pneumonia as outlined in Fig. 1 [11]. The CDC protocol was adapted to better fit the purpose of this study in identifying EOP. Pneumonia was considered microbiologically confirmed if all of the criteria in Fig. 1 were met. Pneumonia diagnosed by clinical assessment that met all criteria in Fig. 1 except criteria 5, and treated with antibiotics was classified as "clinically suspected pneumonia." Pneumonia was considered early onset if the diagnosis was made within the first 4 days of intubation, and late onset if the diagnosis occurred from day 5 to day 30 post-intubation. The time of intubation for all patients in this study was considered to be the time when the first documentation of ventilator settings was recorded in the electronic medical record. Standard practice in the NSICU during the study period was to collect respiratory cultures by endotracheal suction when pneumonia was suspected. Secondary objectives included incidence of clinically suspected EOP, late-onset pneumonia, duration of mechanical ventilation, duration of ICU stay, duration of hospitalization, incidence of pneumonia caused by virulent bacteria (methicillin resistant *Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia*), and ICU antibiotic days within 30 days of intubation.

### Statistical Analysis

Fisher's exact test was used to compare the incidence of EOP between groups as well as to compare categorical baseline demographics. Continuous baseline characteristics were analyzed using the Wilcoxon rank-sum test. Statistical significance was defined as $p$ value $< 0.05$. STATA version 15.0 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

## Results

### Patients

In this study, 3443 patient encounters were screened for inclusion based on admission to the NSICU during the study time period. Of these patients, 3271 were excluded from the analysis as outlined in Fig. 2. Eighty-one patients

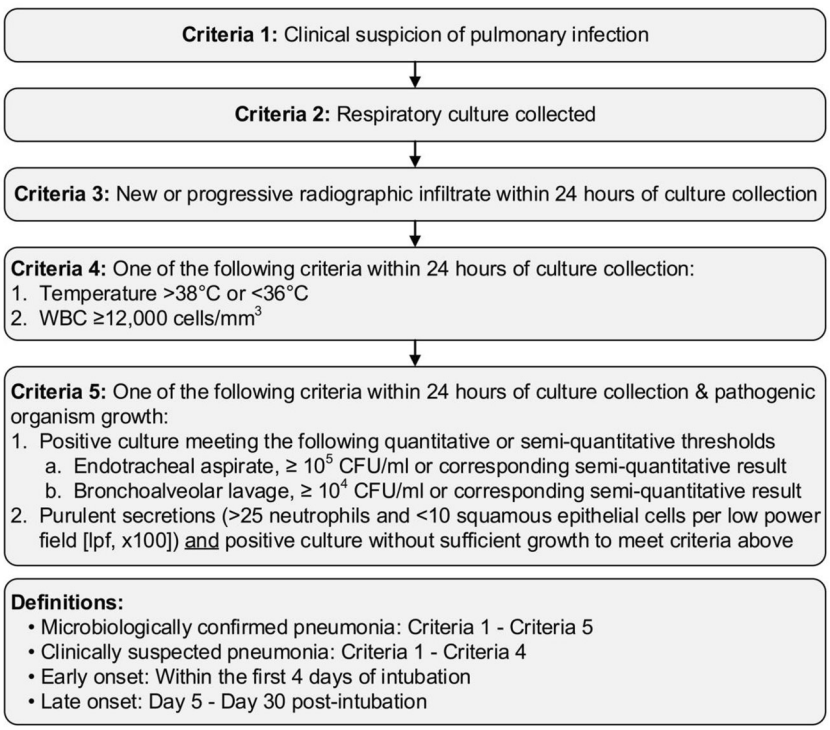


**Fig. 1** Flow diagram of pneumonia diagnosis criteria. *CFU* colony forming units, *WBC* white blood cell count

who met inclusion criteria received EOP prophylaxis after protocol implementation and were compared to 91 patients who did not receive EOP prophylaxis prior to protocol implementation. Baseline characteristics were similar between groups (Table 1) and severity of illness as assessed by the Sequential Organ Failure Assessment Score and Glasgow Coma Scale were also similar. A similar number of patients in each group underwent a neurosurgical procedure and/or interventional radiological procedure. The most common primary hospital diagnosis occurring in 26.2% of patients in the study was subarachnoid hemorrhage. Patients who received EOP prophylaxis at UNCMC were more likely to have been intubated en route to UNCMC or prior to transfer to UNCMC from an outside hospital than those who did not receive prophylaxis (71.6 vs 55.0%, $p = 0.028$). The median time from intubation to antibiotic prophylaxis administration was 3.1 h and all except three patients received ceftriaxone 2 g as the agent of prophylaxis. One patient received levofloxacin 750 mg due to a documented penicillin allergy and two received ceftriaxone 1 g.

### Primary and Secondary Endpoints

A significant reduction in the rate of microbiologically confirmed EOP was observed in the group who received antibiotic prophylaxis compared to those who did not receive EOP prophylaxis (7.41 vs 19.78%, $p = 0.026$) as shown in Table 2. However, there was no difference in the combined outcome of confirmed or clinically suspected EOP (32.21 vs 37.36%, $p = 0.523$). The incidence of microbiologically confirmed late-onset pneumonia was 28 of 81 patients (34.57%) in patients who received EOP prophylaxis compared to 24 of 91 patients (26.37%) in those who did not receive prophylaxis ($p = 0.25$). There was no significant difference in the incidence of clinically suspected or confirmed pneumonia occurring at any time within the first 30 days of intubation between groups (58.02 vs 60.44%, $p = 0.758$). Other outcomes of interest include no difference in the rate of virulent bacterial growth and no difference in the overall incidence of clinically suspected or confirmed respiratory infection. During the first 30 days post-intubation, there was no difference between groups in the median number of days in which a parenteral antibiotic was administered. No difference was observed in the duration of mechanical ventilation, ICU stay, or hospital stay. However, those who received antibiotic prophylaxis were significantly more likely to die in the hospital (45.70 vs 29.67%, $p = 0.04$). Of the patients who died in the hospital, 88% had care withdrawn due to irreversible brain injury. The rate of patients who had care withdrawn was similar between those who received EOP prophylaxis and those who did not (89 vs 85%).

## Discussion

The results of this study demonstrate the effectiveness of a single dose of antibiotic in the prevention of microbiologically confirmed pneumonia that occurs within the first 4 days of mechanical ventilation in patients admitted to the NSICU who are mechanically ventilated > 72 h. This

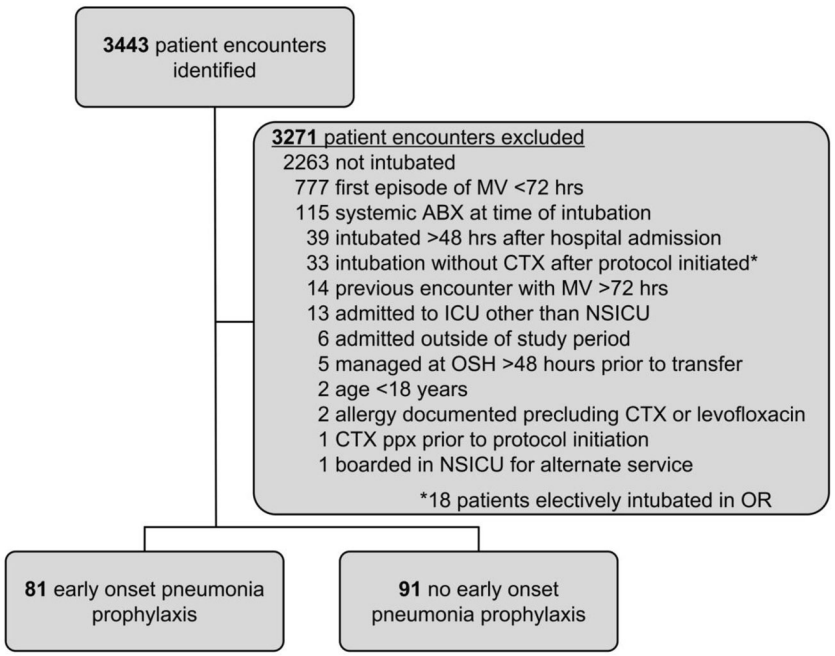


**Fig. 2** Flow diagram of patient identification and inclusion. *ABX* antibiotics, *CTX* ceftriaxone, *hrs* hours, *ICU* intensive care unit, *MV* mechanical ventilation, *NSICU* neurosciences intensive care unit, *OSH* outside hospital, *ppx* prophylaxis

**Table 1** Baseline patient characteristics

| | Pneumonia prophylaxis ($n = 81$) | No pneumonia prophylaxis ($n = 91$) | $p$ value |
|---|---|---|---|
| Age, median years (IQR) | 59 (49–69) | 58 (47–68) | 0.823 |
| Male sex, *n* (%) | 41 (50.6%) | 49 (53.9%) | 0.760 |
| Weight, median kg (IQR) | 79.4 (64.3–86.7) | 80.9 (71.5–97.7) | 0.070 |
| SOFA score, median (IQR) | 6 (5–8) | 6 (4–8) | 0.421 |
| GCS, median (IQR) | 7 (6–10) | 7 (6–10) | 0.493 |
| Neurosurgical procedure, *n* (%) | 31 (38.3%) | 38 (41.8%) | 0.755 |
| Neuroradiological procedure, *n* (%) | 12 (14.8%) | 13 (14.3%) | 1.000 |
| Surgical prophylaxis prior to or within 1 h of intubation, *n* (%) | 4 (4.9%) | 8 (8.8%) | 0.381 |
| Intubation prior to admission to UNCMC, *n* (%) | 58 (71.6%) | 50 (55.0%) | 0.028 |
| *Primary hospital diagnosis, n (%)* | | | |
| Subarachnoid hemorrhage | 22 (27.2%) | 23 (25.3%) | |
| Intracerebral hemorrhage | 24 (29.6%) | 12 (13.2%) | |
| Other | 14 (17.3%) | 19 (20.9%) | |
| Cerebral infarction | 11 (13.6%) | 19 (20.9%) | |
| Traumatic brain injury | 5 (6.2%) | 1 (1.1%) | |
| Subdural hemorrhage | 4 (4.9%) | 13 (14.3%) | |
| Altered mental status | 1 (1.2%) | 4 (4.4%) | |

*GCS* glasgow coma scale, *IQR* interquartile range, *SOFA* sequential organ failure assessment, *UNCMC* university of North Carolina medical center

strategy of prevention did not lead to an increased rate of virulent bacterial growth or a higher incidence of late-onset pneumonia which would preclude the implementation of such a strategy. However, it is important to note that the number of cases of clinically suspected or confirmed pneumonia was not significantly different in the first 4 days or 30 days following intubation. While only 7 of 81 patients who received EOP prophylaxis had a respiratory culture positive for a pathogenic organism in the first 4 days of intubation, 26 of 81 patients were treated for an EOP based on clinical suspicion of infection. This was similar to the 34 of 91 patients treated for EOP in the group who did not receive prophylaxis suggesting EOP prophylaxis did not change the utilization of antimicrobials between groups early after intubation and perhaps limited to ability to isolate a bacteria and narrow antibiotic treatment. In addition, a strategy of EOP prophylaxis did not result in any improvement in clinical outcomes such as duration of intubation, ICU length of stay, or hospital length of stay, suggesting that the use of this protocol is unwarranted due to lack of clinical utility.

The results of this study confirm those presented by Sirvent et al., Acquarolo et al., and Valles et al. [2, 3, 9] with a similar reduction in the rate of EOP through the administration of antibiotic prophylaxis using a similar protocol. Sirvent et al. compared the use of cefuroxime for two doses starting at the time of intubation versus placebo in 100 patients with head injury or stroke who were mechanically ventilated $> 72$ h. The study showed a 25% absolute risk reduction in the incidence of pneumonia with use of cefuroxime, but no difference in hospital length of stay, ICU length of stay, or mortality [2]. In a similar patient population, Acquarolo et al. [9] demonstrated that prophylaxis with 3 days of ampicillin/sulbactam led to a 36.9% absolute risk reduction in EOP without difference in duration of mechanical ventilation, duration of ICU stay, or ICU mortality. Valles et al. described the use of a single dose of ceftriaxone at the time of intubation for the prevention of VAP in 129 comatose patients. This strategy resulted in a significant reduction in the incidence of VAP within the first 4 days of intubation and decreased duration of mechanical ventilation and ICU length of stay without a difference in mortality. The study also did not observe an increased rate of drug resistant bacteria between groups in those who developed late-onset pneumonia. In contrast to Valles et al. [3], the results of this study do not show a reduction in the duration of mechanical ventilation or ICU length of stay. Further, antibiotic prophylaxis was associated with an increased rate of in hospital mortality. The driving factor(s) behind the observed increase in mortality is not clear and do not appear to be driven by pulmonary infection as the overall incidence of any pneumonia in the first 30 days of intubation was not significantly different between groups. In this study, most of the patients who

**Table 2** Endpoint comparisons of an antibiotic prophylaxis protocol

| | Pneumonia prophylaxis ($n = 81$) | No pneumonia prophylaxis ($n = 91$) | $p$ value |
|---|---|---|---|
| Incidence of microbiologically confirmed early-onset pneumonia, *n* (%) | 6 (7.4%)* | 18 (19.8%)* | 0.026 |
| *Haemophilus influenzae* | – | 5 | |
| *Staphylococcus aureus* (oxacillin sensitive) | 3 | 4 | |
| *Streptococcus pneumoniae* | – | 3 | |
| *Pseudomonas aeruginosa* | 2 | 2 | |
| *Moraxella catarrhalis* | – | 2 | |
| *Staphylococcus aureus* (oxacillin resistant) | 1 | – | |
| *Stenotrophomonas maltophilia* | 1 | – | |
| *Escherichia coli* | – | 1 | |
| *Enterobacter cloacae* | – | 1 | |
| *Enterobacter aerogenes* | – | 1 | |
| *Klebsiella pneumoniae* | – | 1 | |
| *Corynebacterium* spp. | – | 1 | |
| *Acinetobacter baumanii* | – | 1 | |
| Other | – | 1 | |
| Incidence of confirmed or clinically suspected early-onset pneumonia, *n* (%) | 26 (32.2%) | 34 (37.4%) | 0.523 |
| Incidence of microbiologically confirmed late-onset pneumonia, *n* (%) | 28 (34.6%) | 24 (26.4%) | 0.250 |
| Incidence of confirmed or suspected pneumonia at any time, *n* (%) | 47 (58.0%) | 55 (60.4%) | 0.758 |
| Incidence of virulent organism growth within 30 days of intubation, *n* (%) | 16 (19.8%) | 13 (14.3%) | 0.416 |
| Duration of intubation, median days (IQR) | 9.3 (5.3–13.7) | 10.2 (5.5–14.8) | 0.770 |
| Duration of ICU stay, median days (IQR) | 12.2 (7.0–17.7) | 12.4 (7.9–20.5) | 0.537 |
| Duration of hospitalization, median days (IQR) | 19.2 (10.1–34.6) | 20.6 (10.3–34.6) | 0.654 |
| In hospital mortality, *n* (%) | 37 (45.7%) | 27 (29.7%) | 0.040 |
| ICU antibiotic days within 30 days of intubation, median days (IQR) | 8 (2–13) | 8 (4–14) | 0.327 |

*ICU* intensive care unit, *IQR* interquartile range

*Number of organisms grown greater than incidence due to some cultures with polymicrobial growth

died in the hospital had life sustaining therapy withdrawn due to irreversible brain injury.

This study expands on the work of Valles et al., Acquarolo et al., and Sirvent et al. [2, 3, 9] by presenting the rate of clinically suspected pneumonia for which patients received antibiotic treatment without evidence of a pathogenic organism on respiratory culture. This outcome better characterizes clinical practice management at this institution as patients with clinical signs and symptoms of respiratory infection and radiographic evidence of infiltrate were often treated with a course of antibiotics despite cultures not growing a pathogenic organism. Although pneumonia prophylaxis has now consistently been shown to decrease the rate of microbiologically confirmed EOP in this patient population, it is less clear if the incidence of clinically suspected EOP is significantly changed as this is the first study identified by the authors to assess this outcome. The results of this study suggest that decontamination by antibiotic prophylaxis may lead to culture sterility or lack of predominant growth on culture, but the clinical course of pneumonia treatment is not altered by antibiotic prophylaxis at this institution. While patients treated for clinically suspected pneumonia exhibited symptoms of respiratory infection, it is possible that this could be attributed to pneumonitis which would not be expected to improve with antibiotic treatment. On the contrary, this would represent unnecessary overtreatment with antibiotics. This explanation is further supported by Lascarrou and colleagues who demonstrated the safety of discontinuing empiric antibiotics in neurologically injured patients

with suspected bacterial aspiration pneumonia but without culture positive infection after telescopic plugged catheter sampling [12]. The authors hypothesize that if EOP prophylaxis were beneficial, it would likely most benefit those intubated emergently in the field or en route to the hospital due to the less sterile environment surrounding the intubation compared to after hospital admission. In this study, significantly more patients who received EOP prophylaxis were intubated prior to admission to UNCMC, further emphasizing the lack of effectiveness of EOP prophylaxis.

The limitations of this study should be noted when considering the clinical application of this research and the implementation of an EOP prophylaxis protocol. Due to limitations in documentation available to the researchers, the start time of mechanical ventilation for patients intubated at an outside hospital prior to transfer to UNCMC or intubated en route to the study site was considered to be when the first mechanical ventilation setting was recorded in the electronic medical record of the study site. Overall, 62.8% of patients were intubated prior to arrival to the study site so the time to administration of antibiotic prophylaxis at UNCMC may have been delayed in these patients altering the response to antibiotic prophylaxis. The 4-day cutoff to define EOP would be extended in these patients due to the time unaccounted for during stabilization and transportation. In addition, while 4 days was used as a mark to define an early- vs late-onset event, this specific time definition is not universally agreed on in similar literature. The authors used the most commonly reported definition of 4 days in this patient population to guide the development of the study methods. Another limitation of this research study is that patients were assessed retrospectively for a pre- and post-implementation of a protocol which occurred during different time periods. Due to the retrospective nature of the study, selection bias of patients who did or did not receive EOP prophylaxis after protocol implementation cannot be excluded. It is also possible that practice changes which occurred during the study period may have influenced the development of pneumonia in either study group and either falsely inflated or deflated the study outcomes. All patients were given chlorhexidine mouth rinse twice daily during their duration of mechanical ventilation during both time periods. No other clinical practice changes targeted with decreasing the incidence of EOP occurred during the study period.

## Conclusion

The administration of a one-time dose of ceftriaxone or levofloxacin at the time of intubation may reduce the incidence of microbiologically confirmed pneumonia that develops within the first 4 days following intubation in patients admitted to the NSICU who are intubated $> 72$ h. A prophylaxis strategy does not appear to increase the rate of virulent organism growth or the rate of late-onset pneumonia. However, this practice is not associated with a decrease in the rate of patients treated with antibiotics for clinically suspected pneumonia, is not associated with any meaningful improvement in clinical outcomes, and may increase mortality. This is the first study identified by the authors to analyze both the incidence of microbiologically confirmed pneumonia as well as clinically suspected pneumonia, which is important to understand when assessing the clinical role of a pneumonia prophylaxis protocol. The results of this study warrant a randomized trial to assess the efficacy and safety of antibiotic prophylaxis for pneumonia in this patient population.

## Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

1. Esnault P, Nguyen C, Bordes J, et al. 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(2):187–98.
2. 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(5):1729–34.
3. Vallés J, Peredo R, Burgueño MJ, et al. Efficacy of single-dose antibiotic against early-onset pneumonia in comatose patients who are ventilated. Chest. 2013;143(5):1219–25.
4. Bronchard R, Albaladejo P, Brezac G, et al. Early onset pneumonia: risk factors and consequences in head trauma patients. Anesthesiology. 2004;100(2):234–9.
5. Lepelletier D, Roquilly A, Demeure dit latte D, et al. Retrospective analysis of the risk factors and pathogens associated with early-onset ventilator-associated pneumonia in surgical-ICU head-trauma patients. J Neurosurg Anesthesiol. 2010;22(1):32–7.
6. Langer M, Cigada M, Mandelli M, Mosconi P, Tognoni G. Early onset pneumonia: a multicenter study in intensive care units. Intensive Care Med. 1987;13:342–6.
7. Ewig S, Torres A, El-ebiary M, et al. Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury. Incidence, risk factors, and association with ventilator-associated pneumonia. Am J Respir Crit Care Med. 1999;159(1):188–98.
8. Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35(Suppl 2):S133–54.
9. 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(4):510–6.

10. Rolfe RD, Finegold SM. Comparative in vitro activity of ceftriaxone against anaerobic bacteria. Antimicrob Agents Chemother. 1982;22(2):338–41.
11. Centers for Disease Control and Prevention: Ventilator-associated event protocol. https://www.cdc.gov/nhsn/acute-care-hospital/vae/. Accessed 3 Mar 2017.
12. Lascarrou JB, Lissonde F, Le thuaut A, et al. Antibiotic therapy in comatose mechanically ventilated patients following aspiration: differentiating pneumonia from pneumonitis. Crit Care Med. 2017;45(8):1268–75.