Intubated Trauma Patients Receiving Prolonged Antibiotics for Pneumonia despite Negative Cultures: Predictors and Outcomes

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Abstract

Background: Despite the excellent negative predictive value of sterile respiratory cultures, antibiotics often are continued after negative endotracheal aspirate (ETA) or bronchoalveolar lavage (BAL) for critically ill trauma patients. We hypothesized that persistent elevation of the Clinical Pulmonary Infection Score (CPIS) would predict continued antibiotic therapy after a negative respiratory culture for intubated trauma patients, and that prolonged antibiotics would provide no benefit.

Methods: We performed a four-year retrospective cohort analysis (May 1, 2011–September 30, 2015), including patients from our trauma database with ETA or BAL, excluding patients with any infection other than pneumonia or bacteremia. Cultures with $<2^+$ organisms on gram stain and $<2^+$ or 10^4 organisms on culture were considered negative. The CPIS was assessed at the time of culture and five days later, when all cultures were final. Multiple logistic regression was used to identify predictors of long-term antibiotic therapy.

Results: A series of 106 patients with negative cultures were included, of whom 61 had ≤ 5 d of antibiotics and 45 had >5 d of antibiotics. There were no differences in injury severity, head or chest trauma, initial CPIS, or subsequent culture results between the groups. Long-term antibiotic therapy did not affect intensive care unit (ICU) length of stay (LOS), ventilator days, hospital LOS, or death. Factors predicting long-term antibiotic therapy included development of a localized chest radiograph infiltrate (odds ratio [OR] 6.8; 95% confidence interval [CI] 1.7–28), CPIS >5 five days after culture (OR 6.1; 95% CI 1.2–32), and a colonized culture (OR 3.3; 95% CI 1.3–8.3).

Conclusions: Long-term antibiotic therapy for intubated trauma patients with negative respiratory cultures provided no benefit and was predicted by development of a localized chest radiograph infiltrate, persistently elevated CPIS, and a contaminated/colonized culture. Although long-term antibiotic use did not worsen outcomes, better strategies are needed to diagnose pneumonia accurately and ensure timely discontinuation of antibiotics when appropriate.

EMPHASIS ON ANTIBIOTIC STEWARDSHIP has emerged from evidence that indiscriminate antibiotic use promotes development of multi-drug resistant organisms [1–3], increases the incidence of *Clostridium difficile* infections [4], and raises healthcare costs [5, 6]. In fact, the President's Council of Advisors on Science and Technology has recommended that the Centers for Medicare & Medicaid enforce a regulatory requirement for hospitals, long-term care facilities, and nursing homes to implement antibiotic stewardship programs by the

end of 2017 [7]. Antibiotics targeting pneumonia are commonly overprescribed, likely because of the inherent difficulties in diagnosing this disease [8, 9]. The Clinical Pulmonary Infection Score (CPIS), developed by Pugin et al. [10], appears to perform as well as other clinical scores, but lacks diagnostic accuracy, is subject to a high degree of interobserver variability, and performs poorly when applied to injured patients [11–15]. Microbiologic tests typically outperform clinical criteria, but also are characterized by mediocre sensitivity and specificity [16], and

gram-negative organisms often are missed on gram stain [17]. Despite the fact that endotracheal aspirates (ETA) and bronchoalveolar lavage (BAL) cultures have excellent negative predictive value [18,19], we observed at our institution that antibiotics often are continued for critically ill trauma patients with negative respiratory cultures. Several factors may play a role. Patients with traumatic brain injury and chest trauma are susceptible to aspiration and pneumonia, are affected commonly by the systemic inflammatory response syndrome (SIRS) [20], and have chest radiographs that often are difficult to interpret [21–24].

The purpose of this study was to characterize antibiotic prescription patterns following negative respiratory cultures for intubated trauma patients, compare outcomes between patients whose antibiotics were discontinued after negative culture and patients who remained on antibiotics, and identify factors predicting prolonged antibiotic administration. We hypothesized that persistent elevation of the CPIS would predict continued antibiotic therapy after a negative respiratory culture for intubated trauma patients and that prolonged antibiotics would provide no benefit.

Patients and Methods

Study subjects were identified by searching our institutional trauma database for patients age 18 or greater who received at least 48 h of mechanical ventilation and had at least one of three tests while intubated: Semi-quantitative endotracheal aspirate (ETA), fiberoptic bronchoscopy and semi-quantitative bronchoalveolar lavage (SQ-BAL), or fiberoptic bronchoscopy and quantitative bronchoalveolar lavage (Q-BAL) during a four-year period ending September 2015. Institutional Review Board approval was obtained. During the study period, methods for diagnosing pneumonia in intubated trauma patients primarily consisted of Q-BAL yielding $\geq 10^4$ pathogenic colony-forming units (CFU)/mL or CPIS >6 as described by Pugin et al. [10]. This study included ETA, SQ-BAL, and Q-BAL samples in order to depict a broad population of patients with negative respiratory cultures. Although BAL techniques have the theoretical advantage of sampling the lower airways, and ETA cultures have a tendency to produce false-positive results [25], ETA results were included for their strong negative predictive value [18,19] and evidence that invasive and non-invasive tests each have a role in evaluating mechanically ventilated patients for pneumonia [26]. Trauma patients managed at an outside

facility for >24 h prior to admission were excluded. Trauma patients on scheduled antibiotics prior to culture and those with any infection other than pneumonia or bacteremia were excluded to ensure that antibiotic prescription patterns reflected empiric treatment of presumed pneumonia. In order to isolate the influence of clinical factors on antibiotic administration, the final study population consisted only of patients with a negative gram stain, finalized negative culture, and survival for at least six days after cultures were obtained (Fig. 1). Although previous work has shown that preliminary BAL cultures at 24–36 hours correlate well with final culture results [27, 28], the final 96-h result was evaluated in this study in order to select the group of patients with definitive evidence of airway sterility.

Cultures yielding $<2^+$ organisms on gram stain and $<2^+$ or 10^4 CFU/mL on culture were considered negative. In clinical practice, a threshold of $>10^5$ CFU/mL avoids overtreatment of colonizing organism by limiting false-positive results while maintaining a low rate of false-negative results in trauma patients [29–31]. However, for the purposes of this study, the threshold of $<10^4$ CFU/mL was chosen to identify true-negative cultures accurately and ensure appropriate classification of *Pseudomonas* and *Acinetobacter* spp. [29]. Cultures containing non-floral bacteria in quantities that did not meet the diagnostic threshold for pneumonia were considered colonized rather than infected. The CPIS was calculated at the time of culture and five d later when all cultures were final, and patients were grouped by antibiotic duration ≤ 5 d vs. >5 d (i.e., long-term antibiotic administration).

All variables were collected by retrospective review of the electronic medical record and institutional trauma registry. Computed tomography (CT) scans at the time of admission were interpreted by a Board-certified attending radiologist. The incidence of diabetes mellitus was determined by the International Classification of Diseases, Ninth Revision, code review and medication reconciliation evidence of outpatient oral hypoglycemic or subcutaneous insulin use. Immunosuppression was defined as medication reconciliation evidence of outpatient or inpatient chemotherapy, high-dose steroids (>30 mg prednisone equivalent/d) [32], or the presence of an active disease that suppresses resistance to infection (i.e., leukemia, lymphoma, and acquired immune deficiency syndrome). Smoking status was determined by medication reconciliation evidence of outpatient or inpatient nicotine replacement therapy and by the documented social history. Blood stream infection was defined as two of four bottles positive for likely contaminants (i.e., *Staphylococcus*

FIG. 1. Study group selection (ETA = endotracheal aspirate, BAL = bronchoalveolar lavage).

epidermidis, *Propionibacterium acnes*, and *Corynebacterium* spp.), or one of four bottles positive for other organisms. Antibiotic administration before culture was defined as any systemic antibiotic given within the 72-h window preceding culture in view of evidence that antibiotic therapy within this window may affect culture results [33]. Secretions described as both thick and discolored were considered purulent. Chest radiographs were interpreted by a Board-certified attending radiologist with no knowledge of study group assignment. Multi-drug resistance was defined as non-susceptibility to at least one agent in three or more antimicrobial categories [34].

The ETA cultures were obtained by advancing a single-use 14F suction catheter kit (Medline Industries, Mundelein, IL) 2 cm past the end of the endotracheal tube and then releasing vacuum suction without use of irrigation. Fiberoptic bronchoscopy and BAL were performed as described by the Memphis International Consensus Report [35]. Specimens were considered adequate if they had <25 epithelial cells under 10 $\times$ magnification. Semi-quantitative respiratory cultures were performed by inoculating the culture plate and then streaking the specimen into four quadrants. Semi-quantitative cultures were reported as "Few" if there were <25 colonies, "1⁺" if there were at least 25 colonies within the first quadrant, "2⁺" if colonies spread to two quadrants, "3⁺" if colonies spread to three quadrants, and "4⁺" if colonies spread to four quadrants.

A protocol for Q-BAL within 48 h of admission for intubated trauma patients with traumatic brain injury or chest trauma was instituted November 1, 2013. In order to abrogate confounding effects on the data, all protocol inclusion criteria were assessed for all patients before and after protocol initiation, and outcomes were compared across ETA, SQ-BAL, and Q-BAL specimens. A protocol for preventing ventilator-associated pneumonia (VAP) was instituted prior to the study start date. The VAP protocol bundle included daily sedation holidays, daily spontaneous breathing trials, head-of-bed elevation to 30 $^{\circ}$, routine peptic ulcer prophylaxis, daily oral hygiene with chlorhexidine, and use of the Hi-Lo Evac endotracheal tube in order to clear subglottic secretions.

Statistical analysis was performed using SPSS V. 23 (IBM, Armonk, NY) to calculate the Fisher exact test to compare categorical variables and one-way analysis of variance to compare normally distributed continuous variables. The Bonferroni correction was employed in comparing diagnostic yield, antibiotic prescription patterns, and outcomes across patients who had ETA, SQ-BAL, and Q-BAL. Clinical predictors of prolonged antibiotic therapy were identified by multiple logistic regression. Independent variables were selected based on bivariate correlation with the dependent variable and absence of significant collinearity with other independent variables. Selected independent variables were entered manually into the regression equation. Alpha was set at 0.05, confidence intervals were set at 95%, and data were reported as mean $\pm$ standard error (SE) or n (%).

Results

One third of the screened trauma patients had a negative gram stain, negative culture, and survived for at least five d after culture. These patients (N = 106) formed the study group (Fig. 1). Forty-three percent of the patients in the study group received more than 5 d of antibiotics (Fig. 2). Trauma patients

FIG. 2. Antibiotic administration after negative respiratory culture.

who received five or more days of antibiotics and those who received more than 5 d of antibiotics were similar in terms of demographic factors, injury severity, risk factors for pneumonia, and potentially confounding factors (Table 1). The two groups also had similar individual CPIS criteria and CPIS scores at the time of culture, although colonization was more common among patients who received prolonged antibiotics (Table 2). Of the 32 patients with a colonized culture, only one was immunosuppressed, and this patient received an 8-d course of antibiotics.

Twenty-five percent of all patients had a second respiratory culture within 5 d, and few were positive (Table 2). Five days after initial culture, the CPIS was a full point higher among patients who received prolonged antibiotic therapy (Table 2). This group also had substantially smaller improvements in PaO₂:FiO₂ and greater rates of localized chest radiograph infiltrates after five d. Half of all patients had a second respiratory culture during admission, and 15% had a positive culture (Table 3). One patient developed a multi-drug-resistant *Enterobacter faecalis* bacteremia 2 d after finishing a 5-d course of antibiotics, and this was the only multi-drug resistant infection identified. The duration of antibiotic therapy did not affect the duration of mechanical ventilation, length of stay, or mortality rate. The type of culture performed (ETA, SQ-BAL, Q-BAL) had no effect on diagnostic yield, antibiotic prescription patterns, or outcomes apart from the finding that patients who had Q-BAL were more likely to receive two or more d of antibiotic therapy than patients who had ETA (95% vs. 84%; Bonferroni-corrected p = 0.016). This was an isolated finding, and there were no substantial differences for one or more d or three or more d of antibiotic therapy.

Three variables consistent with clinical concern for pneumonia were predictive of prolonged antibiotic therapy on multiple binary logistic regression (Table 4). Together, these factors formed a model that was statistically significant (χ^2 (3) = 25.8; p < 0.001), explained 29% of the variability in duration of antibiotic therapy (Nagelkerke R² 0.29), and correctly classified 71% of all cases.

TABLE 1. PATIENT CHARACTERISTICS AT PRESENTATION ACCORDING TO DURATION OF ANTIBIOTIC THERAPY

	$\leq 5 d$ (n=61)	$>5 d$ (n=45)	P Value
Age	51 $\pm$ 2.5	48 $\pm$ 2.5	0.483
Male (%)	54 (89)	38 (84)	0.573
ISS	24 $\pm$ 1.4	25 $\pm$ 1.8	0.632
Head AIS	2.6 $\pm$ 0.2	2.5 $\pm$ 0.2	0.774
GCS	9.3 $\pm$ 0.7	9.4 $\pm$ 0.8	0.879
Blunt trauma (%)	58 (95)	39 (87)	0.164
Field intubation (%)	27 (44)	20 (44)	0.985
Admission CT findings			
Any rib fractures (%)	29 (53)	19 (53)	0.996
Total rib fractures	3.1 $\pm$ 0.5	3.6 $\pm$ 0.9	0.577
Pulmonary contusion (%)	22 (40)	13 (36)	0.826
Aspiration (%)	15 (27)	12 (33)	0.640
Admission WBC count ($\times 10^3$)	15.4 $\pm$ 1.0	13.1 $\pm$ 1.0	0.119
PaO ₂ :FiO ₂ at intubation	275 $\pm$ 15	272 $\pm$ 18	0.992
Diabetes mellitus (%)	7 (12)	7 (16)	0.573
Immunosuppressed (%)	1 (2)	2 (4)	0.573
Active smoker (%)	18 (30)	14 (31)	0.859
BSI within 5 days of culture (%)	0	2 (4)	0.507
Antibiotics before culture (%)	23 (38)	18 (40)	0.842
Total days on antibiotics	2.5 $\pm$ 0.2	9.9 $\pm$ 0.5	<0.001

Data are reported as mean $\pm$ standard error or n (%).

AIS=Abbreviated Injury Score; BSI=blood stream infection; CT=computed tomography; GCS=Glasgow Coma Scale score; ISS=Injury Severity Score; WBC=white blood cell.

TABLE 2. DIAGNOSTIC FINDINGS AT TIME OF CULTURE AND FIVE DAYS LATER ACCORDING TO NUMBER OF DAYS OF ANTIBIOTICS

	$\leq 5 d$ Antibiotics (n=61)	$>5 d$ Antibiotics (n=45)	p
At time of culture			
CPIS	4.7 $\pm$ 0.2	5.0 $\pm$ 0.2	0.326
Temperature (°C)	38.1 $\pm$ 0.1	38.0 $\pm$ 0.2	0.854
PaO ₂ :FiO ₂	291 $\pm$ 13	303 $\pm$ 15	0.555
No tracheal secretions	2 (3)	1 (2)	0.746
Non-purulent tracheal secretions	27 (44)	18 (40)	0.695
Purulent tracheal secretions	32 (53)	26 (58)	0.694
WBC count	11.8 $\pm$ 0.6	13.3 $\pm$ 0.9	0.151
No chest radiograph infiltrate	11 (18)	4 (9)	0.261
Diffuse chest infiltrate	38 (62)	27 (60)	0.842
Localized chest infiltrate	12 (20)	14 (31)	0.253
Colonized Gram stain	8 (13)	8 (18)	0.587
Colonized culture	12 (20)	20 (44)	*0.010
Five days after culture			
CPIS	3.4 $\pm$ 0.2	4.4 $\pm$ 0.2	<0.001
Δ CPIS	-1.3 $\pm$ 0.3	-0.6 $\pm$ 0.3	0.108
Temperature (°C)	37.8 $\pm$ 0.1	37.8 $\pm$ 0.1	0.906
Δ temperature (°C)	-0.3 $\pm$ 0.2	-0.3 $\pm$ 0.2	0.890
PaO ₂ :FiO ₂	385 $\pm$ 17	340 $\pm$ 12	0.065
Δ PaO ₂ :FiO ₂	92 $\pm$ 21	34 $\pm$ 16	0.039
No tracheal secretions	7 (12)	3 (7)	0.512
Non-purulent tracheal secretions	18 (30)	9 (20)	0.367
Purulent tracheal secretions	36 (59)	33 (73)	0.152
New purulent secretions	33 (54)	22 (49)	0.695
WBC count	11.9 $\pm$ 0.6	13.9 $\pm$ 0.6	0.068
Δ WBC count	-3.6 $\pm$ 0.7	1.1 $\pm$ 0.9	0.169
No chest infiltrate	9 (15)	2 (4)	0.112
Diffuse chest infiltrate	47 (77)	24 (53)	*0.013
Localized chest infiltrate	5 (8)	19 (42)	*<0.001
New localized chest infiltrate	3 (5)	13 (29)	*0.001
Second culture	13 (21)	13 (29)	0.494
Second culture positive	1 (2)	3 (7)	0.309

Data are reported as mean $\pm$ standard error or n (%).

CPIS=Clinical Pulmonary Infection Score; WBC=white blood cell.

TABLE 3. OUTCOMES AT TIME OF DISCHARGE

	≤ 5 d Antibiotics (n=61)	>5 d Antibiotics (n=45)	P Value
Second culture	31 (51)	21 (47)	0.698
Second culture positive	11 (18)	5 (11)	0.415
Days between initial and positive cultures	12 $\pm$ 1.5	11 $\pm$ 5.0	0.766
MDR infection	1 (2)	0	0.388
Ventilator days	11 $\pm$ 1.0	13 $\pm$ 1.2	0.269
ICU length of stay	13 $\pm$ 1.1	15 $\pm$ 1.2	0.189
Ventilator-free ICU days	1.9 $\pm$ 0.3	2.4 $\pm$ 0.5	0.391
ICU-free days	5.6 $\pm$ 0.9	7.6 $\pm$ 1.2	0.179
Hospital length of stay	19 $\pm$ 1.5	23 $\pm$ 1.7	0.074
In-house deaths	4 (7)	2 (4)	0.642

Data are reported as n (%) or mean $\pm$ standard error.
ICU = intensive care unit; MDR = multi-drug resistant.

Discussion

Critically ill trauma patients commonly received antibiotics after negative respiratory cultures but did not benefit from prolonged antibiotic therapy. There also was no clear evidence of harm, although this study was underpowered to detect differences in multi-drug resistant organism isolation, and patients with *Clostridium difficile* infections were excluded (along with all infections other than pneumonia and bacteremia) in order to avoid confounding patterns in antibiotic administration. As expected, a persistently elevated CPIS was associated with prolonged antibiotic therapy, likely because of trends in PaO₂:FiO₂ and chest radiograph findings. It is possible that patients with persistently elevated CPIS represented a group with false-negative cultures and therefore actually received therapeutic rather than empiric antibiotic therapy. Unfortunately, it is impossible to make this determination in the absence of lung biopsy specimens. Interestingly, the presence of a colonizing organism on culture was associated with administration of more than five days of antibiotics. Although it may be appropriate to treat immunosuppressed patients who are colonized, this scenario applied only to one of 32 patients. Development of a localized infiltrate on chest radiograph, elevated CPIS five days after culture, and colonized culture were each significant predictors of prolonged antibiotic therapy, but 71% of the variability in antibiotic duration was not explained by these factors or any other prediction model. This sobering statistic indicates that many antibiotic management decisions were not based on objective clinical criteria or microbiologic data.

Previous work also demonstrated highly irregular antibiotic prescription patterns for critically ill patients with sus-

pected pneumonia, particularly when clinical criteria guide management. Swoboda et al. [8] observed substantial variability in diagnosing and treating pneumonia among critically ill surgical patients when using the U.S. Centers for Disease Control and Prevention (CDC) definition of pneumonia, CPIS, or consensus by a committee of experienced clinicians. The authors reported that 50% of antibiotic days in their surgical intensive care unit (ICU) were targeting a presumed diagnosis of pneumonia that did not meet CDC or CPIS criteria [8]. Fagon et al. [36] randomized critically ill medicine patients to diagnosis by clinical criteria alone, by fiberoptic bronchoscopy with BAL, or by protected specimen brush samples and found that clinical diagnosis was associated with increased antibiotic use and a greater mortality rate than in the invasive diagnostic group. In a case-control study of intubated trauma patients, Baker et al. [37] reported that less than half of all patients with clinical suspicion of pneumonia had evidence of pneumonia on quantitative BAL. Several factors likely contribute to these findings. In trauma patients, clinical diagnosis alone is compromised by frequent colonization of the tracheobronchial tree among intubated patients [16]. Also, chest radiography has little predictive value for ventilator-associated pulmonary infection [38], clinical diagnostic criteria are subject to a large degree of inter-observer variability [14], and critically ill patients often have non-infectious instigators of the SIRS response. These factors limit the utility of the CPIS criteria in managing intubated trauma patients.

However, non-invasive and invasive microbiologic diagnostic tests are not fool-proof, and reported efficacy differs across institutions. On systematic review, quantitative BAL specimens had a mean 73% sensitivity (range 42%–93%) and 82% specificity (range 45%–100%) for diagnosing VAP compared with biopsy-proved neutrophil infiltration of alveoli in combination with clinical and microbiologic data [39]. The true value of microbiologic specimens may lie in targeting antibiotic therapy for patients who are likely to have pneumonia and allowing for discontinuation of antibiotics when cultures are negative, although some may question the negative predictive value of respiratory cultures based on the wide range of reported results and the potentially confounding influence of antibiotic administration before cultures are obtained [33, 39]. Nevertheless, targeted antibiotic therapy is clearly superior to empiric therapy, and negative endotracheal aspirates have negative predictive value ranging from 94%–100% in the absence of recent

TABLE 4. FACTORS PREDICTING >5 D OF ANTIBIOTIC ADMINISTRATION AFTER NEGATIVE GRAM STAIN AND CULTURE

	Odds Ratio (95% Confidence Interval)	P
New localized chest infiltrate	6.8 (1.7–28)	0.007
Elevated CPIS 5 d after culture	6.1 (1.2–32)	0.031
Colonized culture	3.3 (1.8– 8.3)	0.014

CPIS = Clinical Pulmonary Infection Score.

changes in antibiotic therapy [18,19]. The strong negative predictive value of the gram stain and respiratory culture may be of particular value among trauma patients, who are commonly affected by SIRS and whose chest radiographs may be difficult to interpret if there has been chest trauma [24,40].

The major limitations of this study are its retrospective design, lack of power to detect differences in multi-drug resistant organism isolation, and propensity to produce false-positive results by making multiple comparisons. However, retrospective analysis has the advantage of avoiding the Hawthorne effect, in which behavior is modified by the knowledge that performance is being observed. When more than two groups were being compared, the Bonferroni correction was employed to reduce the family-wise error rate and avoid false-positive results. In the future, appropriate antibiotic management decisions may be supported by selective utilization of procalcitonin concentrations [41] and quantitative polymerase chain reaction of bronchoalveolar lavage samples, which has the potential to provide accurate diagnostic information within hours of sampling [42]. At our institution, strict adherence to protocolized management of intubated trauma patients with suspected pneumonia may abrogate unnecessary antibiotic administration.

Conclusions

Long-term antibiotic administration for intubated trauma patients with negative respiratory cultures was common and provided no benefit. Risk factors included development of a localized chest radiograph infiltrate, persistently elevated CPIS, and contaminated/colonized cultures. However, many cases of prolonged antibiotic administration after negative cultures could not be explained by clinical or microbiologic criteria. Protocolized antibiotic management and more accurate diagnosis of pneumonia may be necessary to ensure timely discontinuation of antibiotics for intubated trauma patients with negative respiratory cultures.

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Author Disclosure Statement

The authors have nothing to disclose.

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