Can enteral antibiotics be used to treat pneumonia in the surgical intensive care unit? A clinical outcomes and cost comparison

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ABSTRACT

Background: Controlling healthcare costs without compromising patient care is a focus given recent healthcare changes in the United States. The purpose of this study was to assess clinical improvement in surgical intensive care unit (SICU) patients initiated on or transitioned to enteral antibiotics compared to those who solely receive intravenous (IV) antibiotic therapy for treatment of bacterial pneumonia.

Materials and Methods: This retrospective cohort study included patients with a positive quantitative respiratory culture being treated for bacterial pneumonia in a SICU from 1/1/09 to 3/31/11. Two distinct patient groups were identified: Those treated with IV antibiotics exclusively (IV) and those either initiated on or transitioned to enteral antibiotics within 4 days of antibiotic initiation (PO). The primary endpoint of clinical improvement was assessed on day of antibiotic discontinuation.

Results: A total of 647 patients were evaluated; 124 met inclusion criteria (30 patients PO group and 94 IV group). There was no difference in clinical improvement (86.7 PO vs 72.3% IV, P = 0.14) or recurrence (10 PO vs. 12.8% IV, P > 0.99) between groups. Secondary outcomes of duration of mechanical ventilation, ICU and hospital length of stay, and all-cause mortality were also similar. Antibiotic and infection-related costs were significantly decreased in the PO group ($1,042 vs $697, P = 0.04; $20,776 vs $17,381, P = 0.012, respectively).

Conclusions: SICU patients initiated on or transitioned to PO antibiotics for pneumonia had similar clinical outcomes, but significantly less infection-related and antibiotic costs compared to those receiving IV therapy. Further, prospective studies are warranted.

Key Words: Bacterial pneumonia, critical care, enteral, IV to PO

INTRODUCTION

Decreasing healthcare costs while maintaining optimal patient outcomes has been a recent focus of many institutions given changes in United States healthcare. Cost reduction with optimal outcomes has been shown by switching from intravenous (IV) to oral (PO) antibiotics for the treatment of pneumonia in the non-intensive care unit (ICU) population.¹² This practice has potential for significant economic impact if expanded to the ICU population, as pneumonia affects 1.1 million people annually and accounts for more than 50,000 mortalities (16.5 deaths per 100,000) in the United States alone.³ While oral antibiotic therapy is routinely used to treat community-acquired pneumonia (CAP),

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particularly in less severe infections that are treated on an outpatient basis, patients admitted to the ICU are customarily treated with IV antibiotics for the duration of therapy. Acquisition cost for the majority of IV antibiotics is significantly more expensive than their oral equivalents. In addition, IV antibiotics can have additional indirect costs, specifically involving preparation, nursing administration, and waste.

The effectiveness of switching from IV to oral antibiotics has been demonstrated in CAP. A multicenter, randomized trial of clinically stable patients transitioned to oral antibiotics after 3 days of IV therapy for a 10-day total course found no difference in rates of clinical cure, mortality, or clinical deterioration compared to those receiving IV treatment for duration of therapy. However, those transitioned to oral therapy had significantly shorter hospital length of stay. Similarly, a prospective, observational study of patients with CAP who were transitioned from IV to oral therapy within 24 h of clinical improvement demonstrated clinical cure rate of 97%. Guidelines for CAP developed by the Infectious Disease Society of America recommend the switch from IV to oral therapy once patients are clinically improving, hemodynamically stable, and able to adequately absorb and take oral therapy. The recommendations, however, apply only to the non-ICU population. The American Thoracic Society and Infectious Disease Society of America Guidelines for hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia recommend all patients be initiated on IV therapy, but state conversion to enteral may be appropriate in certain patients, citing the proven effectiveness and bioavailability of certain antibiotics. Dosing recommendations in the guidelines, however, are solely for IV administration.

In vitro studies are available for many enteral antibiotic options for treatment of pneumonia, including those caused by multidrug resistant bacteria. Multiple studies have shown that oral linezolid has approximately 100% bioavailability, with equivalent half-life and volume of distribution between enteral and IV administration, even in patients receiving enteral nutrition. Pharmacokinetic studies of ciprofloxacin and moxifloxacin have demonstrated that both enteral and IV administration achieve pharmacokinetic and pharmacodynamic targets when administered in comparable doses.

At present time there are no published data assessing the efficacy of enteral antibiotic therapy for critically-ill patients with bacterial pneumonia. The primary objective of this study was to assess rates of clinical improvement in patients who are initiated on or transitioned to enteral antibiotics compared to those who solely receive IV antibiotic therapy for treatment of bacterial pneumonia in a surgical ICU (SICU).

MATERIALS AND METHODS

Data collection and assessment

A single-center, retrospective, cohort study was performed after obtaining expedited approval from our institution’s Institutional Review Board. Patients treated for bacterial pneumonia in a 44-bed SICU at an academic medical center between 1/1/09 and 3/31/11 were identified electronically. Patients were eligible if they had a positive quantitative bronchoalveolar lavage (BAL) and were treated for bacterial pneumonia for organisms susceptible to antibiotics available in an enteral preparation. Pneumonia was diagnosed with at least one of the following: (i) Temperature > 100.4°F; (ii) white blood count < 4,000 or >11,000 per microliter or ≥50% bands; or (iii) new or worsening altered mental status plus two at least of the following: (a) new or worsening dyspnea, cough, or tachypnea; (b) new-onset purulent sputum or change in sputum character; (c) worsening gas exchange or increased oxygen requirements on ventilator support; (d) rales in combination of >10,000 colony forming units of bacteria per milliliter from protective-catheter BAL quantitative cultures. Patients excluded from data analysis include those <18 or ≥89 years of age, prisoners, pregnant women, pneumonia secondary to Acinetobacter baumannii, Pseudomonas aeruginosa, and/or extended spectrum beta-lactamase (ESBL) producing bacteria, concurrent bacteremia, or total parenteral nutrition (TPN). Patients that had care withdrawn or were transferred out of the SICU during treatment were also excluded from analysis.

Patients were categorized into two distinct patient groups. The first group was composed of patients who were treated with IV antibiotics for the duration of antimicrobial treatment of pneumonia. The second group included those patients that were either initiated on or transitioned to enteral antibiotics within 4 days of initiation of antibiotic therapy based on time frame for culture susceptibilities to be finalized.

Data was retrospectively collected on eligible patients for assessment of clinical improvement of bacterial pneumonia. The de-identified data recorded included demographics (age, gender, weight, height, and primary service), baseline vitals/Clinical Pulmonary Infection Score (CPIS), Acute Physiology and Chronic Health Evaluation II (APACHE II), BAL cultures and sensitivities, chest radiograph (chest X-ray (CXR)) results, ventilator status and requirements, sputum data, duration and type of antibiotic therapy, total healthcare cost, infection related cost, and clinical outcome data (resolution of leukocytosis, hemodynamics, CXR, O₂ saturation, CPIS, vitals, length of ICU and hospital stay, and mortality). CAP was defined as pneumonia occurring within 48 h of admission, with HAP including patients with infection ≥48 h following admission, and VAP
defined as infection >48 h following endotracheal intubation.

The primary study outcome was clinical improvement of bacterial pneumonia on day of antibiotic discontinuation. Clinical improvement was defined as improvement in at least two of the following signs and symptoms of pneumonia: Temperature, sputum production, CXR, white blood cell (WBC), hemodynamic stability, O\textsubscript{2} saturation, or CPIS. CPIS were calculated based on temperature (36.5–38.4 = 0, 38.5–38.9 = 1, and ≥39.0 or ≤36.5 = 2), leukocytosis (4–11,000 = 0, <4 or >11,000 = 1, and <4 or >11,000 and bands ≥50% or >17,000 = 2), tracheal secretions (none/scant = 0, non-purulent = 1, and purulent = 2), oxygenation (PaO\textsubscript{2}/FiO\textsubscript{2} <240 = 1), and radiography (no infiltrate = 0, diffuse/patchy = 1, and localized = 2), with radiography assessments being performed by the lead physician.

Secondary outcomes included rate of recurrence, total healthcare, infection-related and antibiotic cost, ICU and hospital length of stay, and infection-related and all-cause mortality. Patients were deemed to have recurrence if a repeat quantitative culture was positive with initial causative organism following either clinical improvement or documented microbiological clearance following completion of initial antibiotic therapy. Microbiological outcomes were assessed for all patients, whether or not they had microbiological cultures upon completion of antibiotic therapy. Patients with clinical improvement in absence of repeat microbiological data were classified as a presumed microbiological cure. Conversely, patients without end of therapy microbiological data and failure to meet criteria for clinical improvement were presumed microbiological failures. Patients with microbiological data upon completion of antibiotic course were appropriately classified as either documented microbiological cure or documented microbiological failure. Total healthcare cost was calculated for the patient’s entire hospital length of stay. In an effort to explain related to infection, we assessed cost sustained for the period during which the patient was treated with antibiotics for bacterial pneumonia.[12]

Infection-related mortality was assessed by the lead physician of the study, who was blinded to the subjects’ group assignment. The lead physician (RCF) reviewed the events preceding the death, as well as the death summary, to determine if pneumonia was the underlying or immediate cause of death. Infection-related mortality was defined as death that could be attributed to pneumonia as either the immediate or underlying cause. The term “immediate cause of death” is defined as the disease or injury directly leading to death, and the term “underlying cause of death” is defined as the disease or injury that initiated the sequence of events leading directly to death or the circumstances of the accident or violence that produced the fatal injury.[13]

**Statistical analysis**

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 19 (IBM Armonk, NY). Categorical variables were analyzed using Chi-square statistics and Fisher’s exact test and are presented as number and percentage. Continuous data with normal distribution was assessed using the Student’s t-test and is presented as mean ± standard deviations, while non-normally distributed continuous variables were analyzed using Mann–Whitney U and is presented as median (intraquartile range (IQR)). Prior to initiation of the study, statistical significance was set for a P value < 0.05.

**RESULTS**

**Patient characteristics**

A total of 647 patients with BAL cultures were screened for inclusion based on treatment of bacterial pneumonia. A total of 124 patients met inclusion criteria for analysis [Figure 1]. Baseline characteristics were similar between groups [Table 1]. There was no difference in surgical services between the groups and the majority of patients in each group were admitted to the trauma/acute care surgery service. Greater than 90% of all patients were mechanically ventilated, although administration of vasopressors on day of antibiotic initiation was low in both groups [Table 1]. Most patients were admitted to the ICU on hospital day 1, however time to BAL collection was approximately 1 week for all patients. On day of antibiotic initiation, median CPIS was 6 in both groups, correlating with pneumonia diagnosis.

**Clinical data**

VAP accounted for the majority of infections, followed by HAP and CAP [Table 1]. Causative
organism was susceptible to initial antibiotic therapy in 29 patients (96.7%) in the PO group and 90 patients (95.7%) in the IV group (>0.99). All nonsusceptible organisms were *Stenotrophomonas maltophilia*. There was no difference in initial antibiotic therapy between groups [Table 2]. The majority of patients were started on empiric therapy for nosocomial infections in the SICU, consisting of linezolid, piperacillin/tazobactam, and either tobramycin or amikacin for double coverage of gram-negative organisms. Thirteen patients (43.3%) in the PO group and 24 (26%) in the IV group had multi-organism growth (*P* = 0.07). Causative organism was similar between groups; multiple organisms were reported in the setting of polymicrobial growth [Table 3]. There was significantly more methicillin-susceptible *Staphylococcus aureus* (MSSA) and Serratiaspecies in the PO group, but significantly less Enterobacterspecies compared to the IV group [Table 3]. As expected, de-escalated antibiotics were quite different between groups [Table 2]. There was significantly more linezolid, amoxicillin/clavulanic acid, and ceftazolin in the PO group compared to the IV group. Both groups included patients de-escalated to ciprofloxacin, linezolid, and moxifloxacin. Median duration of antibiotics was similar between groups, with 8 (7–9) days in the PO group and 9 (8–10) days for patients on IV therapy (*P* = 0.17).

There was no difference in the primary outcome of clinical improvement between groups. Twenty-six patients (86.7%) in the PO group exhibited clinical improvement, with 71 patients (75.5%) on IV antibiotics achieving this outcome (*P* = 0.31). Median CPIS on day of antibiotic discontinuation was decreased to 3 in both groups, no longer correlating with presence of pneumonia. Secondary outcomes, including duration of mechanical ventilation, SICU and hospital length of stay, and all-cause and infection-related mortality were similar between groups [Table 4]. Microbiological data, assessed independently of the primary outcome, was not different between groups [Table 4]. Recurrence rates were low, with one patient (3.3%) in the PO group and seven patients (7.4%) in the IV group exhibiting recurrence with the initial causative organism (*P* >0.99).

While there was no significant difference in median total healthcare cost ($55,787 (42,410–84,248) PO group versus $67,690 (41,200–105,632) IV group, *P* = 0.39) those in the PO group had a significant lower infection-related cost ($17,381 (14,779–20,310) versus $20,776 (16,267–31,497), *P* = 0.012) and antibiotic cost ($697 (513–1,176) versus $1,042 (825–1,303), *P* = 0.04).

### Table 1: Patient characteristics for enteral verses intravenous antibiotics

|                      | Enteral (n = 30) | Intravenous (n = 94) | *P* value |
|----------------------|-----------------|---------------------|-----------|
| Male gender, n (%)   | 22 (73.3)       | 68 (72.3)           | >0.99     |
| Age, years           | 62 (55-76)      | 57 (43-68)          | 0.12      |
| Height, cm           | 68 (66-70)      | 69 (66-70-5)        | 0.63      |
| Weight, kg           | 79 (68-95)      | 86 (70-94)          | 0.24      |
| Primary service, n (%) |                 |                     |           |
| Trauma               | 12 (40)         | 30 (31.9)           | 0.51      |
| General surgery      | 2 (6.7)         | 14 (14.9)           | 0.36      |
| Neurosurgery         | 6 (20)          | 22 (23.4)           | 0.81      |
| Surgical oncology    | 3 (10)          | 4 (4.3)             | 0.36      |
| Burn                 | 5 (16.7)        | 11 (11.7)           | 0.53      |
| Other                | 2 (6.7)         | 13 (13.8)           | 0.52      |
| Vasopressor at antibiotic initiation, n (%) | 1 (3.3) | 12 (12.8) | 0.29 |
| Mechanical ventilation at antibiotic initiation, n (%) | 28 (93.3) | 88 (97.8) | >0.99 |
| Hospital day admitted to intensive care unit | 1 (1-1) | 1 (1-1) | 0.67 |
| Hospital day BAL collected | 8.5 (3.5-13) | 7 (4-12) | 0.27 |
| CPIS upon antibiotic initiation | 6 (5-7) | 6 (4-7) | 0.40 |
| APACHE II            | 19 (16-21.5)    | 17 (14-22.5)        | 0.44      |
| Community-acquired pneumonia, n (%) | 5 (16.7) | 10 (10.6) | 0.36 |
| Hospital-acquired pneumonia, n (%) | 8 (26.7) | 34 (36.2) | 0.38 |
| Ventilator-associated pneumonia, n (%) | 16 (53.3) | 50 (53.2) | >0.99 |

Data presented as median and interquartile range unless otherwise noted. BAL: Bronchoalveolar lavage, CPIS: Clinical Pulmonary Infection Score, APACHE II: Acute Physiology and Chronic Health Evaluation II

### Table 2: Empirical and de-escalated antibiotic therapy for enteral verses intravenous antibiotics

| Antimicrobial, n (%) | Enteral (n = 30) | Intravenous (n = 94) | *P* value |
|----------------------|-----------------|---------------------|-----------|
| **Initial antibiotic therapy** |                     |                     |           |
| Linezolid           | 25 (83.3)       | 76 (80.9)           | >0.99     |
| Piperacillin/tazobactam | 24 (80)       | 72 (76.6)           | 0.81      |
| Cefepime            | 1 (3.3)         | 5 (5.3)             | >0.99     |
| Imipenem            | 1 (3.3)         | 8 (8.5)             | 0.69      |
| Ciprofloxacin       | 4 (13.3)        | 11 (11.7)           | 0.72      |
| Tobramycin          | 11 (36.7)       | 19 (20.2)           | 0.09      |
| Moxifloxacin        | 2 (6.7)         | 4 (4.3)             | 0.63      |
| Vancomycin          | 0 (0)           | 1 (1.1)             | >0.99     |
| Amikacin            | 11 (36.7)       | 41 (43.6)           | 0.53      |
| **De-escalated antibiotic therapy** |               |                     |           |
| Linezolid           | 11 (36.7)       | 17 (18.1)           | <0.001    |
| Moxifloxacin        | 3 (10)          | 4 (4.3)             | 0.36      |
| Amoxicillin/clavulanic acid | 2 (6.7)   | 0 (0)               | 0.06      |
| Cephalexin          | 6 (20)          | 0 (0)               | 0.001     |
| Ciprofloxacin       | 3 (10)          | 9 (9.6)             | >0.99     |
| Cefpodoxime         | 1 (3.3)         | 0 (0)               | 0.24      |
| Cefazolin           | 0 (0)           | 10 (10.6)           | 0.12      |
| Ampicillin/sulbactam | 0 (0)          | 10 (10.6)           | 0.12      |
This retrospective analysis suggests that initiation of or early transition to enteral antibiotics produces comparable clinical outcomes to IV therapy in a SICU population, as evidenced by no difference in rates of clinical improvement between groups. Secondary clinical outcomes were similar between groups with the exception of cost analysis. Patients in the PO group had a significant reduction in antibiotic cost and overall infection-related costs compared to those patients receiving IV antibiotics for the duration of therapy. While a reduction in antibiotic cost was predicted, the decrease in infection-related costs may be attributed to indirect costs such as fewer procedures for line placement and no need for additional radiographs for placement confirmation.

On the day of BAL collection, initial antibiotic therapy and patient characteristics were similar between groups. However, there was significantly more MSSA and Serratia pneumonia in the PO group, likely due to the fact that these organisms are often less resistant and generally thought to be easier to eradicate. Thus, clinicians may be more inclined to initiate or transition to enteral antibiotics for treatment. On the other hand, Enterobacter species were more commonly isolated in the IV group, which may be a result of practitioner’s concern for antimicrobial resistance with these organisms. While many of the antibiotics, specifically those for gram-negative coverage, were not transitioned to an enteral preparation until causative organism was identified, it is common practice in our SICU for linezolid to be initiated enterally for empiric coverage.

This was the first study assessing clinical outcomes for surgical critically-ill patients treated with enteral antibiotics for bacterial pneumonia. Benefits of utilizing enteral antibiotics are substantial, including decreased medication and labor costs, ease of administration for nurse and patient, and reduction in length of stay.[13] With changes in healthcare in the United States, decreasing healthcare cost is becoming more of a priority to institutions. While we expected the antibiotics cost to be significantly less in the PO group, we were surprised that the infection related cost was significantly lower. Patients may avoid additional line placement for administration of IV antibiotics (e.g., central or peripherally inserted central catheters), additional radiographs to confirm line placement, and use of these lines may put patients at risk for catheter-related bloodstream infections.[14] However, there remain concerns regarding enteral administration in the critically-ill population. Due to acute physiologic changes, including changes in volume of distribution, organ function, and medication clearance, there is concern that bioavailability may be compromised. This is particularly of concern in the surgical population, when impaired gastrointestinal motility and adequacy of enteral absorption are potential issues.[15] The majority of these patients are also receiving enteral feeding, which may compromise exposure of certain antibiotics if nutrition is not appropriately held surrounding enteral antibiotic administration.

This study is not without limitations. It was a single-center, retrospective study that relied on documentation in the electronic medical record. Sample size was also limited, particularly for those meeting criteria for inclusion into the enteral group. Patients included in this study belong to a specific subset of the critically-ill population, the SICU; thus extrapolation to other critically-ill populations should be done with caution. Bacterial pneumonia caused by multidrug resistant organisms was also excluded, which may make these results less applicable to certain institutions based on local antibiograms. While not statistically significant, there was a trend toward increased clinical improvement in patients treated with enteral antibiotics. This may be partially attributed to the fact that clinicians are less likely to initiate or transition to enteral therapy in unstable or severely ill patients, thus artificially inflating the clinical improvement in the enteral group. Although CPIS and APACHE II scores were similar between groups; differences in these patient populations or clinical status may not have been captured when utilized for analysis due to inherent limitations with such scoring systems.[16]
CONCLUSION

Critically-ill surgical patients initiated or transitioned to enteral antibiotics for treatment of pneumonia had similar outcomes as those treated solely with IV antibiotics. The results of this study show potential for significant cost savings via utilization of enteral antibiotics for the treatment of bacterial pneumonia. Decreased infection-related cost and antibiotic cost savings, as well as advantages regarding administration, exist while producing comparable clinical outcomes in a critically-ill surgical population. However, prospective studies are necessary to confirm the appropriateness of enteral therapy for bacterial pneumonia in the critically-ill surgical patients.

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Conflicts of interest
There are no conflicts of interest.

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