Causative Pathogen Dictates Optimal Duration of Antimicrobial Therapy for Ventilator-Associated Pneumonia in Trauma Patients

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BACKGROUND: Recent ventilator-associated pneumonia (VAP) guidelines recommend considering abbreviated therapy in patients with non−*Pseudomonas aeruginosa* VAP if clinical signs resolve. However, using an arbitrary day cutoff or clinical signs can be suboptimal for some, especially multiply injured patients, resulting in relapse and/or antibiotic resistance. Previously, we showed that repeat bronchoalveolar lavage (BAL) could guide antimicrobial duration for community-acquired VAP in trauma patients. The purpose of this study was to determine the appropriate duration of antimicrobial therapy for VAP in trauma patients secondary to hospital-acquired pathogens.

STUDY DESIGN: Patients with VAP secondary to MRSA, *Pseudomonas aeruginosa* (PA), *Acinetobacter baumannii* (AB), *Stenotrophomonas maltophilia* (SM), or *Enterobacteriaceae* (ENB) during 6 years were evaluated. All received empiric antimicrobial therapy based on duration of ICU stay. Therapy was tailored based on culture data. Repeat BAL was performed on day 4 of appropriate therapy. Microbiological resolution was defined as $\leq 10^3$ colony-forming units/mL. Recurrence was defined as $\geq 10^5$ colony-forming units/mL on subsequent BAL performed within 2 weeks after completion of appropriate therapy.

RESULTS: Six hundred and fifty-nine patients were identified. Seventy-seven percent of patients underwent repeat BAL: 96 with MRSA, 100 with AB, 139 with PA, 50 with SM, and 120 with ENB. The majority of patients with MRSA or PA achieved microbiological resolution after 14 days. Nearly 60% of patients with AB, SM, or ENB achieved microbiological resolution after 10 days. Overall recurrence was 2%.

CONCLUSIONS: Repeat BAL provides objective evidence for VAP resolution in the face of potentially confounding clinical factors. Hospital-acquired VAP can be managed effectively by a defined course of therapy with a low recurrence. Duration of antimicrobial therapy for VAP in trauma patients should be dictated by the causative pathogen. (J Am Coll Surg 2011;212:476–486. © 2011 by the American College of Surgeons)

The emergence of antibiotic resistance in the ICU poses a considerable challenge in the optimal management of ventilator-associated pneumonia (VAP). Prolonged exposure to unnecessary antibiotics remains one of the strongest predictors for development of antibiotic resistance.[1,2]

Because of its frequency and severity,[3,4] VAP represents one of the principal driving forces behind antibiotic use in the ICU.[5] Determining the optimal duration of definitive antibiotic therapy for VAP remains the key to limiting unnecessary antibiotic exposure.

The recommended duration of definitive antibiotic therapy for VAP had been 14 to 21 days.[6] However, recent VAP guidelines[7] recommend considering abbreviated therapy (ie, 7 days) in patients with non−*Pseudomonas aeruginosa* (PA) VAP if clinical signs resolve. Unfortunately, resolution of clinical signs can be nonspecific in trauma patients, with other reasons for systemic inflammation (eg,

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Abbreviations and Acronyms
AB = *Acinetobacter baumannii*
BAL = bronchoalveolar lavage
CFU = colony-forming units
ENB = *Enterobacteriaceae*
MR = microbiological resolution
PA = *Pseudomonas aeruginosa*
SM = *Stenotrophomonas maltophilia*
VAP = ventilator-associated pneumonia

ARDS, systemic inflammatory response syndrome, operations), leading to subjectively prolonged therapy (14 to 21 days). In fact, using an arbitrary day cutoff or clinical signs might be suboptimal for some patients with VAP secondary to hospital-acquired pathogens resulting in relapse and/or antibiotic resistance.

One approach to decrease unnecessary antibiotic therapy for VAP is to use a bacteriologic diagnostic strategy in which the clinical suspicion of pneumonia is confirmed using a quantitative diagnostic threshold of bacterial growth on pulmonary culture. This approach allows the clinician to reliably differentiate pneumonia from noninfectious causes of pulmonary and systemic inflammation,[8-11] discontinue antibiotic therapy in patients without confirmed pneumonia,[11-13] and narrow broad-spectrum empiric antibiotic therapy according to culture and sensitivity results.[13,14]

Previously, we showed that repeat bronchoalveolar lavage (BAL) could be used to guide antimicrobial duration for VAP in trauma patients, specifically, in those with community-acquired VAP (methicillin-sensitive *Staphylococcus aureus*, *Hemophilus spp, Streptococcus spp*).[15] The purpose of this study was to determine the appropriate duration of antimicrobial therapy for VAP in trauma patients secondary to hospital-acquired pathogens based solely on the causative pathogen by using quantitative cultures on repeat BAL.

METHODS

Identification of patients

After approval from the Institutional Review Board at the University of Tennessee Health Science Center, patients admitted to the trauma ICU at the Presley Regional Trauma Center in Memphis, TN during a 6-year period (ending October 2009) with VAP diagnosed on BAL ($\geq 10^5$ colony-forming units [CFU]/mL in the effluent) were identified from the VAP database. Only patients with VAP secondary to MRSA, PA, *Acinetobacter baumannii* (AB), *Stenotrophomonas maltophilia* (SM), or *Enterobacteriaceae* (ENB; *Escherichia coli, Enterobacter spp, Klebsiella pneumoniae,* and *Proteus mirabilis*) were evaluated. Data were merged with additional patient information in the trauma registry (NTRACS version 3.5, Digital Innovations) to compile the database for this study.

Diagnosis and management of VAP

Diagnosis of VAP was made by quantitative culture of BAL effluent obtained via fiber-optic bronchoscopy (Fig. 1). The clinical triggers for bronchoscopy with BAL included any 3 of the following: abnormal temperature (>38.3°C or <35.6°C), abnormal white blood cell count (>10,000 or <4,000 cells/mm^3), macroscopically purulent sputum, and new or changing infiltrate on chest x-ray. BAL was only performed in the presence of clinical triggers and the diagnosis of VAP was established strictly by quantitative culture (no episodes of VAP were diagnosed in the absence of BAL). After recognition of clinical signs of VAP,[11,16] all patients underwent diagnostic fiber-optic bronchoscopy with BAL culture. All BAL procedures were performed in a uniform manner by the treating surgeon as described previously.[11,12,17]

Briefly, after blind endotracheal suctioning through the ventilator circuit, the bronchoscope was advanced, without using suction, into the lung segment, where radiographic changes were seen, or into the left lower lobe of patients who had diffuse bilateral infiltrates. With the bronchoscope wedged into the appropriate lung segment, 100 mL sterile, nonbacteriostatic saline was instilled into the lung and immediately aspirated in five 20-mL aliquots. The effluent was pooled and sent to the microbiology laboratory for Gram stain and quantitative aerobic and anaerobic culture. Generally, results of Gram stain were reported within 30 minutes of effluent arrival to the microbiology department, preliminary quantitative results were reported within 24 to 36 hours, and final results were reported between 48 to 96 hours. VAP was confirmed using a BAL threshold of $\geq 10^5$ CFU/mL.[11,12,17,18]

All patients received empiric antibiotic therapy based on the duration of ICU stay.[12,19] Patients in the ICU for 7 days or less (early) received 3 g ampicillin/sulbactam intravenously every 6 hours (or equivalent alternative in penicillin-allergic patients), and patients in the ICU longer than 7 days (late) received 2 g cefepime intravenously every 8 hours and vancomycin 20 mg/kg intravenously every 12 hours (dose adjusted to maintain steady-state peak serum vancomycin concentrations 35 to 45 mg/L and trough concentrations 15 to 20 mg/L). Empiric antibiotic therapy was considered appropriate if at least one antibiotic included in the empiric regimen demonstrated in vitro activity against the identified pathogen(s).[20-24] Empiric antibiotic therapy was de-escalated based on final susceptibility results according to guideline recommendations.[7] All patients received a minimum of 7 days of antimicrobial ther-