Vancomycin Versus Linezolid for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia

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A. Introduction

Nosocomial pneumonia defined as occurring 48 hours after hospital admission is the leading cause of death due to hospital-acquired infection with estimated mortality rates ranging from 20 to 50 percent. The majority of cases of nosocomial pneumonia occur outside of intensive care units. However, the highest risk for the development of hospital-acquired pneumonia exists in patients on mechanical ventilation. Historically, Gram negative aerobes were the most frequently reported pathogens in nosocomial pneumonia, but Gram positive pathogens including *Staphylococcus aureus* have recently been reported with increasing frequency. Methicillin-resistant *S aureus* (MRSA) accounted for 60 percent of *S aureus* isolates in the European Prevalence of Infection in Intensive Care (EPIC) Study. Vancomycin has been the standard of care for the treatment of MRSA, and until the advent of Linezolid the only option for the treatment of MRSA infections. Only limited data exists on the treatment of patients with MRSA nosocomial pneumonia.

Two double-blind, prospective studies of patients with Gram-positive nosocomial pneumonia were recently completed which randomized patients to receive empiric treatment with vancomycin or linezolid to treat potential MRSA, each with aztreonam to treat potential *Pseudomonas aeruginosa* prior to the reporting of sputum gram stain and culture results. Each registration study was powered for equivalence between the two groups with the outcome of no significant outcome difference between groups. Retrospective analysis of data from the above two prospective, randomized, double-blind studies after investigators demonstrated that subset analyses revealed a survival benefit favoring linezolid when patients were stratified by APACHE (acute physiology and chronic health evaluation) II scores. Kaplan-Meier survival rates for linezolid and vancomycin were 80% versus 63.5% respectively for the MRSA subset ($p=0.03$). Logistic regression analysis confirmed that the survival difference favoring linezolid remained significant after adjusting for baseline variables (odds ratio [OR], 2.2 95% confidence interval [CI], 1.0 to 4.8; $p=0.05$)

B. Hypotheses

1. Linezolid therapy for MRSA nosocomial pneumonia is associated with a significantly lower mortality rate than vancomycin.
2. The baseline variables of age less than 65 years, APACHE II score ≤ 20, single lobed pneumonia, absence of pleural effusion, bacteremia, and mechanical ventilation, bilirubin $\leq$ 2.4 mg/dL, creatinine $\leq$ 2.4 in men and $\leq$ 2.6 in women, CD4+ T cell count >200, and absence of cardiac, diabetic, hepatic, oncologic, renal, and respiratory comorbidities are all associated with a significantly lower mortality rate.

C. Methods

The primary study outcome is mortality at 21 days from participant enrollment in the study. The study design will be prospective, longitudinal, and interventional. The study will be randomized and double-blinded, and will have a parallel-arm. The study will also administer the parallel treatment to participants who appear to be failing their antibiotic regimen at the discretion of the investigators on an intention to treat basis. Patients will be randomized to receive either linezolid 600 mg IV q 12 hours or

vancomycin 1 gram IV q 12 hours (or renally dosed if necessary) for 21 days for the treatment of presumed MRSA nosocomial pneumonia with aztreonam 2 grams IV q 8 hours for the treatment of presumed Pseudomonal pneumonia until BAL gram stain and culture results are reported. All patients will receive a BAL prior to the commencement of antibiotic therapy. The chi-square test will be used to compare mortality rates between the linezolid and vancomycin groups. Logistic regression analysis will be used to determine if patient characteristics including sex, ethnicity, APACHE II scores, ventilator associated pneumonia, chest radiographic variables, bacteremia, serum creatinine, bilirubin, CD4+ T cell count, and comorbidities are significantly different between the two treatment groups. Logistic regression analysis will also be used to assess which baseline variables are associated with significantly lower mortality. The chi-square test was utilized as evidenced below to compute the projected sample size using 80% power and 80% survival in the linezolid group versus 63% in the vancomycin group as demonstrated in the retrospective study discussed above.

$$n = 8\ \frac{0.8(0.2) + 0.63(0.37)}{0.0289} + \frac{2}{0.17} + 2$$

n = 123 subjects in each group

D. Subjects Selection

The population of patients for the study will include men and women with pneumonia acquired after 48 hours of hospitalization. Patients must demonstrate at least two of the following: cough, purulent sputum, auscultatory findings consistent with pneumonia, dyspnea, tachypnea, or hypoxemia. Patients must also have had least two of the following findings: fever or hypothermia, respiratory rate > 30 breaths/min, systolic BP < 90 mm Hg, heart rate ≥ 120 beats/min, altered mental status, need for mechanical ventilation, total peripheral WBC count > 10,000/μL or < 4,500/μL, or > 15 % immature neutrophils. Finally, patients must demonstrate radiographic evidence of pneumonia including new or progressive infiltrates, consolidation, or pleural effusion. Exclusion criteria for the study include, isolation of MRSA that is resistant to either study medication, gram-negative organism on gram stain, hypersensitivity to either study medication, and women who are pregnant or lactating. Informed consent will be obtained from all study subjects prior to enrollment in the study. The obtaining of informed consent may be difficult or impossible in patients receiving mechanical ventilation limiting their enrollment in the study. When possible, consent will be obtained in advance in individuals identified as at risk of developing nosocomial pneumonia to avoid excluding this important population from enrollment in the study. The location of the study will be Columbia Presbyterian Medical Center.

E. Literature Cited

Wunderlink, R, Rello, J, Cammarata, S et al. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. Chest 2003; 124:1789.

Guideline for prevention of nosocomial pneumonia. Centers for Disease Control and Prevention. Respiratory Care 1994; 39:1191.

Celis, R, Tores, A, Gatell, J, et al. Nosocomial pneumonia a multivariate analysis of risk and prognosis. Chest 1988; 93:318.

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