A Multicenter Randomized Clinical Trial of 4 vs. 8 Days of Definitive Antibiotic Therapy for Early Ventilator-Associated Pneumonia in the Surgical Intensive Care Unit:

The Duration of Antibiotic Therapy for Early VAP (DATE) Trial

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Background:

The prevalence of multi-drug resistant (MDR) pathogens in intensive care units (ICUs) worldwide has reached epidemic proportions [1, 2]. In some cases, the choice of potential therapy is limited or even non-existent [3]. Antibiotic prescription, through selection pressure, represents the main mechanism by which resistance emerges [4]. Limitations in the development of new antibiotics [5] underscores the importance of adherence to the principles of antibiotic stewardship [6].

Ventilator associated pneumonia (VAP) is the most common serious infection in mechanically ventilated, critically ill patients [7]. Approximately one half of antibiotic prescription in the ICU is related to VAP, including prophylactic, empiric, and definitive therapy [8]. The development of evidence-based algorithms for the rational use of antibiotics in the management of patients with both suspected and confirmed VAP is pivotal to decreasing the emergence of MDR pathogens.

Shortening the duration of antimicrobial therapy for VAP represents one strategy to curtail the emergence of MDR pathogens. Although current guidelines recommend a treatment course of 8-14 days [9], both clinical and microbiologic resolution (MR) of infection typically occur much sooner [10, 11]. In one study of ICU patients ventilated for > 5 days who developed VAP, 8 days of antimicrobial therapy was equally as effective as 15 days, provided VAP was not caused by a non-lactose fermenting gram negative bacillus [12]. Favorable results following courses of therapy < 8 days have been reported, albeit in small, uncontrolled series [13].

One subset of patients for whom a decreased duration of antimicrobial therapy may be particularly effective is those who develop VAP ≤ 7 days after intubation (early VAP). Early VAP comprises the majority of cases of pneumonia diagnosed in the ICU[14] . Furthermore, as compared to patients who develop late VAP, patients who develop early VAP are more likely to be infected with community-acquired pathogens sensitive to narrow spectrum antibiotics [14]. Finally, nearly all cases of

early VAP caused by sensitive pathogens demonstrate MR after relatively short (3-5 days) courses of therapy [10].

The hypothesis of this randomized clinical trial (RCT) is that 4 days of antibiotic therapy, as compared to 8 days, is equally effective and results in decreased antibiotic exposure among surgical ICU patients with early VAP.

Methods:

Study Design: Randomized, double-blind (until treatment day 5) clinical trial.

Intervention: Default 4 vs. 8 days of antibiotic therapy.

Screening Pool: Trauma-Surgical ICUs.

Inclusion Criteria:

1) Surgical patient
2) Early VAP, defined as:
    a. Duration of Intubation: 2-7 days [9] (via endotracheal or tracheostomy tube).

b. Clinical suspicion of pneumonia: New or progressing infiltrate on chest radiograph (CXR) along with ≥ 1 of the following: Temperature ≥ 38.5°C or < 36.5°C; blood leukocytes >11,000 mm^3 or <4,000 mm^3; purulent tracheal secretions; or P_aO_2:F_iO_2 < 200 [15].

c. Quantitative microbiologic confirmation: Bronchoalveolar lavage (BAL) culture showing ≥10^5 cfu/mL of at least one pathogen [16]. The quantitative microbiology threshold will be lowered to ≥10^4 cfu/mL if the patient was being treated with antibiotics to which the pathogen is sensitive at the time of the BAL.

3) Hospital LOS ≤ 10 days at the time that the BAL was obtained.

Exclusion Criteria:

1) Age < 18 years.

2) Prior episode of VAP for the index admission (the patient may have had prior BALs sent for culture, but these cannot have met the above mentioned diagnostic criteria for VAP).

3) VAP caused by a MDR pathogen: Early VAP is rarely caused by MDR pathogens; in a recent analysis of our surgical ICU, 94% of cases of early VAP were caused by highly sensitive pathogens (Methicillin-sensitive staphylococcus aureus 39%, Haemophilus influenza 35%, Streptococcus pneumoniae 16%, Esterichia coli 9%) [14]. Patients with early VAP caused by the following MDR pathogens will be excluded: Methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-intermediate Staphylococcus aureus (VISA), pseudomonas aeruginosa, Vancomycin-resistant enterococcus (VRE), Acinetobacter baumannii, Stenotrophomonas maltophilia, carbapenem-

resistant enterobacteriaceae (CRE), and extended-spectrum beta lactamase producing gram negative bacilli.

4) Causative pathogen not sensitive to choice of initial empiric antibiotic.

5) Antibiotic therapy for ≥ 5 of the last 10 days preceding the BAL.

6) Septic shock, defined as evidence of tissue hypoperfusion after adequate volume expansion, due to infection, and requiring ≥ 1 vasopressor [17].

7) Current or recent (within 30 days) use of immunosuppressive medications.

8) Length of stay ≥ 72 hours in a transferring facility.

9) Pregnancy or lactation.

10) Legal arrest or incarceration.

11) Moribund state in which death is imminent.

Outcomes:

The two main outcomes will be effectiveness of treatment and antibiotic exposure. Effectiveness of treatment will be assessed in three ways: 1) Clinical response, 2) MR, and 3) biomarker response.

Clinical Response: Current guidelines state that appropriately treated patients with VAP should have a favorable clinical response by day 3, and a substantial improvement by day 6 [9]. Clinical variables used to access for treatment response are organized into the Clinical Pulmonary Infection Score (CPIS). The original CPIS, as described by Pugin et al. [18], included five clinical variables [temperature, white blood

cell count (WBC), tracheal secretions, ratio of P_aO_2 to F_iO_2 (P:F), and chest radiograph findings) and one microbiologic variable (culture of tracheal aspirate and its relationship to the gram stain). Several authors have since modified the score to exclude the microbiologic variable in order to both screen for VAP and monitor efficacy of treatment [11, 19]. This modified score, herein referred to as $CPIS_{clinical}$, omits the microbiologic variable and ranges from 0-10.

The $CPIS_{clinical}$ will be calculated at baseline and daily thereafter during the study period. In the case that certain individual variables are not available for abstraction, they will be left blank rather than obtained solely for the purpose of the study. The worst values (those associated with the highest number of points) for each variable over the 24 hours prior to the BAL will be used. Tracheal secretions will be scored based on daily progress notes from the respiratory therapist. Chest radiograph findings will be scored based on attending final radiologist reads.

It is important to note that $CPIS_{clinical}$ possesses limited accuracy for monitoring VAP resolution in surgical ICU patients [20, 21]. Furthermore, a multicenter RCT reported decreased organ failure, mortality, and antibiotic use for patients with suspected VAP managed using a microbiologic endpoint as compared to a clinical one [22]. For these reasons, efficacy of treatment will also be assessed both microbiologically and using a biomarker of infection (*see below*).

Microbiologic Response: The definition of microbiologic response for VAP reported most commonly ranges from $<10^2$ cfu/mL [23] to $<10^3$ cfu/mL [10] from a repeat BAL culture obtained the day after the end of therapy. For the purposes of this trial, microbiologic response will be defined as growth of the original pathogen of $<10^3$ cfu/mL from a BAL culture obtained the day after the end of treatment. Repeat BALs will thus be obtained on day 5 for the 4-days of antibiotics group and day 9 for the 8 days of antibiotics group. If the patient is no longer intubated at this time, a repeat BAL will not be obtained and MR will be inferred. The treatment team will have access to the results of the repeat BAL.

Biomarker Response: Circulating levels of calcitonin precursors, including procalcitonin, are elevated in bacterial infections [24, 25]. Normalization of procalcitonin concentration in patients receiving therapy for VAP has been shown to both correlate with clinical response and guide discontinuation of antibiotics [26]. The relationship between clinical response, MR, and procalcitonin concentration has not been evaluated prospectively in critically ill patients being treated for VAP and will be the focus of a sub-analysis.

Currently, procalcitonin concentration is measured in all surgical ICU patients for whom a BAL is sent on the day of the BAL as part of a separate non-interventional study. For the purposes of the current trial, procalcitonin concentration will also be measured during treatment in order to assess response, as well as following treatment in order to assess for recurrence. Because study entry will occur at the time that VAP is confirmed microbiologically (approximately 72 hours following the BAL and initiation of empiric antibiotics), these measurements will begin after three days of antibiotic therapy. Procalcitonin concentration will then be measured daily for the remainder of treatment, as well as daily for 72 hours following treatment. Thus, the 4 day group will have procalcitonin concentration measured at baseline, treatment days 3 and 4, and post treatment days 1-3. The 8 day group will have procalcitonin measured at baseline, treatment days 3-8, and post-treatment days 1-3. The treatment team will have access to the results of these measurements. For the purposes of the trial, biomarker resolution will be defined as a procalcitonin concentration < 0.5 μg/L or a decrease of $\geq 80\%$ relative to the day of the BAL [26].

Additional Outcomes: Days of antibiotics, antibiotic days (defined as the product of days of antibiotics and number of antibiotics per day), recurrence, ventilator days, empyema, need for tracheostomy, non-pulmonary infections, ICU length of stay (LOS), hospital LOS, and mortality. Recurrence is defined using the same clinical and microbiologic criteria as the initial episode of VAP, and occurring 2-14 days

following completion of initial therapy. Relapse is defined as recurrent VAP caused by the initial pathogen; super-infection is defined as recurrent VAP caused by ≥ 1 new pathogen. VAP occurring > 14 days following completion of initial therapy will be considered a second episode of pneumonia as opposed to a recurrence. The incidence of recurrent VAP due to a MDR pathogen, as well as any other infection caused by a MDR pathogen, will also be abstracted.

Baseline Variables: Age (years), gender, admission diagnosis, associated diagnoses, admission APACHE II score, comorbidity index [27], prior and current antibiotic exposure, base deficit, serum lactate concentration, time from ICU admission to BAL, presence of organisms on gram stain, and presence of polymorphonuclear lymphocytes on gram stain.

Study Flow & Stop Criteria: The trial will be reported in accordance with the recommendations of the CONSORT Statement [28]. IRB approval will be obtained. All subjects or their legally authorized representative will provide written consent for study participation. The trial is registered with the US National Institutes of Health (ClinicalTrials.gov Identifier NCT01994980).

Screening will occur daily by study personnel. Eligible patients will be approached as soon as possible after inclusion criteria are met (i.e., 1-3 days prior to randomization). Randomization will occur using a computer-generated block pattern on the morning following the fourth day of appropriate antibiotic therapy.

Empiric antibiotic therapy will be instituted as soon as possible following BAL acquisition. The default antibiotic will be ceftriaxone 2 gram IV q24 hours. Patients with potential allergies to cephalosporins will receive levofloxacin 750 mg IV q24hours. Pre-existing treatment for a non-

pulmonary infection with at least one antibiotic that has appropriate activity against the VAP pathogen may be substituted for the default antibiotic. Once sensitivity data become available (approximately 72 hours after BAL acquisition), therapy may be de-escalated to a more narrow-spectrum agent (e.g., cefazolin) as indicated.

The default duration of antibiotic therapy will be determined by study group assignment; the treatment team will be asked to adhere to study group assignment whenever possible. However, the treatment team may choose to extend the duration of antibiotic therapy based on clinical circumstances, such as deterioration in hemodynamic or respiratory status that is believed to be related to incompletely treated VAP, or continued treatment of a non-pulmonary infection. The treatment team may also decide to extend the duration of antibiotic therapy based on the results of serial procalcitonin measurements. Finally, the treatment team may decide to extend the duration of antibiotic therapy based on the results of the BAL obtained the day after completion of therapy. These clinical decisions will take precedence over study group assignment.

Patients will be followed for 28 days or until hospital discharge, whichever occurs first. Please see attached data collection tool for detailed information.

Sample acquisition and processing: The default method for BAL specimen acquisition will be via the blind or "mini" BAL technique [18], using an 85 mm by 4 mm bronchial diagnostic catheter (Combicath, ® Prodimed, Neuilly-en-Thelle, France). The catheter is passed through the artificial airway until resistance is met. It is then withdrawn approximately 1 cm and the inner lavage catheter is deployed. Lavage is then performed with 20 – 40 mL of sterile saline.

The BAL will be obtained bronchoscopically if bronchoscopy is being performed for another indication (e.g., pulmonary toilet, percutaneous dilational tracheostomy). Lavage is performed using 20-40 mL of normal saline lavage into the lobar bronchus that appears most abnormal on CXR.

Using a 0.001 calibrated loop, vortexed BAL specimens will be plated onto sheep blood, MacConkey, and Chocolate agar at 35°C - 37°C in CO_2. Plates will be examined after 24, 48, and 72 hours prior to issuing a final negative report. 100 or more colonies per plate is considered significant and represents ≥ 10^5 cfu/mL.

Statistical Analyses:

Power analysis: Power analysis was performed using SAS Version 9.1 (SAS, Inc., Carey, NC, *proc power*). The Analysis was based on a non-inferiority study design, defined as a difference in outcomes between the 4 day and 8 day groups of < 10%. Furthermore, as the intention was to show non-inferiority, tests were one-sided using an alpha error level of 0.10. The beta error level was set at 0.20 for 80% power. Analysis for the outcome of VAP recurrence returned the largest sample size. From 2010-2012, during which time VAP was treated with ≥ 8 days of therapy, the incidence of recurrent VAP in the DHMC surgical ICU was approximately 25%. Projecting a recurrence rate after 4 days of treatment of 35% returns a total sample size of 103..

Interim Analysis: An interim analysis will be conducted for all outcomes after 50% accrual (n_{total}=50).

Data Analysis: Data analyses will be performed using SAS Version 9.1 (SAS, Inc., Carey, NC). Data will be analyzed using an intention-to-treat strategy (i.e., patients randomized to receive 4 days of antibiotic therapy will be analyzed with this group even if they receive longer courses). Data will be expressed as median (range) or number (%). Normality of continuous variables will be assessed using the

Kolmogorov-Smirnov test. Differences in the means of continuous variables that are distributed normally will be assessing using the Student's t-test. Differences in the medians of continuous variables that are not distributed normally will be assessed using the Wilcoxon Rank Test. Proportions of categorical variables will be compared using the chi-squared test. When expected cell counts are < 5, Fischer's exact test will be used. Univariate analysis of categorical outcomes will be expressed as the relative risk with 95% confidence intervals. A logistic regression model will be fit to address possible confounding by differences in baseline parameters between groups. Baseline variables associated with randomization status at the $p<0.25$ level by univariate analysis will be added to the model using a forward selection method. The overall contribution of the fitted model to predicting variability in the outcome of interest will be assessed using the likelihood ratio chi-squared test. The independent contribution of individual variables will be assessed using the Wald chi-squared test. Model fit was will be assessed using the Hosmer-Lemeshow goodness-of-fit chi-squared statistic, with $p>0.05$ indicating acceptable model calibration. The alpha error level is defined at 0.05, with statistical significance set at $p<0.05$.

Adverse Event Monitoring and Reporting: Adverse event monitoring will occur daily. The safety of the study will be monitored by an independent, external Data Safety Monitoring Board, consisting of a medical intensivist, and an infectious disease physician. The committee will meet biannually and submit written reports to the IRB.

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