Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit*

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Context: In critically ill intubated patients, signs of respiratory infection often persist despite treatment with potent systemic antibiotics.

Objective: The purpose of this study was to determine whether aerosolized antibiotics, which achieve high drug concentrations in the target organ, would more effectively treat respiratory infection and decrease the need for systemic antibiotics.

Design: Double-blind, randomized, placebo-controlled study performed from 2003 through 2004.

Setting: The medical and surgical intensive care units of a university hospital.

Patients: Critically ill intubated patients were randomized if: 1) ≥18 yrs of age, intubated for a minimum of 3 days, and expected to survive at least 14 days; and 2) had ventilator-associated tracheobronchitis defined as the production of purulent secretions (≥2 mL during 4 hrs) with organism(s) on Gram stain. Of 104 patients monitored, 43 consented for treatment and completed the study. No patients were withdrawn from the study for adverse events.

Intervention: Aerosol antibiotic (AA) or aerosol saline placebo was given for 14 days or until extubation. The responsible clinician determined the administration of systemic antibiotics (SA). Patients were followed for 28 days.

The combination of mechanical ventilation and a tracheal tube often results in respiratory infection. We have previously described ventilator-associated tracheobronchitis (VAT) and its treatment in stable chronically ventilated patients (1, 2). In those studies, aerosolized antibiotics (AA) eradicated respiratory pathogens, decreased the volume of secretions, and were not associated with increased resistance. After AA, peak antibiotic concentrations in respiratory secretions were 200-fold greater than the levels achieved in the blood of patients who received systemic therapy, and sputum trough levels remained 20-fold greater than acceptable serum trough concentrations. These concentrations were achieved by using specially designed methods of aerosol delivery, which were developed in our laboratory, tested in intubated patients, and demonstrated to provide optimal aerosol deposition (3, 4).

In the intensive care unit (ICU), early observational studies of VAT in critically ill patients suggested that VAT has an impact on ICU stay but the relationship of VAT to ventilator-associated pneumonia (VAP) has not been fully elucidated (5–8). Our group originally defined VAT simply by the observation of measurable purulent secretions in the presence of an endotracheal or tracheostomy tube associated with mechanical ventilation (1, 2).

The primary objective of the present study was to use AA in the intensive care unit to treat VAT in critically ill patients. Based on our previous experience in chronically ventilated patients, our goal was to eliminate proximal airway infection in the critically ill intubated patient.
We hypothesized that treating the proximal airway infection (VAT) with high concentrations of antibiotics would reduce or prevent signs and symptoms of deep respiratory tract infection (VAP) and also decrease bacterial resistance and use of systemic antibiotics. To meet our randomization criteria for VAT, patients’ secretions were measured daily from time of intubation until they produced at least 2 mL of purulent lower respiratory tract secretions aspirated during a 4-hr period, a criterion derived from preliminary data characterizing tracheobronchitis in the ICU. To measure secretion volume, we used our previously published technique developed in our chronic ventilator unit (2).

Primary end points included reduction in indices of respiratory infection, including the Centers for Disease Control National Nosocomial Infection Survey (9) (CDC-NNIS) VAP and clinical pulmonary infection score (CPIS) comprised of points for radiographic changes, white blood cell count (WBC), fever, the characteristic of the respiratory secretions, oxygenation, and the presence of pathogens (10). Secondary clinical end points included systemic WBC, systemic antibiotic use, mortality, and weaning from mechanical ventilation. Microbiological end points included semiquantitative tracheal aspirate cultures and the development of bacterial resistance.

METHODS

Patients

This study was a double-blind, randomized, placebo-controlled trial conducted at a single center. Critically ill patients requiring mechanical ventilation were included if they met the following criteria: ≥18 yrs of age, intubated and mechanically ventilated for a minimum of 3 days, and expected to survive at least 14 days. Exclusion criteria included: 1) pregnancy, 2) use of immunosuppressive agents other than corticosteroids, neutropenia (<1000 WBC/mm³), 3) history of allergy to study drugs, 4) mechanical ventilation for >60 of the last 90 days, and 5) a primary diagnosis of community-acquired pneumonia defined as pneumonia diagnosed within the first 3 days of admission. Patients who completed treatment for community-acquired pneumonia and remained intubated were not excluded. Forty-three subjects, or their proxy, provided proper two-staged, written, informed consent as approved by the Human Investigations Committee. Data from five patients were not analyzed (four patients in the AA group and one from the placebo arm) because of deviation from consent protocol. The deviation was identified after randomization.

Clinical Measurements

After informed consent, study candidates were initially placed in an observational cohort and underwent daily assessment of clinical variables, including daily volume assessment of secretions produced during 4 hrs (2). Briefly, our technique does not allow saline instillation or subglottic suctioning, and the collection is performed in the morning during a period of 4 hrs. During 12 months of observation in the ICU, we measured daily sputum volume in 63 patients starting with the first day after intubation. Using this technique, patients usually have no measurable secretions immediately after intubation. After 1 week, sputum volume averaged 0.96 ± 1.06 (mean ± sd) mL during 4 hrs in patients who did not meet CDC-NNIS criteria for pneumonia. Based on those data, we defined VAT in the ICU as the production of ≥2 mL during 4 hrs (mean + 1 sd to include the majority of patients with measurable secretions). In the present study, as in the preliminary study summarized above, all patients were on enteral feeds via nasogastric tube and active humidification. Patients who produced at least 2 mL of sputum with organisms on Gram stain and who signed a second consent for aerosol therapy were randomized to AA or aerosolized saline placebo.

At the time of randomization, severity of illness was assessed by Acute Physiology and Chronic Health Evaluation II score (11).

Treatment arm was determined by the pharmacy using rotating block randomization (block of 4). Choice of aerosolized antibiotic in the randomization arm was defined on the basis of the Gram stain of the aspirated tracheal secretions. Gram-positive bacteria were treated with vancomycin HCL, 120 mg in 2 mL normal saline every 8 hrs, and Gram-negative organisms were treated with gentamicin-sulfate, 80 mg in 2 mL normal saline every 8 hrs. Both antibiotics were administered serially if Gram-positive and Gram-negative organisms were present. Medication and placebo were nebulized via an AeroTech II nebulizer (CIS-US, Bedford, MA). On the ventilator, the nebulizer was operated via breath actuation with ventilator humidification turned off. Aerosol treatment was given for 14 days unless extubation preceded day 14, then the day of extubation defined “end of treatment.” Patients who were tracheotomized during the study received the full 14 days of therapy. If weaned, aerosol was administered with the nebulizer connected to the tracheostomy via a heated T tube (CIS-US) and run continuously with oxygen at 10 L/min. Nine AA patients and 13 placebo patients underwent tracheostomy during the treatment period. Although measurements of lung dose were not determined in the present study, we estimate that approximately 22% of the antibiotic placed in the nebulizer was deposited in the lower respiratory tract (1, 12). Clinical indices, including vital signs, signs of respiratory infection, VAP (as defined by the CDC-NNIS criteria), CPIS, WBC, and adverse events were recorded on a daily basis.

After the 14-day randomized treatment period, patients were followed an additional 14 days for mortality and weaning from mechanical ventilation (defined as a minimum of 48 hrs free from mechanical ventilation). Ventilator-free days were expressed as the number of days off mechanical ventilation during the 28-day study period. All patients received daily sedation holidays and spontaneous breathing trials per standard ICU protocol when appropriate.

Weekly cultures of tracheal aspirates obtained before the morning aerosol treatment were quantified using a scale of 0 to 4 on the basis of growth after four-quadrant plating. Bacterial isolates from sputum fluid were assessed for resistance by minimum inhibitory concentration and/or Kirby Bauer and analyzed retrospectively. Resistant organisms were defined as those organisms that were resistant to gentamicin and vancomycin or multiple-drug-resistant Gram-negative bacteria as well as methicillin-resistant Staphylococcus aureus.

Systemic antibiotic use was monitored during the treatment period. The need for systemic agents was based on clinical criteria and cultures utilized by the attending physician who was blinded to the aerosol regimen.

Statistical Analysis

For detection of a 25% change in the incidence of VAP (assuming an incidence of 5–80% [13]), at a power of 80% with alpha = 0.05, it was calculated that a total of 180 eligible patients were needed. However, at 48 patients, an interim analysis revealed effects on VAP and CPIS and the study was stopped. Categorical variables, such as gender, were summarized as frequency and percent. Continuous variables were described using means, medians, and sd and/or ranges. Typically, continuous variables were not normally distributed. Therefore, nonparametric methods were used. Wilcoxon’s rank-sum test was used to test for group difference between continuous variables. Kendall’s correlation test was used to test for linear correlation between percentages in categorical variables. Multivariable methods were used to examine the relationship between VAP and treatment, controlling for age and baseline factors.
pneumonia status. We applied generalized estimating equation approach, which incorporates both between and within individual variability (14). We used the logit link function and binomial distribution, and specified the autoregressive working correlation matrix.

Two-tailed tests were used. The significance level was fixed at an alpha level of \( p \leq .05 \). All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC), SPSS 15 (SPSS, Inc., Chicago, IL), and StatXact 9 (Cytel, Inc., Cambridge, MA).

RESULTS

Patients

The final study sample consisted of 28 men and 15 women ranging in age from 19 to 92 yrs. There were no significant differences between the AA (\( n = 19 \)) and placebo (\( n = 24 \)) groups regarding demographic characteristics, clinical status, or sputum Gram-negative stain (Table 1). Bacterial sputum isolates at randomization are listed in Table 2. Typical respiratory pathogens were distributed throughout both groups.

Effect on VAP and CPIS

Signs of respiratory infection as measured by CDC-NNIS-defined VAP decreased significantly in the treatment group from 73.6% at day 1 to 35.7% for patients who received the full 14 days of treatment compared with 75% and 78.6% in the placebo group (Table 3). As shown in Table 3, fewer patients were treated at day 14 than at “end of treatment” because treatment was discontinued at time of extubation. Intragroup differences were highly significant at end of treatment. In general, patients in the antibiotic aerosol treatment group who had pneumonia at baseline got well, whereas those who did not have pneumonia at baseline did not develop respiratory signs and symptoms to meet criteria for CDC-NNIS-defined VAP. This pattern of benefit with respect to CDC-NNIS-defined VAP persisted to the last day of treatment (\( p = .007 \)). The placebo group did not show this same pattern on the last day of treatment (\( p = .28 \)) or at any other evaluation time point. Controlling for age, patients in the AA group were 71% less likely to demonstrate CDC-NNIS defined VAP compared with the placebo (adjusted odds ratio, .29; 95% confidence interval, 0.13–0.66; \( p = 0.006 \)).

The AA treatment group also showed a statistically significant reduction in CPIS, a decrease of 1.42 (±SE, 2.36; \( p = .021 \)) on the last day of treatment (initial CPIS: 6.89, final: 5.47), whereas the placebo group did not (initial CPIS: 6.13, final: 6.08, with a decrease of \( p = .01 \)).
Microbiological Response

Figure 1 shows the effect of treatment on bacterial growth in tracheal aspirates by the semiquantitative technique at time of randomization, week 1, and week 2 of treatment. Patients treated with AA had marked reduction in bacterial growth. Gram stains of cultures with zero growth revealed that in AA, seven of 12 (58%) during week 1 and six of eight (75%) during week 2 had no organisms on Gram stain. In placebo, only three of 14 cultures (21%) and four of 18 (22%) had Gram stains with no organisms.

Eight of 24 placebo subjects acquired resistant organisms that were present at end of treatment compared with 0 of 19 AA patients ($p = .0056$). In the placebo group, four subjects had initially sensitive bacteria (three *Pseudomonas aeruginosa* and one *Klebsiella pneumoniae*) that developed resistance on treatment, two subjects acquired a resistant *Acinetobacter*, and two methicillin-resistant *Staphylococcus aureus*. One of 19 AA subjects transiently acquired a resistant organism: a resistant *Acinetobacter* that resolved during therapy. All patients who acquired resistant organisms received systemic antibiotics.

Effect on Systemic WBC

At randomization, WBC in both groups was elevated (Table 4). During the course of therapy, WBC for the AA patients decreased as indicated by data from 7 and 14 days. Differences between AA and placebo were significant ($p = .016$) at 14 days. For AA patients, WBC at 14 days also was significantly different from WBC at randomization ($p = .016$). WBC did not decrease in the placebo group.

Effect on Systemic Antibiotic Use

At randomization, both groups had similar numbers of patients on systemic antibiotics in general and when stratified by sensitivity to organisms in the spu-

Table 3. Summary of patients meeting National Nosocomial Infection Survey-criteria for ventilator-associated pneumonia

<table>
<thead>
<tr>
<th></th>
<th>AA (n = 19)</th>
<th>Placebo (n = 24)</th>
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<tr>
<td><strong>n (%)</strong></td>
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<tr>
<td><strong>Treatment day</strong></td>
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<tr>
<td>1</td>
<td>14/19 (73.6)</td>
<td>—</td>
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<tr>
<td>End of treatment</td>
<td>6/19 (31.6)</td>
<td>.007</td>
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<tr>
<td>14</td>
<td>5/14 (35.7)</td>
<td>.06</td>
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<td></td>
<td>18/24 (75.0)</td>
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<tr>
<td></td>
<td>14/24 (58.3)</td>
<td>.28</td>
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<td>11/14 (78.6)</td>
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*McNemar’s test compared to baseline; †Fisher’s exact test: aerosolized antibiotics (AA) compared with placebo; ‡end of treatment. Treatment discontinued before 14 days because of extubation.*

Mortality

Mortality within the 28-day study period was similar for both groups: four of 19 (21.1%) patients on antibiotic aerosol treatment died compared with four of 24 (16.7%) patients who received placebo aerosol ($p = .99$). Deaths were the result of multiorgan system failure.

Weaning from Mechanical Ventilation

Twelve of 19 (84.2%) AA patients were weaned vs. 13 of 24 (54.1%) in the placebo group ($p = .052$) (Table 5). We also analyzed this effect in the survivors (15 AA, 20 placebo) because nonsurviving patients who died were terminally extubated (one in AA group) or made comfortable before death (three in AA group and four in placebo). Eighty percent of AA survivors were weaned compared with 45% of the control group ($p = .046$). In the tracheostomized patients, four AA and two placebo patients were weaned from mechanical ventilation. The number of ventilator-free days was higher in the AA group (mean = 10, range = 26; placebo: mean = 24, median = 0, range = 27), although not reaching statistical significance ($p = .069$).
DISCUSSION

We view ventilator-associated airway infection as a continuum requiring the presence of a tube (endotracheal or tracheostomy) and a ventilator. In the ICU, VAT is initiated by intubation and may progress to VAP. VAT and VAP frequently are present simultaneously and are difficult to separate clinically. During the past 30 yrs, an enormous effort has been expended attempting to define and treat VAP while reducing exposure to systemic antibiotics (13, 15–17). Because the clinical markers used as indicators of infection and as end points of therapy reflect both proximal and distal airways infection (e.g., sputum samples vs. quantitative bronchoalveolar lavage), these markers may inadequately describe a particular infection.

We approached respiratory infection by defining its onset simply as the presence of measurable (=2 mL in 4 hrs) purulent secretions in the proximal airways. Based on these criteria, 11 of our 43 patients presented only with VAT, the rest had signs and symptoms of VAP as defined by CDC-NNIS and CPIS. The latter received systemic therapy as well as the aerosol.

We found that intensive therapy of VAT with AA directed by a simple Gram-negative stain of the tracheal aspirate significantly reduced signs of respiratory infection as assessed by the scores used to define VAP: CDC-NNIS and CPIS. Furthermore, in the five AA patients with VAT only, none progressed to VAP. In addition, AA facilitated weaning, moderated systemic WBC, and reduced the use of systemic antibiotics.

Assessing resolution of respiratory infection during therapy is as difficult as making the initial diagnosis. There is no consensus on which end points represent successful treatment (15). In previous studies and in our study, systemic antibiotics only partially resolve the signs and symptoms of VAP. After 8 to 10 days of systemic antibiotics, Chastre et al. (16) found that neither WBC nor temperature had normalized; these parameters did not normalize until day 28 of their study. Similar findings were described by Dennese et al. (17) who observed that neither WBC nor temperature returned to normal after 14 days of therapy and by Kollef et al. who suggested that systemic WBC may not normalize after successful treatment of pneumonia as a result of multiple inflammatory stimuli from the underlying critical illness (13). In our investigation, in the presence of AA, WBC did normalize in the setting of the same inflammatory stimuli. None of these authors reported an effect of intravenous antibiotics on time to extubation. Our treatment approach suggests that use of AA facilitates weaning with equal effectiveness against Gram-positive and Gram-negative organisms.

The microbiological results of our study showed that AA therapy had an impact on bacterial growth in proximal airways (tracheal aspirate). These findings are consistent with our previous observation that AA sterilize the proximal airways for days after cessation of therapy (1). This was not an in vitro effect of the high antibiotic concentrations in sputum because the cultures without growth had no organisms present on Gram stain.

Antibiotics administered as instillations through the endotracheal tube or as aerosols have been used anecdotally during the past 30 yrs (1, 18–25). However, failure of these trials to show significant efficacy may relate to the design of the studies, the way the antibiotics were delivered, and/or lack of statistical power because of the relatively small number of patients enrolled.

We propose that respiratory tract infection in this patient population ranges from purulent tracheobronchitis (VAT) to parenchymal pneumonia (VAP). In the ICU, proximal airway secretions in the intubated or newly tracheostomized patient are not sterilized with systemic treatment and remain a reservoir of pathogenic bacteria. The most important predisposing factor for VAT is the presence of the airway tube with its rapid colonization and developing biofilm; this process facilitates the distal progression of infection into VAP. In patients with VAP, AA therapy augments systemic antibiotics while serving as local therapy for the proximal airways.

A major goal in the ICU is to reduce the amount and duration of systemic antibiotic use, thereby reducing the emergence of resistance (13). Our findings demonstrated reduced need for additional systemic antibiotics in patients receiving AA. During aerosol treatment, significantly more patients receiving placebo were begun on additional antibiotics during the treatment period, indicating that their physicians believed that they were failing therapy. The increased need for systemic antibiotics in the placebo group was not due to inadequate antibiotic choice at the beginning of systemic therapy because before randomization similar proportions of both groups were receiving systemic antibiotics to which the tracheal organisms were sensitive. Furthermore, in our placebo patients, the use of systemic antibiotics was associated with the emergence of resistant organisms. No resistance was found in our AA patients. Contrary to our findings, treatment with AA has been linked to increased antimicrobial resistance. Feeley et al. (24) reported increased resistance to Pseudomo-
duced bacterial resistance and decreased benefits were realized in the context of re-
the ventilator in patients with VAT. These rapid resolution of signs of respiratory in-
findings.

data would have further strengthened our WBC was increased. Inclusion of these extubated during treatment, and the single placebo patient excluded was not the restricted AA patients were extubated and placebo patients received equivalent choices for the patients' organisms. AA and placebo patients received equivalent systemic therapy by randomization and the positive impact of AA was still readily detectable. Finally, we could not perform a true intention-to-treat analysis because of the institutional review board restriction on five patients. However, we believe our reported results are biased conserva-
tively against AA. For example, all four of the restricted AA patients were extubated and had a decrease in systemic WBC. The single placebo patient excluded was not extubated during treatment, and the WBC was increased. Inclusion of these data would have further strengthened our findings.

In conclusion, AA were effective in the rapid resolution of signs of respiratory in-
fection with extubation and weaning from the ventilator in patients with VAT. These benefits were realized in the context of re-
duced bacterial resistance and decreased use of systemic agents. Further testing of AA therapy in intubated patients in larger confirmatory trials is needed.

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