Risk Factors for an Outbreak of Multi-Drug-Resistant Acinetobacter Nosocomial Pneumonia Among Intubated Patients*

Rola N. Husni, MD; Laurence S. Goldstein, MD; Alejandro C. Arroliga, MD, FCCP; Geraldine S. Hall, PhD; Cynthia Fatica, RN; James K. Stoller, MD, FCCP; and Steven M. Gordon, MD

Introduction: Acinetobacter baumanii is a Gram-negative coccobacillus that is normally a commensal pathogen but can be a nosocomial pathogen. An epidemiologic study was performed to investigate an outbreak of A baumanii that occurred in our medical intensive care unit (MICU) from March to September 1995.

Methods: A case-control study was performed by retrospective chart review, comparing case patients to randomly selected patients who were mechanically ventilated in the MICU for at least 1 week during the outbreak. A case patient was defined as any patient with an Acinetobacter infection in which the epidemic strain was considered to be a pathogen. The epidemic strain was defined by its antibiogram. Case patients and control patients were compared for age, gender, underlying disease, acute physiology and chronic health evaluation III score, length of MICU stay, prior antibiotic use, presence of fever, sepsis, type of pulmonary infiltrate, and outcome. Environmental and hand-washing studies also were performed during the period of the outbreak. Molecular typing was performed on available bloodstream isolates.

Results: There were 15 cases of A baumanii nosocomial pneumonia. Fifty percent were bacteremic; one chart was unavailable for review. Twenty-nine patients were identified as control patients. The mean age for case patients was 50 (range, 21 to 84). The mean duration of time from admission to the ICU to infection was 12.8 days (range, 4 to 40). Sepsis developed in 35% of the case patients. Forty-three percent of the case patients died during their hospitalization, with two of those deaths attributed to Acinetobacter infection. Univariate analysis showed that prior use of ceftazidime was associated with infection with Acinetobacter (11/14 case patients compared to 11/29 control patients; p < 0.01). Pulsed-field gel electrophoresis revealed two strains to be responsible for the outbreak. Hand washing was performed before patient contact by only 10% of health-care workers, and only 32% washed their hands after patient contact.

Conclusion: The use of ceftazidime was associated with an increased risk of nosocomial pneumonia with resistant strains of Acinetobacter. Health-care workers need to improve compliance with hand-washing recommendations. (CHEST 1999; 115:1378–1382)

Key words: Acinetobacter baumanii; nosocomial infections; pneumonia

Abbreviations: APACHE = acute physiology and chronic health evaluation; MIC = mean inhibitory concentration; MICU = medical intensive care unit

Acinetobacter1 spp are ubiquitous, small, aerobic, Gram-negative bacilli that prefer moist environments.1 Acinetobacter spp are usually considered to be opportunistic pathogens but have been increasingly reported as the cause of outbreaks of nosocomial pneumonia and bloodstream infections.2 These organisms can withstand desiccation and may acquire resistance to many antimicrobial agents, especially β-lactam antibiotics.3 We report an out-

For editorial comment see page 1226

Materials and Methods

Background

The Cleveland Clinic Foundation is a 950-bed tertiary care hospital with a 17-bed MICU. Infection control personnel noted
an increase in the number of nosocomial infections with Acinetobacter baumanii in MICU patients during the spring and summer of 1995. To identify risk factors for infection with this organism, a case-control study was performed.

Case Definitions

A case patient was defined as any patient in the MICU between March and August 1995 with a nosocomial pneumonia and/or bloodstream infection due to a resistant A baumanii (the epidemic strain). Resistant A baumanii was defined by the following antimicrobial susceptibility pattern: susceptible only to ticarcillin/clavulanate (mean inhibitory concentration ([MIC], < 16 µg/mL) and imipenem (MIC, < 4) intermediate to amikacin (MIC, 32) and resistant to tobramycin (MIC, > 8), gentamicin (MIC, > 8), cefazidime (MIC, > 16), and ciprofloxacin (MIC, > 2). Acinetobacter pneumonia was defined as including the presence of increased respiratory secretions, new lung infiltrate identified on a chest radiograph, and a sputum culture positive for A baumanii. Fever was defined as an oral temperature of > 38°C and sepsis syndrome was determined by previously defined criteria.1

Control Patients

Control patients were defined as all patients mechanically ventilated in the MICU for ≥ 1 week during the epidemic period.

Case Ascertainment

Infection control personnel reviewed all microbiology cultures to identify all MICU patients with A baumanii isolated from clinical cultures. Medical records of all patients were reviewed to identify case and control patients. Information abstracted included demographic data, clinical presentation, disease severity score, underlying diseases, prior antibiotics, treatment, and outcome.

Infection Control Practices

A review of infection control practices was performed by infection control personnel. Cleaning and disinfecting of flexible bronchoscopes and ventilators, including the use of disposable and reusable items, was observed. In-service education was provided to the physicians, nursing staff, and respiratory therapists in regard to A baumanii infections and body substance isolation.6 Flexible bronchoscopes were routinely cleaned and sterilized by a trained equipment technician (Steris process; Steris Corporation; Mentor, OH). Ventilators were cleaned and disinfected within the Department of Respiratory Therapy, and reusable items were cleaned and sterilized in the Central Service Department. All practices were in compliance with our current policy and procedure.

Hand-Washing Survey

A hand-washing survey was conducted in the MICU by infection control personnel during the outbreak period. This survey consisted of six 2-h observation periods (three on the day shift and three on the evening shift), during which all health-care providers (physicians, nurses, and respiratory therapists) were unaware that they were being observed regarding compliance with hand washing and glove use as appropriate for body substance isolation.

Culture and DNA Preparation for Pulsed-Field Gel Electrophoresis of A baumanii Isolates

After bacterial growth of 18 to 22 h, the isolates were inoculated into sterile saline to a density approximately equal to McFarland number 4, sonicated, and centrifuged. The pellet was resuspended in 1 mL of cold cell-suspension buffer (Bio-Rad; Hercules, CA). Agarose gel plugs were prepared with the sonicated isolates and digested with SmaI, a restriction enzyme. The digested DNA plugs were placed in wells of agarose gel molds, and electrophoresis was carried out in a contour-clamped homogenous electric field apparatus (Gene-Path; Bio-Rad), using a No. 12 program that allowed for the separation of molecular weights of 5 to 300 kb. Gels were stained with ethidium bromide and photographed under ultraviolet light. The restriction patterns were analyzed following criteria by Tenover et al.7 If there were identical banding patterns, the isolates were said to be identical; if there were one to three band differences between isolates, they were considered to be closely related. If they differed by more than three bands, they were said to be unrelated.

Data Analysis

The data was subjected to statistical analysis using (Epi-info, version 6.0; Centers for Disease Control and Prevention; Atlanta, GA). Differences between case patients and control patients were analyzed with the χ² test and Fisher’s exact test (two-tailed). A p value of < 0.05 was chosen to assign statistical significance.

RESULTS

Fifteen cases of A baumanii pneumonia were identified in MICU patients between March and August 1995 that met the case definition (Fig 1). One patient was excluded from the study because the chart was not available for review.

Characteristics of the Case Patients

The mean age of the case patients was 50 (range, 21 to 84 years), and 79% were male (Table 1). Indications for MICU admission included respiratory failure (eight patients), sepsis (three), cardiac tamponade (one), encephalitis (one), and acidosis (one) (Table 2). Underlying chronic diseases included cirrhosis (four), collagen vascular disease (three), chronic renal failure (one), AIDS (one), and leukopenia (one). The mean acute physiology and chronic health evaluation (APACHE) III score on admission to the MICU was 95.3. Clinical manifestations included fever (79%), sepsis syndrome (35%), and leukocytosis (mean WBC count, 14,634/mL; range, 700 to 26,360). All patients were intubated and mechanically ventilated. Radiographic evidence of pneumonia was present in all patients at the time of the Acinetobacter infection. Lobar infiltrates occurred in seven patients (50%), and seven had diffuse infiltrates. Acinetobacter was isolated from respiratory secretions in 12 patients (79%). Seven
patients had concomitant bacteremias, accounting for 15% of all bacteremias in the MICU during the study period.

The mean interval from admission to the MICU to the first respiratory culture for Acinetobacter was 12.8 days (range, 4 to 40 days). All case patients were on antimicrobial agents at the time the Acinetobacter infections were identified. The most common antimicrobials that patients received at the time of Acinetobacter infections were vancomycin (100%), ceftazidime (78%), and ciprofloxacin (50%). Antimicrobial treatment for Acinetobacter infections included administration of ticarcillin/clavulanate (64%), imipenem (21%), and a combination of both (15%). Amikacin was used in three patients. The mean duration of antimicrobial therapy for Acinetobacter infections was 26 days (range, 2 to 71 days). Nine patients (64%) were successfully treated for Acinetobacter infections, while three patients failed therapy and two were lost to follow-up. Six patients (43%) died during their hospital admissions. In two patients the death was directly attributed to Acinetobacter sepsis, and in two other patients Acinetobacter infection contributed to death.

**Case-Control Study**

Twenty-nine patients who underwent mechanical ventilation for at least 7 days without developing A baumanii infection or colonization were included in the case-control study. The mean age of control patients was 60 years, and 41% were male. Indications for MICU admission were acute respiratory failure (20 patients), sepsis (4), cardiac disease (2), gastrointestinal disorders (2), and acidosis (1). The mean APACHE III score on admission to the MICU was 92.4. Twenty-two patients (76%) received vancomycin and 11 (37%) received ceftazidime during their MICU admissions. The only significant risk factor associated with Acinetobacter infection was prior use of ceftazidime (11/14 case patients vs 11/29 control patients; \( p < 0.01 \); odds ratio, 6; 95% confidence intervals, 1.1 to 35; Table 1). There were no significant differences between case patients and control patients in age, gender, indications for MICU admission, underlying diseases, use of other antimicrobials, or the presence of sepsis syndrome.

**Hand-Washing Survey**

Hand washing was practiced before patient contact in only 10% of the 111 physicians, nurses, and respiratory therapists observed. After patient contact, the rate of hand washing was 32%. Donning of gloves was practiced by all respiratory therapists, but only 13 (72%) removed their gloves immediately after completing the patient encounter.

**Pulsed-Field Gel Electrophoresis Assay**

Of the four A baumanii isolates (all in the bloodstream) available for pulsed-field gel electrophoresis, two distinct banding patterns were identified.

**Discussion**

Our study found an association between the prior administration of ceftazidime and the subsequent development of A baumanii infections. This finding is in agreement with an earlier study by Mulin et al\(^8\) that associated the use of third-generation cephalosporins with colonization and infection by A baumanii. Other studies have noted an association between other antibiotic classes and Acinetobacter infection. One study, interestingly, found an association between the use of cefazolin and Acinetobacter infection but not with higher generation cephalosporins.\(^9\) Recently, in a report of three case-control studies on a retrospective cohort study, it was found that epidemic infections may coexist with endemic infections of A baumanii.\(^10\) Previous use of a fluoroquinolone antibiotic (perfl Roxacin, ofloxacin, norfloxcin, or ciprofloxacin) was a risk factor found for the development of endemic A baumanii infection. Other risk factors for the development of nosocomial Acinetobacter pneumonia in an MICU, Cleveland Clinic Foundation, 1993.

| Table 1—Characteristics of Case and Control Patients |
|---------------------------------|------------------|-----------------|-----------------|------------------|
| Case Patients                  | n = 14 | Control Patients | n = 29 | p Value |
| Mean age, yr                   | 50     | 60               | 0.4              |
| Men                             | 11 (79%) | 12 (41%) | 0.05          |
| APACHE III score               | 95.3   | 92.4             | 0.79           |
| Admitted for acute respiratory failure | 8 (57%) | 20 (68%) | 0.5             |
| Vancomycin received            | 14 (100%) | 22 (76%) | 0.08          |
| Ceftazidime received           | 11 (78%) | 11 (37%) | < 0.01       |
| Died                            | 6 (43%) | 11 (32%) | 0.9           |
bacter pneumonia in intubated patients included recent neurosurgery, head trauma, large aspiration, and ARDS. A case-control study by Baraibar et al\textsuperscript{11} examined patients who developed Acinetobacter pneumonia and compared the infections to other etiologies of ventilator-associated pneumonia; the study could not detect risk factors common to both groups. That patient population differed from ours in that the ICU's were combined medical-surgical units, with 10 of 12 patients being admitted post-trauma or post-operatively. Seventy-seven percent of patients in the Baraibar study had been on antibiotics in the 10 days preceding the development of ventilator-associated pneumonia.

Lortholary et al\textsuperscript{12} noted that 32 of 40 patients (75\%) in an ICU who were colonized or infected with Acinetobacter had previously taken antimicrobials, although in their experience only previous infection and high severity of illness were statistically significant risk factors for Acinetobacter infection. Because of the difficulty in identifying a specific cause of infection in this patient population, the choice of antimicrobials is often empiric. At the time of the outbreak, ceftazidime and ticarcillin/clavulanic acid were the antimicrobials most commonly used for empiric Gram-negative rod coverage in our MICU. This was the most common indication for case patients to receive ceftazidime. In our study, all of the case patients and most of the control patients (76\%) had received vancomycin for empiric Gram-positive bacteria coverage. The p value for this comparison was not significant, and it is doubtful that the prior use of vancomycin plays any role in the development of Acinetobacter infection. Our study did not confirm the findings of Lortholary et al\textsuperscript{12} that a high disease-severity score was a risk factor for Acinetobacter infection.

Because Acinetobacter resistance is acquired rather than inherent, prior exposure to antibiotics plays a role in the subsequent acquisition of resistant Acinetobacter.\textsuperscript{2} All strains of Acinetobacter identified in our epidemic were susceptible to imipenem, which is consistent with prior reports that show rare but increasing resistance to carbapenams.\textsuperscript{13} In contrast, Marques et al\textsuperscript{14} found that 70\% of isolates of Acinetobacter were resistant to at least two extended-spectrum penicillins and two aminoglycosides but that imipenem and an aminoglycoside resulted in at least partial synergy in all of the highly resistant isolates. Unfortunately, detailed descriptions of imipenem-resistant outbreaks are unavailable. However, the account of one outbreak in New York noted that the epidemic of imipenem-resistant Acinetobacter occurred after imipenem had been heavily prescribed for an outbreak of ceftazidime-resistant Acinetobacter.\textsuperscript{15}

Single-strained nosocomial outbreaks may originate from a common environmental source. We cannot rule out transmission from patient to patient via the hands of health-care workers, especially in light of the hand-washing survey that documented poor adherence to the hand-washing policy by health-care workers before and after patient contact. However, we did not identify a reservoir for Acinetobacter in the MICU, and molecular typing suggested that at least two epidemic strains were present during the outbreak. The availability of

### Table 2—Characteristics of Case Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Days Intubated Before Infection</th>
<th>Underlying Disease</th>
<th>Prior Use of Antibiotics*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>24</td>
<td>Pneumonia, respiratory failure</td>
<td>A,C,G,I,M,V,T,AK,T/S</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>9</td>
<td>Renal failure, pancreatitis</td>
<td>C,G,V</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>40</td>
<td>ARDS, respiratory failure</td>
<td>A,C,G,E,I,M,V,T</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>12</td>
<td>Respiratory failure, pulmonary hemosiderosis</td>
<td>V,T,TO,C</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>9</td>
<td>Respiratory failure, colon carcinoma</td>
<td>E,C,VA,G,M,T,V</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>4</td>
<td>Sepsis, cirrhosis</td>
<td>C,V,G</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>8</td>
<td>Sepsis, cirrhosis, renal failure</td>
<td>V,C,TO</td>
<td>Died</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>14</td>
<td>Sepsis, cirrhosis, respiratory failure</td>
<td>C,G,V</td>
<td>Died</td>
</tr>
<tr>
<td>9</td>
<td>39</td>
<td>15</td>
<td>Respiratory failure, pneumonia, encephalitis</td>
<td>A,C,CE,CI,V,CI</td>
<td>Survived</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>10</td>
<td>Cirrhosis, chronic renal failure, acidosis</td>
<td>V,G</td>
<td>Survived</td>
</tr>
<tr>
<td>11</td>
<td>67</td>
<td>11</td>
<td>Alveolar hemorrhage, collagen vascular disease, respiratory failure</td>
<td>V,T,EC</td>
<td>Died</td>
</tr>
<tr>
<td>12</td>
<td>84</td>
<td>7</td>
<td>Collagen vascular disease, \textit{Pneumocystis carinii} pneumonia, respiratory failure</td>
<td>C,E,V,T/S</td>
<td>Died</td>
</tr>
<tr>
<td>13</td>
<td>37</td>
<td>9</td>
<td>Cardiac tamponade, collagen vascular disease</td>
<td>C,V</td>
<td>Died</td>
</tr>
<tr>
<td>14</td>
<td>20</td>
<td>8</td>
<td>AIDS, \textit{Pneumocystis carinii} pneumonia, respiratory failure, sepsis syndrome</td>
<td>T/S,V,CI,TO</td>
<td>Died</td>
</tr>
</tbody>
</table>

* A = ampicillin; Ak = amikacin; c = ceftazidime; cef = cefotaxime or cefuroxime; Cl = ciprofloxacin; E = erythromycin; G = gentamicin; I = imipenem; M = metronidazole; T = ticarcillin/clavulanic acid; To = tobramycin; T/S = trimethoprim/sulfamethoxazole; V = vancomycin.
only four bacteria for molecular typing is a limitation of our study and leaves open the possibility that more strains were responsible for the outbreak, but it does not invalidate the finding that some of the outbreaks of Acinetobacter infections may be caused by several strains.10

Our study identified prior use of ceftazidime as a risk factor for acquiring an infection with a resistant Acinetobacter sp. The use of ceftazidime as a first-line antibiotic in treating nosocomial infections has increased over the past years because of the increased incidence of resistant organisms like Pseudomonas spp. Now, it seems that ceftazidime has been overused, selecting out even more resistant Gram-negative bacteria. Therefore, the empiric use of these agents should be reserved for instances where there is a high probability of *Pseudomonas aeruginosa* infections. Another goal we recommend is better attention to good hand-washing practices among health-care workers.

**References**