Surveillance Cultures Growing Carbapenem-Resistant *Acinetobacter baumannii* Predict the Development of Clinical Infections: A Retrospective Cohort Study

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**Background.** We aimed to determine the effect of the presence of carbapenem-resistant *Acinetobacter baumannii* in accordance with surveillance cultures on the subsequent development of clinical infections by this organism.

**Methods.** This retrospective cohort study was conducted at a tertiary hospital from January 2010 to November 2011. We included all consecutive patients admitted to the trauma intensive care unit, who had weekly surveillance cultures performed (from rectum, and if intubated, respiratory secretions), and without evidence of *A. baumannii* infections prior to the collection of the first surveillance culture. Univariable and multivariable analyses were performed using log-binomial regression. Survival analyses were performed using Cox proportional hazards.

**Results.** Three hundred sixty-four patients were included, of whom 49 (13.5%) had carbapenem-resistant *A. baumannii* on surveillance cultures. Patients with positive surveillance cultures had 8.4 (95% confidence interval [CI], 5.6–12.7; *P* < .0001) times the risk of developing a subsequent *A. baumannii* infection compared with patients who remained negative on surveillance cultures. Multivariable analysis showed significant associations between clinical infection and both positive surveillance cultures (relative risk [RR], 5.9 [95% CI, 3.8–9.3]; *P* < .0001) and mechanical ventilation (RR, 4.3 [95% CI, 1.03–18.2]; *P* = .05). On survival analyses, the only variable associated with the development of clinical infections was the presence of positive surveillance cultures (hazard ratio, 16.3 [95% CI, 9.1–29.1]; *P* < .001).

**Conclusions.** Presence of carbapenem-resistant *A. baumannii* on surveillance cultures is strongly associated with subsequent development of carbapenem-resistant *A. baumannii* infections. Prevention efforts should be focused at limiting the acquisition of this organism during hospitalization.

**Keywords.** *Acinetobacter baumannii*; carbapenem-resistant; surveillance cultures; clinical infections; intensive care unit.

*Acinetobacter baumannii* is a gram-negative coccobacillus, frequently identified as resistant to most commercially available antibiotics, including carbapenems [1–3]. In 2013, the Centers for Disease Control and Prevention (CDC) named carbapenem-resistant *A. baumannii* as one of the serious health threats for the US population. *Acinetobacter baumannii* is especially problematic in intensive care units (ICUs), and is associated with high morbidity and mortality as well as longer hospital stays [4,5]. Therefore, it is imperative to prevent the development of *A. baumannii* infections by identifying and modifying risk factors for these infections.

Patient-to-patient transmission of *A. baumannii* among hospitalized cases has been described in the literature and linked to contaminated hospital environment, suboptimal disinfection of communal objects,
and contaminated healthcare workers’ hands [1, 6, 7]. Patients colonized with Acinetobacter carry this organism on their body surfaces and contaminate their immediate environment [8, 9]. Gowns, gloves, and hands of healthcare workers become contaminated after contact with either an Acinetobacter-positive patient or their contaminated environment [10]. Finally, being exposed to an environment contaminated with A. baumannii has been associated with a higher risk of acquiring this pathogen [11]. Therefore, interventions aimed at containing Acinetobacter outbreaks consist of a combination of surveillance cultures, hand hygiene, heightened environmental cleaning, and contact precautions [12].

In 2009, as part of a bundle of interventions designed to limit the spread of carbapenem-resistant A. baumannii, we implemented weekly surveillance cultures among consecutive admissions to our adult ICUs [12]. Subsequently, the trauma ICU (TICU) was identified as one of the units with the highest rates of acquisition of A. baumannii [13]. We used surveillance cultures to cohort Acinetobacter-positive patients, and the staff caring for them, within a section of an inpatient unit. However, we did not know the clinical implications of being an asymptomatic carrier of this multidrug-resistant pathogen. Thus, the primary aim of this study was to evaluate a cohort of patients admitted to TICU in order to characterize their differential risk of developing carbapenem-resistant A. baumannii infections based on the presence of this organism on surveillance cultures. Secondly, we aimed to determine the effect of other covariates (comorbidities, antibiotic exposure, and invasive procedures) on the primary association, and explore the effect of time to positive surveillance cultures on primary and secondary associations.

METHODS

This was a retrospective cohort study conducted at a 1500-licensed-bed public teaching hospital in South Florida with a documented carbapenem-resistant A. baumannii endemi city [13]. Over the years, the unit with highest prevalence of this organism was the TICU, a 25-bed open-layout unit located in a freestanding trauma center. We evaluated all consecutive patients admitted to TICU from 1 November 2010 to 30 November 2011. During this period, the TICU had a monthly hospital acquired rate of carbapenem-resistant A. baumannii of 55.9 ± 8.95 cases per 10,000 patient-days [12]. This study was reviewed and approved, and informed consent was waived by the Institutional Review Board of the University of Miami Miller School of Medicine.

Since 2009, as part of a bundle of interventions, all adult ICUs performed surveillance cultures to rule out carriage of carbapenem-resistant gram-negative bacilli, including carbapenem-resistant A. baumannii. As previously described [14], surveillance cultures were performed on admission to the unit and weekly thereafter throughout ICU admission. Surveillance cultures included rectal swab cultures and, if mechanically ventilated, lower respiratory cultures. Samples were streaked in MacConkey agar plates with a 10-µg ertapenem disk and incubated overnight at 37°C. Colonies were selected based on color and morphology and final identification was performed using Vitek II [14].

A patient was considered to be Acinetobacter-positive on surveillance cultures if either rectal or respiratory secretions grew carbapenem-resistant A. baumannii. Patients excluded from the analysis included all subjects who failed to have at least 1 surveillance culture during their ICU stay or who failed to have surveillance cultures prior to the development of an A. baumannii infection. Carbapenem-resistant A. baumannii infections were defined using the CDC definitions [15]; these determinations were ascertained by 2 independent reviewers using the hospital’s electronic medical records. Any discrepancy on determination of clinical infection was reviewed and discussed by the team to achieve a resolution. Additional information collected included demographics, comorbidities, and the use of mechanical ventilation.

Antibiotic exposures were obtained both as a composite of any antibiotic use (“any antibiotic”) and as the exposure to individual antibiotic classes (eg, cephalosporins, carbapenems). For patients who remained negative on surveillance cultures, antibiotic exposures were collected from hospital admission until unit discharge, death, or development of first positive clinical culture, whichever occurred first. For patients with positive surveillance cultures, the initial exposure period expanded from admission to the hospital to the date of collection of first positive surveillance culture. The second period encompassed the time from first positive surveillance culture until unit discharge, death, or development of a carbapenem-resistant A. baumannii infection, whichever occurred first.

Statistical Analysis

This study was designed to test the association between surveillance cultures growing carbapenem-resistant A. baumannii (independent variable) and the subsequent development of clinical infections caused by the same organism (dependent variable). Baseline characteristics of the groups (age, sex, comorbidities, antibiotic exposure, invasive procedures) based on surveillance cultures, the initial exposure period expanded from admission to the hospital to the date of collection of first positive surveillance culture. The second period encompassed the time from first positive surveillance culture until unit discharge, death, or development of a carbapenem-resistant A. baumannii infection, whichever occurred first.

To obtain relative risks (RRs) rather than odds ratios, univariable and multivariable analyses were performed using logistic binomial regressions. Variables included in the multivariable model were selected based on statistical significance obtained in univariable analyses ($P \leq .5$). The presence of multicollinearity
was explored for all significant antibiotic exposures prior to the building of multivariable models [16].

Cox proportional regression was used to include time-to-positive surveillance cultures. For these analyses, “time zero” was the time of admission to TICU. *Acinetobacter baumannii* infections were considered the “events.” Patients who either died or were discharged from TICU before the development of the “event” were censored. Additionally, to account for the different risks of a patient to develop clinical infections during the periods before and after positive surveillance cultures, a time-dependent covariate was created using the date of first positive surveillance culture [17]. All analyses were performed using SAS software, version 9.3 (Cary, North Carolina).

**RESULTS**

During 13 months, 479 consecutive patients were admitted to TICU (Figure 1). Ninety-three patients were excluded due to lack of surveillance cultures; these 93 patients either failed to have orders for surveillance cultures or orders were entered incorrectly in the system (e.g., “rule out vancomycin-resistant enterococci” rather than “rule out carbapenem-resistant gram-negative

![Flow Chart](https://example.com/flowchart.png)

*Figure 1.* Patient selection flow algorithm. Abbreviation: TICU, trauma intensive care unit.
rods”). Twenty-two patients were excluded due to evidence of A. baumannii infections prior to their first surveillance culture. Three hundred sixty-four patients were included in the final analysis: 49 patients (13.5%) had positive surveillance cultures for carbapenem-resistant A. baumannii, and the remaining 315 patients (86.5%) had negative surveillance cultures throughout their ICU stay. Baseline characteristics of the groups based on the status of their surveillance cultures are displayed in Table 1. Variables found to be statistically different at baseline included sex (group with positive surveillance cultures had higher proportion of females; P = .005) and mechanical ventilation (all patients with positive surveillances were mechanically ventilated; P < .0001). Additionally, the group with positive surveillance cultures had greater exposure to antibiotics than the group that remained negative on surveillance cultures (P = .04). In regard to specific antibiotic classes, the group with positive surveillance cultures had higher exposures to both vancomycin and carbapenems (P = .003 and P < .0001, respectively).

Carbapenem-resistant A. baumannii infections occurred in 60 of the 364 (16.5%) patients who underwent surveillance cultures. Twenty-eight patients (47%) developed ventilator-associated pneumonia, 22 (37%) had either primary or secondary bloodstream infection, 7 (12%) had urinary tract infection, 2 (3%) had intra-abdominal infection, and 10 (17%) had some combination of skin and soft tissue infection. Of the 60 patients with clinical infections, 34 (56.7%) had previously documented positive surveillance cultures. Table 2 describes the variables associated with the development of carbapenem-resistant A. baumannii infections. Patients with positive surveillance cultures had 8.4 times the risk (95% confidence interval [CI], 5.6–12.7; P < .0001) of developing carbapenem-resistant A. baumannii infections than patients who remained negative on surveillance cultures. Univariable analyses showed that sex, mechanical ventilation, and exposures to either carbapenem, aminoglycosides, vancomycin, or “any antibiotics” were associated with the development of clinical infection (Table 2). After controlling for other variables, only positive surveillance cultures (RR, 5.9 [95% CI, 3.8–9.3]; P < .0001) and being on mechanical ventilation (RR, 4.3 [95% CI, 1.03–18.2]; P = .05) were associated with the development of carbapenem-resistant A. baumannii infection (Table 2).

Cox proportional regression showed a high hazard for carbapenem-resistant A. baumannii infections among patients growing this organism on surveillance cultures (hazard ratio, 18.8 [95% CI, 10.8–32.8]; P < .0001; Table 3). Sex, mechanical ventilation, and exposure to cephalosporins were also significantly associated with the outcome. However, after adjusting for all significant variables, the only exposure that remained significant was the growth of carbapenem-resistant A. baumannii on surveillance cultures. At 30 days of admission to the unit,
the proportion of patients free of clinical infections among groups with positive and negative surveillance cultures was 0.50 (95% CI, .33–.76) and 0.89 (95% CI, .82–.97), respectively. Figure 2 shows the probability of remaining free of carbapenem-resistant *A. baumannii* infections based on results of surveillance cultures.
DISCUSSION

This study characterizes the clinical implications of detecting carbapenem-resistant A. baumannii on surveillance cultures. We found that patients with positive surveillance cultures were 8 times more likely to develop carbapenem-resistant A. baumannii infections, even after controlling for other variables. Furthermore, among the group with positive surveil- lances, the median time for the development of carbapenem-resistant A. baumannii infections was approximately 30 days from ICU admission.

Prior studies have described the presence of colonization as a factor associated with the development of A. baumannii infections [18, 19]. Our results are in agreement with these conclusions; nevertheless, our findings are framed in the context of an active surveillance program within a retrospective cohort, thus ensuring that surveillance cultures, if positive, preceded the development of clinical infections.

Previously identified risk factors for the development of A. baumannii infections include mechanical ventilation [20], prior exposure to antimicrobials [20, 21], high Acute Physiology and Chronic Health Evaluation (APACHE II) score at the onset of infection [21], long duration of hospital stay, recent central venous catheter insertion [22], female sex [23], length of transducer catheter usage, and hyperalimentation [24]. In regard to antibiotic exposure, the definition of this variable is not unified across the literature, and its quantification differs across different studies [18, 19]. Our study collected antibiotic exposures as dichotomous variables across specified periods of time. Receipt of carbapenems, aminoglycosides, vancomycin, and the composite variable of any antibiotic exposure were associated with a greater risk of developing carbapenem-resistant A. baumannii infections. However, none of these variables were identified as independent risk factors on multivariable analyses. Previous

Table 3. Hazard Ratios for the Development of a Clinical Infection Due to Acinetobacter baumannii

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Surveillance culture, positive</td>
<td>18.8 (10.8–32.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>6.1 (1.5–25.1)</td>
<td>.01</td>
</tr>
<tr>
<td>Charlson score &gt;2</td>
<td>0.9 (.4–2.5)</td>
<td>.99</td>
</tr>
<tr>
<td>Charlson score &gt;5</td>
<td>1.5 (.4–6.1)</td>
<td>.58</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.6 (.3–.9)</td>
<td>.03</td>
</tr>
<tr>
<td>Age &gt;50 y</td>
<td>0.9 (.5–1.6)</td>
<td>.79</td>
</tr>
<tr>
<td>Exposure to penicillin</td>
<td>0.8 (.5–1.3)</td>
<td>.41</td>
</tr>
<tr>
<td>Exposure to cephalosporins</td>
<td>0.5 (.3–.9)</td>
<td>.03</td>
</tr>
<tr>
<td>Exposure to quinolones</td>
<td>0.6 (.3–1.1)</td>
<td>.08</td>
</tr>
<tr>
<td>Exposure to vancomycin</td>
<td>1 (.5–2.4)</td>
<td>.90</td>
</tr>
<tr>
<td>Exposure to aminoglycosides</td>
<td>1 (.4–2.2)</td>
<td>.96</td>
</tr>
<tr>
<td>Exposure to carbapenems</td>
<td>1.3 (.7–2.2)</td>
<td>.40</td>
</tr>
<tr>
<td>Exposure to any antibiotic</td>
<td>0.7 (.2–2)</td>
<td>.52</td>
</tr>
</tbody>
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Antibiotic exposures spanned from hospital admission to development of clinical infection, discharge from unit, or death. Differential risks for development of clinical infections (ie, before and after positive surveillance cultures) were accounted for using a time-dependent variable within the model.

Abbreviations: CI, confidence interval; HR, hazard ratio.

Figure 2. Survival curves with the probability to develop clinical infections with carbapenem-resistant Acinetobacter baumannii based on results of surveillance cultures. Curves represent the probability of staying free of clinical infection caused by carbapenem-resistant A. baumannii. Days represent the days from admission to the unit until the development of the outcome or censoring. Solid line represents the group that remained negative for carbapenem-resistant A. baumannii on surveillance cultures. Dashed line represents the group that became positive for carbapenem-resistant A. baumannii on surveillance cultures. Shaded area depict the 95% confidence intervals.

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studies that found antibiotic exposures as risk factors for acquisition of *A. baumannii* quantified the use of antibiotics as either grams per time period [25], “unit pressure” [18], days of exposure [22], or dichotomous variables [20]. Additionally, severity of illness has been recognized as a risk factor for the development of *A. baumannii* infections [26], as well as a marker for poor prognosis [27, 28]. The Charlson comorbidity index was used in our cohort and failed to show an association with the development of clinical infections. In a previous study [11], higher Charlson comorbidity index was shown to be associated with lower risk of acquiring *A. baumannii* in ICU patients.

Limitations of this project include being a single-center study, where surveillance cultures were performed weekly rather than on a daily basis. Additionally, surveillance cultures are an insensitive method to detect carriage, predisposing to classification bias (high number of false negatives), although this would have skewed our results toward a nonsignificant association. Another caveat of our study is the lack of molecular typing of surveillance and clinical isolates; thus, we can only assume that surveillance and clinical isolates were related within individual patients. Moreover, antibiotic exposures were evaluated as dichotomous rather than continuous variables, lacking number of days and exact onset of exposure. This lack of time-dependent covariates for antibiotic exposures predisposes our analysis to immortal time bias [29], which could have overestimated the impact of antibiotics in our associations. Even though comorbidity index was used to categorize patients’ comorbidities, acuity of illness (APACHE score) was not determined. APACHE II determination upon unit admission was not included given that the outcomes occurred many days after admission. Nevertheless, we admit that the lack of serial acuity of index scores for each individual patient is a major limitation of this study.

In conclusion, this study shows that positive surveillance cultures were strongly associated with the subsequent development of carbapenem-resistant *A. baumannii* infections. Furthermore, survival analyses demonstrated 16.3 times the risk to develop carbapenem-resistant *A. baumannii* infections among patients who grew this pathogen on surveillance cultures during their ICU stay. Surveillance cultures upon admission to ICUs are a valuable infection control tool [30] that should be used not only for cohorting patients but also as a signature marker for subsequent clinical infections. We now know that we should target prevention of acquisition of carbapenem-resistant *A. baumannii* (eg, infection control bundles, antibiotic stewardship, vaccination [31]) as well as focus our efforts on patients who are known to be colonized. The latter could include not only selective digestive decontamination [32] but, most importantly, manipulation of the gut or lung microbiome to prevent the progression of colonization to clinical infections [33]. Remaining questions that should be explored are the effect of antibiotic exposures treated as continuous variables and modeled as time-dependent covariates. The effect of timing of these exposures will allow us to establish the impact of antibiotics on the acquisition of *A. baumannii*, and also their subsequent effect on the development of clinical infections by this organism, especially among previously colonized patients. Establishing the timing of these associations is important, as it will further highlight the interdependence between acquisition of multidrug-resistant organisms and antibiotic use in our inpatient population.

**Note**

*Potential conflicts of interest.* All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**