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## Major Article

## Risk factors for endemic *Acinetobacter Baumannii* colonization: A case–case study

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Antibiotic resistance  
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**Background:** *Acinetobacter baumannii* causes increasingly resistant nosocomial infections worldwide. Although some patients are already colonized with *A baumannii* on hospital admission, others become colonized with endemic strains that are more likely to be antibiotic-resistant. Colonization increases risk of infection and transmission to others. This study aimed to identify risk factors for colonization with endemic compared to sporadic *A baumannii* among hospitalized patients.

**Methods:** The study population were patients colonized with *A baumannii* at a single medical center during a 17-month period of active surveillance. Endemic *A baumannii* (cases) had a repetitive extragenic palindromic (REP) type that occurred 10 or more times during the surveillance period. Cases carrying 1 of the 5 endemic REP types were matched to comparison cases (controls) carrying sporadic strains by facility and time.

**Results:** There were 69 cases with REP-1, and 64 with REP-2-5. After adjustment, each unit increase in Schmid score was associated with a 70% increase in REP-1 carriage ( $P = .04$ ) and a 50% increase in REP-2-5 ( $P = .07$ ). Days in the intensive care unit prior to colonization, longer length of stay, immunosuppression, and the Charlson comorbidity index were not significantly associated with carriage of endemic strains.

**Conclusions:** Following best practices for antibiotic stewardship and hygiene will help minimize the emergence and persistence of *A baumannii* strains adapted to the health care environment.

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*Acinetobacter baumannii* is a gram-negative organism that causes a range of infections primarily among those already ill. Its treatment and associated infection control procedures can be challenging as *A baumannii* has developed resistance to multiple antibiotics and can survive in the environment for several days.<sup>1</sup> In the United States between 2002 and 2008, the number of multiclass antibiotic-resistant *A baumannii* infections increased 3.7-fold.<sup>2</sup> Multidrug-resistant strains of *A baumannii* are a health care issue worldwide.<sup>3-7</sup> The reported mortality from *A baumannii* infections resistant to antibiotics is roughly twice that of antibiotic susceptible infections: 58%–70% versus 34%–45%.<sup>1,4,8,9</sup>

Hospitalized patients frequently become colonized, particularly when in intensive care units (ICU) or with a longer length of stay. In a New York study of hand and nares colonization among 98 patients in the ICU and rehabilitation units of 2 hospitals, 14.3% were colonized with *A baumannii*.<sup>10</sup> Among 822 patients transferred from other hospitals to a hospital in occupied Palestinian territory, 9% were colonized with multidrug-resistant *A baumannii*.<sup>11</sup> Colonization with *A baumannii* increases risk of infection.<sup>3</sup> Once colonized, known risk factors for infection include longer length of stay,<sup>3</sup> >30 days bedridden,<sup>12</sup> immunosuppression, invasive procedures/devices, surgical history,<sup>7</sup> age, pneumonia, and ICU stay.<sup>8</sup> Some *A baumannii* strains have adapted to the hospital environment. In a Brazilian cohort study of newly admitted patients to an adult ICU 13.6% of the 216 oropharyngeal swabs were positive for *A baumannii* in the 10-week study period; 55% of these were with a single clone. This clone also accounted for two-thirds of the positive hand samples from personnel.<sup>13</sup> A longer (2.5 year) Philadelphia cohort study of multidrug-resistant *A baumannii* also observed a pattern of a predominant strain, with strain replacement and succession over a 3.5-year period.<sup>14</sup> A comparison of endemic

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strains, defined as occurring 10 or more times, to sporadic strains from a tertiary care facility found that endemic strains were resistant to more antibiotic classes and were more likely to carry *bla*<sub>OXA-23</sub>, which encodes for the carbapenemase OXA-23.<sup>15</sup>

We hypothesized that risk factors for *A baumannii* colonization or infection, such as patient's ambulatory status/mobility and their recent antibiotic exposure, might differ for patients infected or colonized with sporadic strains compared with those infected with strains endemic to a particular hospital. To test this hypothesis, we used a case–case design to compare characteristics of patients colonized with endemic *A baumannii* (case), defined as a repetitive extragenic palindromic (REP) type occurring in 10 or more patients, to patients colonized with sporadic strains (comparison case).

## METHODS

### Study population

The study was conducted at the Detroit Medical Center (DMC), a tertiary care facility with >2,000 licensed beds located in Detroit, Michigan. Eligible patients were admitted as an inpatient to a DMC facility between January 2010 and May 2011 and had an incident positive culture for *A baumannii* during their hospital stay. The isolates were part of a larger surveillance study for common nosocomial agents (ESKAPE pathogens) within the DMC. Isolates were collected from a variety of specimens: blood, urine, sputum or other respiratory, wound, skin, and eye exudates. Isolates were included from both patients who were asymptomatic (colonized but not infected) and those with symptomatic infection. If a patient had multiple positive isolates, one was randomly selected for study. The study protocol was reviewed and deemed exempt by the institutional review board at University of Michigan [HUM00064166].

### Isolate typing

*A baumannii* isolates were collected and typed as described previously.<sup>15</sup> Briefly, *A baumannii* were identified and tested for antibiotic susceptibility using MicroScan (Beckman Coulter, Brea, CA) and genotyped using REP-PCR. Isolates were considered endemic to the DMC if the REP-PCR type occurred 10 or more times. Five REP-PCR types were identified as endemic. REP-PCR types that occurred <10 times were considered sporadic.

### Endemic case and sporadic case definition

Cases were defined as patients colonized or infected with an endemic *A baumannii* strain.<sup>15</sup> Cases were further differentiated into 2 case groups: those with the most commonly observed genotype, REP-1, and the remaining endemic strains (REP-2 through REP-5). The remaining endemic strains were grouped together for analysis as the risk factors were similar and the numbers in each group were small. Cases were matched to other case patients with sporadic strains by facility and time of positive culture (plus or minus 30 days of case culture date).

### Data measurement

Medical records were reviewed for demographic, risk factor, and outcome data of interest. Time sensitive variables, such as 3-month mortality, 3-month prior hospitalization, 3-month readmission, ICU days before index culture, ICU days after index culture, and hours at risk and used the index culture date as the reference time point. Prior antibiotic use was defined using the 3-month time period leading up to the index date and was operationalized into a multilevel categorical variable. Comorbidity data included those conditions needed to compute the Charlson comorbidity score; a weighted score of 19 comorbidities was used to index the risk of mortality for use in

longitudinal studies.<sup>16</sup> Schmid score, a fall risk assessment tool for hospitalized patients, was measured and included a total score of risk based on mobility, mentation, elimination, fall history, and current medication use.<sup>17</sup> The maximum score is 5; a patient with a score of 3 or more is considered at risk for falls.

Device use was defined as the presence of any of the following devices within 48 hours prior to the index culture: tracheostomy, central intravenous catheters, Foley catheter, and percutaneous endogastric tubes.

### Statistical analysis

We described differences between endemic and sporadic isolates using simple descriptive statistics, and tested differences in categorical variables using the  $\chi^2$  test. We estimated crude and adjusted odds ratios using univariate and multivariate conditional logistic regression and the associated 95% confidence intervals. We included in the multivariate analysis all potential risk factors that were statistically significant at  $P < .05$  or had an effect size  $>1.5$  in the univariate analysis. For the purposes of this study, a level of 95% confidence was used to determine significance. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

## RESULTS

Of the 290 isolates collected and typed using REP-PCR previously,<sup>15</sup> 169 were classified as endemic, with 96 isolates from REP-1, 27 isolates from REP-2, 16 isolates each from REP-3 and REP-4, and 14 isolates from REP-5. The remaining 121 isolates were classified as sporadic. The respiratory tract was the most common site of isolation for most REP types, followed by wound, tissue, or abscess sources. Given the smaller sample sizes of REP types 2–5, results for REP-2–5 were collapsed for presentation. Endemic types were matched by DMC facility and using a 60-day window of plus or minus 30 days of index culture date. This resulted in 69 REP-1 sporadic pairs and 64 REP-2–5 sporadic pairs used for analysis.

Most patients presented with symptoms that led to specimen collection, however, it is difficult to ascertain from medical records whether the infection was indeed attributable to *A baumannii*. In 109 patients (37.6% of the total), only *A baumannii* was isolated, suggesting the infection was likely caused by *A baumannii*. From the remaining specimens up to 5 other organisms were detected using a panel that included *Escherichia coli* (n = 28), *Klebsiella pneumoniae* (n = 41), *Klebsiella oxytoca* (n = 2), *Proteus mirabilis* (n = 32), *Enterobacter* spp (n = 10), methicillin-resistant *Staphylococcus aureus* (n = 66), vancomycin-intermediate *S aureus* (n = 47), *Pseudomonas* spp (n = 61), and vancomycin-resistant *Enterococcus* (n = 34). The distribution of REP types from specimens in which only *A baumannii* was isolated was not significantly different from that in which multiple bacteria were isolated ( $\chi^2$ ;  $P = .78$ ).

### Characteristics of endemic-sporadic pairs

The average age of study participants was similar for endemic cases and sporadic cases in both pairs, and almost three-quarters of participants in each group were African American (Supplemental Table 1). Although the percentage of men was similar among the REP-1 pairs, men were more common among endemic isolates for REP-2–5 pairs. Prior antibiotic exposure, ICU days after admission, Schmid score on admission, and presence of dementia, a tracheostomy, or a urinary catheter were positively associated with REP-1. These variables were also associated with REP-2–5, but the effect sizes were smaller and failed to reach statistical significance in many cases (Table 1). Other known risk factors for *A baumannii* carriage, including isolate source, Charlson index, and service, were not associated with endemic strains. See Supplemental Table 1 for

the distribution of all variables for REP-1 and REP-2-5 pairs and the crude associations for endemic colonization.

### Antibiotic resistance

A higher proportion of REP-1 strains than matched sporadic strains were resistant to all tested antibiotics in at least 3 of the 5 following classes (multidrug-resistant): cephalosporins, carbapenems,  $\beta$ -lactam + inhibitor combinations, fluoroquinolones, and aminoglycosides (64% vs 34%). They were also more likely to be pandrug-resistant (resistant to all antibiotic representatives in all 5 of the following classes: cephalosporins, carbapenems,  $\beta$ -lactam + inhibitor combinations, fluoroquinolones, and aminoglycosides, and resistant to tetracycline and trimethoprim-sulfamethoxazole: 6% vs 0%). This was also true for REP-2-5 strains, but the differences were less dramatic (multidrug-resistant: 41% vs 32%; pandrug-resistant: 3% vs 0%) (Table 1).

### Multivariate analysis

We included in the multivariate analysis all potential risk factors that were statistically significant at  $P < .05$  or had an effect size  $> 1.5$

in the univariate analysis (Table 1). After adjustment, only Schmid score on admission was significantly associated with REP-1: each unit increase in Schmid score increased risk of colonization with an endemic strain by 70% ( $P = .04$ ) (Table 1). There was a trend of increasing risk of REP-1 colonization with increasing number of antibiotics used in the previous 3 months, but none of the associations were statistically significant. The odds ratios for dementia (3.0) and urinary catheter use (1.6) changed little but were no longer statistically significant after adjustment. By contrast, after adjustment men were more strongly associated with REP-2-5 colonization (odds ratio: 2.6;  $P = .04$ ), and Schmid score was slightly attenuated (odds ratio: 1.5; 95% confidence interval: 1.0, 2.3).

### DISCUSSION

In this case–case study comparing characteristics of patients colonized with endemic REP types of *A baumannii* to those colonized with sporadic strains, colonization with an endemic REP type was associated with Schmid score on admission, prior antibiotic exposures, and male sex. Consistent with the literature, the endemic strains were

**Table 1**  
Univariate and multivariate conditional logistic regression results for endemic versus sporadic *Acinetobacter baumannii* isolates by REP—polymerase chain reaction type for case–case analysis—2010–2011

Variables of interest	Univariate regression					Multivariate regression		
	1:1 case–case REP-1					1:1 case–case REP-1**		
	Endemic (n = 69)	Sporadic (n = 69)	Crude odds ratio	95% CI	P value	Adjusted odds ratio	95% CI	P value
Age: mean (SD)	59.43 (18.39)	59.87 (16.69)	1.0	(0.98, 1.02)	.89			
Male: n (%)	36 (52.17)	35 (50.72)	1.1	(0.51, 2.29)	.85			
Number of antibiotics in previous 3 months n (%)								
0 (reference)	7 (10.14)	13 (18.84)	1.0					
1–2	16 (23.19)	22 (31.88)	1.4	(0.40, 4.61)	.62	1.1	(0.3, 4.8)	.87
3–4	25 (36.23)	25 (36.23)	2.1	(0.64, 6.83)	.23	1.5	(0.3, 6.7)	.61
>4	21 (30.43)	9 (13.04)	4.3	(1.20, 15.54)	.02	2.9	(0.6, 13.4)	.18
ICU days before: mean (SD)	8.16 (12.46)	4.16 (10.04)	1.0	(0.99, 1.07)	.06			
ICU days after: mean (SD)	8.77 (15.17)	4.43 (9.55)	1.0	(1.00, 1.08)	.04	1.0	(1.0, 1.1)	.19
Schmid score on admission: mean (SD)	1.38 (1.16)	0.99 (0.91)	1.7	(1.10, 2.53)	.02	1.7	(1.0, 2.7)	.04
Dementia	17 (24.64)	7 (10.14)	3.5	(1.15, 10.63)	.03	3.0	(0.9, 10.4)	.09
Tracheostomy: n (%)	35 (50.72)	24 (34.78)	1.8	(0.93, 3.44)	.08	1.1	(0.4, 2.6)	.91
Urinary catheter: n (%)	42 (60.87)	30 (43.48)	1.8	(0.96, 3.38)	.07	1.6	(0.7, 3.6)	.30
Antibiotic resistance*								
Multidrug-resistant	43 (64.17)	22 (34.37)						
Pandrug-resistant	4 (5.97)	0 (0)						
	1:1 case–case REP-2-5					1:1 case–case REP-2-5***		
	Endemic (n = 64)	Sporadic (n = 64)	Crude odds ratio	95% CI	P value	Adjusted odds ratio	95% CI	P value
Age: mean (SD)	58.5 (18.44)	56.86 (17.55)	1.0	(0.99, 1.02)	.62			
Male: n (%)	41 (64.06)	30 (46.88)	1.9	(0.95, 3.85)	.07	2.6	(1.1, 6.5)	.04
Number of prior antibiotics: n (%)								
0 (reference)	9 (14.06)	11 (17.19)	1.0					
1–2	12 (18.75)	22 (34.38)	0.5	(0.13, 1.80)	.28	0.2	(0.0, 1.1)	.06
3–4	30 (46.88)	20 (31.25)	2.0	(0.66, 6.26)	.22	1.6	(0.5, 5.6)	.48
>4	13 (20.31)	11 (17.19)	1.3	(0.33, 4.78)	.74	0.7	(0.1, 3.1)	.60
ICU days before: mean (SD)	5.66 (10.36)	5.42 (12.87)	1.0	(0.97, 1.03)	.91			
ICU days after: mean (SD)	5.08 (7.92)	4.83 (9.25)	1.0	(0.96, 1.05)	.87			
Schmid score on admission: mean (SD)	1.44 (1.11)	0.95 (0.91)	1.6	(1.08, 2.23)	.02	1.5	(1.0, 2.3)	.07
Dementia	14 (21.88)	6 (9.38)	2.6	(0.93, 7.29)	.07	2.7	(0.8, 9.0)	.11
Tracheostomy: n (%)	25 (39.06)	22 (34.38)	1.2	(0.60, 2.38)	.60			
Urinary catheter: n (%)	33 (51.56)	30 (46.88)	1.3	(0.59, 2.67)	.56			
Antibiotic resistance*								
Multidrug-resistant	25 (40.98)	20 (32.26)						
Pandrug-resistant	2 (3.27)	0 (0.0)						

CI, confidence interval; ICU, intensive care unit; REP, repetitive extragenic palindromic.

\*Resistance data not available for all pairs. Multidrug-resistant: any combination of 3 or more of the 5 drug classes commonly used to treat gram-negative infections: cephalosporins, carbapenems,  $\beta$ -lactam +  $\beta$ -lactamase inhibitor combinations, fluoroquinolones, and aminoglycosides. Resistance to an antibiotic class was defined as resistance to all drugs representative of that class in our panel. Pandrug-resistant: resistance to all 5 antibiotic classes plus resistance to tetracycline and trimethoprim-sulfamethoxazole.

\*\*Variables included in the REP-1 adjusted model: prior antibiotic exposure, ICU days after, Schmid score on admission, dementia, tracheostomy, and urinary catheter.

\*\*\*Variables included in the REP-2-5 adjusted model: male, prior antibiotic exposure, Schmid score on admission, dementia.

more likely than sporadic strains to be multidrug- or pandrug-resistant to antibiotics.<sup>15</sup>

We found no previous studies identifying Schmid score on admission as a risk factor for endemic *A baumannii* colonization. However, Schmid score identifies functional dependence, which is a risk factor for *A baumannii* colonization. For example, in a Michigan nursing home study of 25 cases of laboratory confirmed *A baumannii* colonization among patients with at least one indwelling device, higher levels of functional disability were significantly associated with having multidrug-resistant *A baumannii* colonization.<sup>18</sup> A Northern Italy study of 68 matched laboratory-confirmed *A baumannii* infection or colonization case–case pairs also found that increasing disability to attend to personal needs was associated with having an *A baumannii* infection or colonization.<sup>6</sup> Similar to the current study, in the Italian study urinary catheter use was not statistically significantly associated with carriage after adjustment for other variables, including functional disability, in the multivariate analysis.<sup>6</sup> By contrast, we found no association between colonization with endemic strains and mortality risk, or an association with Charlson comorbidity index, days in the ICU, or length of hospital stay.

Antibiotic exposure is well documented as a risk factor for drug-resistant *A baumannii* colonization.<sup>5,19,20</sup> For example, a Greek study of 204 intensive care patients found that prolonged exposure to antibiotics increased the probability of acquiring a multidrug-resistant *A baumannii* isolate from the dominant circulating REP type.<sup>19</sup> Our study is not comparable as we compared prevalent cases carrying endemic isolates to matched cases carrying sporadic isolates. This may explain why we did not see a strong association with previous antibiotic use. Although we observed a trend of increasing REP-1 colonization with increasing numbers of antibiotics in the previous 3 months, the association was not statistically significant after adjustment. Further, we did not observe a similar association for REP-2-5. This is probably because REP-2-5 were not significantly more likely than matched sporadic cases to have >12 resistances, whereas REP-1 was almost 10 times more likely than matched sporadic cases to have >12 resistances.

The exact reason for the association of REP-2-5, but not REP-1, with male sex is unknown but may be related to differences in hygiene practices across sex, patient sampling, and grouping of the 2-5 REP types for analysis. The current literature regarding sex and *A baumannii* colonization is mixed. In a 3,200-bed 1:2 matched case-control study in Hong Kong, male sex was significantly more prevalent among 244 cases with gastrointestinal colonization of carbapenem-resistant *A baumannii* as compared with the 488 matched controls.<sup>21</sup> However, in several other studies, male sex was not associated with *A baumannii* colonization.<sup>6,18,19</sup>

## CONCLUSIONS

This study has all the limitations of other medical record review studies. Further, as there is local variation in the prevalence of drug-resistant *A baumannii*,<sup>20</sup> the generalizability to other facilities may vary. Although the definition of endemic using in this study was somewhat arbitrary, the results offer new insights into differences between endemic and sporadic *A baumannii* colonization in a multi-hospital medical center. These findings underscore the importance of supporting antibiotic stewardship programs, limiting unnecessary antibiotic exposures, and putting greater emphasis on both patient and staff hygiene care, particularly in vulnerable populations with higher levels of functional dependence.

## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.ajic.2019.04.179>.

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