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EPIDEMIOLOGY AND SURVEILLANCE

Risk Factors and Outcomes Associated with Multidrug-Resistant *Acinetobacter baumannii* upon Intensive Care Unit Admission

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ABSTRACT Multidrug-resistant (MDR) *Acinetobacter baumannii*, associated with broad-spectrum antibiotic use, is an important nosocomial pathogen associated with morbidity and mortality. This study aimed to investigate the prevalence of MDR *A. baumannii* perirectal colonization among adult patients upon admission to the intensive care unit (ICU) over a 5-year period and to identify risk factors and outcomes associated with colonization. A retrospective cohort analysis of patients admitted to the medical intensive care unit (MICU) and surgical intensive care unit (SICU) at the University of Maryland Medical Center from May 2005 to September 2009 was performed using perirectal surveillance cultures on admission. Poisson and logistic models were performed to identify associated risk factors and outcomes. Four percent of the cohort were positive for MDR *A. baumannii* at ICU admission. Among patients admitted to the MICU, those positive for MDR *A. baumannii* at admission were more likely to be older, to have received antibiotics before ICU admission, and to have shorter length of stay in the hospital prior to ICU admission. Among patients admitted to the SICU, those colonized were more likely to have at least one previous admission to our hospital. Patients positive for MDR *A. baumannii* at ICU admission were 15.2 times more likely to develop a subsequent positive clinical culture for *A. baumannii* and 1.4 times more likely to die during the current hospitalization. Risk factors associated with MDR *A. baumannii* colonization differ by ICU type. Colonization acts as a marker of disease severity and of risk of developing a subsequent *Acinetobacter* infection and of dying during hospitalization. Therefore, active surveillance could guide empirical antibiotic selection and inform infection control practices.

KEYWORDS *Acinetobacter*, colonization, multidrug resistance

Colonization with multidrug-resistant (MDR) *Acinetobacter baumannii* may have important clinical implications, as colonization often precedes clinical infection with this pathogen (1). Intensive care unit (ICU) patients are already disproportionally at risk to develop nosocomial MDR *A. baumannii* infections (2), and the identification of

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TABLE 1 Demographic and clinical characteristics of the study population based on colonization status with MDR *Acinetobacter baumannii* at ICU admission

Characteristic	No. of patients (%) unless specified otherwise[a]		
	Positive for MDR AB strains (n = 320)	Negative[b] for MDR AB strains (n = 7,605)	P value
Age of 65 yrs or older	100 (31.3)	2,205 (29.0)	0.38
Female sex	136 (42.5)	3,447 (45.3)	0.32
ICU type			<0.01
MICU	261 (81.6)	4,557 (59.9)	
SICU	59 (18.4)	3,048 (40.1)	
Length of stay in hospital before ICU admission of 2 or more days	47 (14.7)	1,868 (24.6)	<0.01
Previously admitted 1 or more times	150 (46.9)	2,791 (36.7)	<0.01
Antibiotic use in hospital prior to ICU admission	161 (50.3)	3,338 (43.9)	0.02
Surgery	40 (12.5)	867 (11.4)	0.54
Total Elixhauser comorbidity index [median (range)]	4.00 (9.0)	4.00 (11.0)	0.57

[a]MDR AB, multidrug-resistant *Acinetobacter baumannii*.
[b]This group includes patients colonized with susceptible (non-MDR) *Acinetobacter baumannii* strains.

their colonization status upon admission to the ICU may provide important insights. This study aims to shed some light on the gap in our knowledge by investigating the prevalence of MDR *A. baumannii* perirectal colonization among adult ICU patients over a 5-year period and identifying risk factors and outcomes associated with colonization. As far as we know, we are conducting the longest study focusing on MDR *A. baumannii* perirectal colonization upon ICU admission.

RESULTS

After exclusion of patients without an perirectal culture upon admission to the ICU (n = 657) or with a previous ICU admission with a positive *A. baumannii* surveillance culture (n = 301), the study cohort was made up of 7,925 ICU patients over a 5-year period (2005 to 2009). Fifty-five percent of the cohort were male, 71% were younger than 65 years old, 61% were admitted to the medical ICU (MICU) compared to the surgical ICU (SICU), and 76% were hospitalized for less than 2 days before being transferred to the ICU (Table 1). Four percent (320 out of 7,925) of our cohort were positive for MDR *A. baumannii* at ICU admission. In addition, 1.3% (n = 104) were positive for susceptible *A. baumannii* strains. Those positive for MDR *A. baumannii* at admission were more likely to be admitted to the MICU (than the SICU), to have had previous hospital admissions, and to have received antibiotics in the hospital before ICU admission than those negative at admission (Table 1). At least 90% of the isolated MDR strains were resistant to fluoroquinolones, cephalosporins, antipseudomonal penicillins, and tetracyclines. Eighty-three percent were resistant to carbapenems.

As admission-positive patients were more likely to be admitted to the MICU than to the SICU, we stratified the risk factor analysis by ICU type. In the multivariate analysis, those positive for MDR *A. baumannii* upon admission to the MICU were more likely to be older (relative risk [RR] of 1.46 [95% confidence interval {95% CI}, 1.14 to 1.88]) and less likely to have spent 2 or more days in the hospital before ICU admission (RR = 0.20 [95% CI, 0.12 to 0.32]). Being positive for MDR *A. baumannii* at admission to the MICU was also strongly associated with uncomplicated hypertension, paralysis, and other neurological disorders. In addition, aminoglycoside, penicillin, and carbapenem use during the current hospital stay but prior to ICU admission was also associated with MDR *A. baumannii* positivity (Table 2). In a separate multivariate analysis, those positive for MDR *A. baumannii* upon admission to the SICU were more likely to have previous admissions to our hospital (RR = 2.07 [95% CI, 1.24 to 3.44]). Positive colonization in the

TABLE 2 Risk factors associated with MDR *Acinetobacter baumannii* colonization at ICU admission by type of ICU

	MICU (n = 4,818)[a]		SICU (n = 3,107)[a]	
Risk factor	**RR**	**95% CI**	**RR**	**95% CI**
Age (65 yrs or older)	1.46	1.14–1.88		
Previous admissions[b] (1 or more)			2.07	1.24–3.44
Time before ICU admission (2 or more days)	0.20	0.12–0.32		
Elixhauser comorbidity index				
Congestive heart disease			2.15	1.20–3.84
Uncomplicated hypertension	0.68	0.50–0.90		
Paralysis[c]	3.36	2.45–4.61	3.53	1.54–8.12
Other neurological disorders[d]	1.77	1.35–2.32		
HIV-AIDS			4.23	1.11–16.04
Rheumatoid arthritis			2.69	1.07–6.79
Antibiotic use before ICU[e]				
Penicillins	1.82	1.33–2.49		
Aminoglycosides	2.56	1.42–4.60		
Carbapenems	2.85	1.85–4.38		

[a]The multivariate model initially included all the covariates that were significant at the $P < 0.10$ level in the bivariate models. The final multivariate model retained only covariates that were significant at the $P < 0.05$ level. The total Elixhauser comorbidity index score was not included in the multivariate model, as its significant components were included. Both the relative risk (RR) and 95% confidence interval (95% CI) were adjusted.

[b]This variable only includes previous admission to our facility.

[c]The paralysis category includes flaccid hemiplegia, spastic hemiplegia, quadriplegia, quadriparesis, and other paralytic syndromes (3).

[d]Other neurological diseases include cerebral degeneration (unspecified), Parkinson's disease, Huntington's chorea, other choreas, spinocerebellar disease, hereditary spastic paraplegia, primary cerebellar degeneration, other cerebellar ataxia, anterior horn cell disease, spinal muscular atrophy, motor neuron disease, multiple sclerosis, Schilder's disease, some types of acute (transverse) myelitis, demyelinating disease of the central nervous system (unspecified), epilepsy and recurrent seizures, anoxic brain damage, encephalopathy (not elsewhere classified), some types of convulsions, and some types of aphasia (3).

[e]For both stratas (ICU types), the following four antibiotic classes were included in the analysis: penicillins, aminoglycosides, carbapenems, and cephalosporins.

SICU was also strongly associated with congestive heart disease, paralysis, HIV-AIDS, and rheumatoid arthritis. In the multivariate analysis, antibiotic use in the hospital before SICU admission was not a significant risk factor (Table 2).

Of the 320 patients who were positive for MDR *A. baumannii* at admission, 101 (31.6%) had at least one subsequent clinical culture positive for *A. baumannii* during the current hospital admission. Eighty-nine percent (90 out of 101) were attributed to MDR strains. These 101 clinical strains were isolated from the following sources of samples: sputum (45%), bronchial fluid (22%), blood (9%), urine (10%), and other sources such as wounds or catheter tips (14%). In contrast, 3% (228 out of 7,605) of the patients negative for MDR *A. baumannii* at ICU admission developed a subsequent clinical culture attributed to *A. baumannii*. Seventy-one percent (162 out of 228) were attributed to MDR strains. Patients positive with MDR *A. baumannii* at ICU admission were 15.24 (95% CI, 11.44 to 20.31) times more likely to develop a subsequent positive clinical culture for *A. baumannii* while in the hospital after adjusting for the total Elixhauser comorbidity index (3) (Table 3).

Patients positive for MDR *A. baumannii* at ICU admission were more likely to die

TABLE 3 Outcomes associated with MDR *Acinetobacter baumannii* colonization at ICU admission for the overall cohort[a]

Outcome	**RR[b]**	***P* value**
Subsequent positive clinical culture in the hospital	15.24	11.44–20.31
Death during hospital stay	1.40	1.08–1.82
Death during ICU stay	1.68	1.27–2.23

[a]There were 7,925 patients in the overall cohort.

[b]Relative risk (RR) adjusted by the total Elixhauser comorbidity index.

during hospitalization than those negative at admission (24.4% versus 18.7%; $P = 0.01$); after adjustment for the total Elixhauser comorbidity index, patients colonized with MDR *A. baumannii* were 1.40 (95% CI, 1.08 to 1.82) times more likely to die during the current hospital stay than those negative at admission. Similarly, patients positive for MDR *A. baumannii* at ICU admission were more likely to die during their current ICU stay than those negative at admission (20.0% versus 13.0%; $P < 0.01$); after adjustment for the total Elixhauser comorbidity index, patients positive for MDR *A. baumannii* at admission were 1.68 (95% CI, 1.27 to 2.23) times more likely to die during their current ICU stay than those who were negative at ICU admission (Table 3).

DISCUSSION

Four percent of the patients admitted to the ICU were positive for MDR *A. baumannii* at the time of ICU admission. Risk factors associated with positivity at admission differed by ICU type. Furthermore, patients positive for MDR *A. baumannii* at ICU admission were more likely to develop a subsequent clinical culture with this bacterium and were also more likely to die during their current hospitalization than those negative at ICU admission.

The perirectal colonization rate of MDR *A. baumannii* observed in the population is similar to other reported rates in health care settings (4, 5). Latibeaudiere et al. reported a 14% prevalence of carbapenem-resistant *A. baumannii* among 364 patients admitted to the trauma ICU at a tertiary hospital from January 2010 to November 2011 (6). While Latibeaudiere et al. (6) investigated risk factors and outcomes associated with colonization, our study was much larger and of longer duration. We compare the main study findings with previous studies below.

Regarding risk factors associated with MDR *A. baumannii* colonization, a different set of risk factors was observed depending on the ICU type. In this medical center, MICU-admitted patients were more likely to be colonized than SICU-admitted patients. Furthermore, age, shorter hospitalization time before ICU admission, and use of antibiotics before ICU admission were important risk factors associated with positivity among MICU patients but not among SICU patients. These results highlight that not all ICU patients are alike and that each population may have different clinical and epidemiological characteristics influencing risk. For example, we believe that the risk associated with a shorter hospitalization time before ICU admission reflects the common practice of direct admission of chronically ventilated patients from other facilities.

Among our MICU-admitted patients, those on penicillins, carbapenems, or aminoglycosides were approximately two times more likely to be colonized with MDR *A. baumannii* at admission. Previous studies have also reported a strong association between antibiotic use and antibiotic-resistant *A. baumannii* colonization. Munoz-Price et al. reported that carbapenem exposure quadrupled the risk of acquiring carbapenem-resistant *A. baumannii* on surveillance cultures even after controlling for the severity of illness in a cohort of 350 ICU patients (7). Latibeaudiere et al. also reported that exposure to any antibiotic was associated with surveillance positivity for carbapenem-resistant *A. baumannii* among 364 trauma ICU patients (6). However, neither of the previous studies were able to report a significant association between prior exposure to penicillins, cephalosporins, or aminoglycosides and detection of carbapenem-resistant *A. baumannii*.

Results also confirmed previous reports linking *A. baumannii* colonization with subsequent clinical infection. Corbella et al. previously reported in a smaller study that clinical infections due to MDR *A. baumannii* strains occurred more frequently in ICU patients with fecal colonization than those without fecal colonization (26% versus 5%) (8). Similarly, Latibeaudiere et al. reported that patients with surveillance cultures positive for carbapenem-resistant *A. baumannii* had 8.4 times the risk of developing a subsequent *A. baumannii* infection in a 13-month cohort study of patients admitted to the trauma ICU (6). Performing active surveillance for MDR *A. baumannii* in select populations in which there is a high prevalence has the potential to prevent transmission and alert providers to challenges in treatment for empirical infection. However,

more research is needed to determine which populations or prevalence levels would benefit most from active surveillance. Likewise, further research is needed on the effectiveness and cost-effectiveness of active surveillance of MDR *A. baumannii* for reducing infection rates.

Furthermore, a significant positive association between mortality and colonization with MDR *A. baumannii* was observed. Few published studies have examined the relationship between colonization with this resistant pathogen and mortality; however, there are several studies researching the link between *A. baumannii* infection and mortality. Abbo et al. reported clinical isolation of MDR *A. baumannii* as a significant predictor of mortality (odds ratio [OR] = 6.2; $P = 0.02$) even after adjusting for several variables, including a McCabe score of 3, which indicates life expectancy of less than 6 months (9). In contrast, other studies have not found *Acinetobacter* infection to be independently associated with increased mortality after adjusting for the severity of the illness (10, 11). However, MDR *A. baumannii* may be a marker of increased mortality in patients with severe underlying illness but not an independent predictor of mortality (12).

We were unable to investigate potentially important risk factors, such as interfacility transfer of patients, use of artificial ventilation, or overall previous hospitalization outside the University of Maryland Medical Center (UMMC), due to unavailability of information on these variables for our cohort participants. Likewise, we excluded patients that had a history of a prior positive surveillance culture from the cohort. Moreover, we were unable to adjust the analyzed outcomes for severity of illness. Nevertheless, our study is strengthened by its large sample size and long duration. As far as we know, we are conducting the longest study focusing on MDR *A. baumannii* perirectal colonization upon ICU admission and studying the largest number of colonized patients.

Overall, this study highlights the key infection control and clinical roles that active surveillance of MDR *A. baumannii* can play among ICU patients. In ICUs with higher than expected or increasing numbers of MDR *A. baumannii*, active surveillance cultures could aid control efforts, an approach supported by the CDC guidelines for the control of multidrug-resistant organisms in healthcare settings (13). Previous studies have reported a significant reduction of drug-resistant *A. baumannii* infection rates after the implementation of a comprehensive and multifaceted infection control program (bundle), which included contact and isolation precautions for all patients colonized or infected with this pathogen (14, 15). Furthermore, physicians could utilize active surveillance data to inform their decision-making process for patients who might be especially vulnerable to infections.

MATERIALS AND METHODS

Study population. This study utilized an ongoing cohort of adult patients admitted to the MICU and SICU at the University of Maryland Medical Center (UMMC), who have routine admission perirectal surveillance cultures obtained as part of an active surveillance program for vancomycin-resistant enterococcal (VRE) infection prevention. The UMMC is a 816-bed hospital located in Baltimore, MD.

A retrospective cohort analysis of patients admitted to the above cohort from 14 May 2005 to 11 September 2009 was performed to investigate the prevalence of MDR *A. baumannii* perirectal colonization. Patients who did not have admission surveillance cultures obtained were excluded from the cohort analysis. Patients with multiple admissions during the study period were allowed to enter the cohort multiple times as at-risk patients as long as they were not positive for *A. baumannii* on any prior surveillance culture. This study was approved by the institutional review board of the University of Maryland, Baltimore.

Data collection. Data for several demographic, clinical, and epidemiological variables were pulled and validated from the UMMC central data repository, a relational database containing patient administrative and laboratory data. Variables included ICD9 (International Classification of Diseases, ninth revision) discharge codes used to build the total Elixhauser comorbidity index (3). In addition, antibiotic use during the current hospitalization but prior ICU admission was collected. We focused on four antibiotic categories mainly used in ICU settings: penicillins, aminoglycosides, carbapenems, and cephalosporins.

Laboratory analysis. All perirectal swabs were enriched in brain heart infusion (BHI) broth and then plated on both a MacConkey plate with 6 μg/ml of imipenem and a MacConkey plate containing no antibiotics. All plates were incubated at 37°C for 24 to 48 h. Any resulting isolates were subcultured onto

blood agar plates and identified by the API 20E or Vitek system. Antimicrobial susceptibility testing was performed for all *A. baumannii* strains by disk diffusion and interpreted in accordance with Clinical and Laboratory Standards Institute guidelines (16). Multidrug resistance was defined using the standard definition of an isolate that was resistant to one or more agents in three or more antimicrobial categories (17).

Statistical analysis. Individuals positive for MDR *A. baumannii* by perirectal culture upon admission to the ICU were classified as colonized with MDR *A. baumannii* before ICU admission. In contrast, individuals negative for *A. baumannii* or positive for susceptible strains of *A. baumannii* by perirectal culture upon admission to the ICU were classified as not colonized with MDR *A. baumannii*. Patient characteristics were compared based on their colonization status at admission using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Analysis of variance (ANOVA) was used to estimate differences in colonization across seasons or years. Risk factors associated with positivity at admission were identified using Poisson models using generalized estimating equations (GEE) to adjust for repeat admissions. Potential confounding variables were examined in a bivariate analysis also using GEE. Covariates that were significant at the level of *P* values of <0.10 were then added to the model and retained in the final model if they were significant at the level of *P* values of <0.05. Similarly, outcomes associated with positivity at admission were identified using GEE/logistic models. Multivariate models of associated outcomes were then adjusted by the total Elixhauser comorbidity index. All analyses and graphs were performed using SAS version 9.4 (The SAS Institute, Cary, NC) and STATA 14 (StataCorp LLC., College Station, TX).

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