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Carbapenem-Resistant Enterobacterales Bacteriuria and Subsequent Bacteremia: A Population-Based Study

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Abstract

Objective: To describe the epidemiology of carbapenem-resistant Enterobacterales (CRE) bacteriuria and determine if urinary catheters increase the risk of subsequent CRE bacteremia.

Design: Using active population- and laboratory- based surveillance we described a cohort of patients with incident CRE bacteriuria and identified risk factors for developing CRE bacteremia within one year.

Setting: 8 county Georgia Health District 3 (HD3) in Atlanta, GA.

Patients: Residents of HD3 with CRE first identified in urine between 2012–2017.

Results: We identified 464 patients with CRE bacteriuria (mean yearly incidence 1.96 cases/100,000 population). Of 425 with chart review, most had a urinary catheter (56%), and many resided in long term care facilities (48%), had a Charlson comorbidity index >3 (38%) or a decubitus ulcer (37%). 21 (5%) patients developed CRE bacteremia with the same organism within one year. Risk factors for subsequent bacteremia included presence of a urinary catheter (odds ratio [OR] 8.0, 95% confidence interval [CI] 1.8–34.9), central venous catheter (OR 4.3, 95% CI 1.7–10.6) or another indwelling device (OR 4.3, 95% CI 1.6–11.4), urine culture obtained as an inpatient (OR 5.7, 95% CI 1.3–25.9) and being in the ICU in the week prior to urine culture (OR 2.9, 95% CI 1.1–7.8). In a multivariable analysis, urinary catheter increased the risk of CRE bacteremia (OR 5.3, 95% CI 1.2–23.6).

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Potential conflicts of interest

All authors report no conflicts of interest relevant to this article.

Conclusions: In patients with CRE bacteriuria, urinary catheters increase the risk of CRE bacteremia. Future interventions should target reducing inappropriate insertion and early removal of urinary catheters.

The World Health Organization and US Centers for Disease Control and Prevention (CDC) consider carbapenem-resistant Enterobacterales (CRE) an urgent threat to public health because of high transmissibility, limited treatment options and significant mortality.[1–3] While CRE is most commonly identified in the urine, most of the literature focuses on invasive infections where CRE is isolated from a sterile site, rather than bacteriuria.[4,5] CRE bacteriuria, however, can have a high rate of relapse with bacteriuria and urinary tract infections, and further study on patient outcomes is needed.[6,7]

Patients with invasive CRE infections have a higher mortality than patients with CRE bacteriuria. In a meta-analysis of over 20 studies, the pooled mortality for carbapenem-resistant *Klebsiella pneumoniae* bacteremia was 54%, but only 14% for urinary tract infections.[8] Additionally, patients with CRE bacteremia are over twice as likely to die in the hospital than those with a CRE urinary tract infection or colonization, making it imperative to understand which patients with CRE bacteriuria are likely to develop bacteremia.[9] The risk of subsequent bacteremia in patients with CRE bacteriuria in prior studies ranges from 0–15%, but has been limited to single hospital systems with limited follow-up.[5,7,10]

In this study we used active, population-based surveillance data to describe the epidemiology of patients with CRE bacteriuria in metropolitan Atlanta, GA and identify risk factors associated with developing CRE bacteremia in patients with prior CRE bacteriuria. We assessed the effect of urinary catheters, which are often placed and retained without a clear indication and thus a potentially modifiable target to prevent development of bacteremia in patients with CRE bacteriuria.[11,12]

Methods

Study Population and Design

Since 2011, the CDC-funded Georgia Emerging Infections Program (EIP) has conducted active, population- and laboratory-based surveillance of CRE in eight counties of metropolitan Atlanta through the Multi-site Gram-negative Surveillance Initiative. Cases are identified by routine queries of laboratory automated testing instruments in the catchment area and include all carbapenem-resistant *Escherichia coli*, *K. pneumoniae*, *Klebsiella oxytoca*, *Klebsiella* (formerly *Enterobacter*) *aerogenes, and Enterobacter cloacae* isolated from a sterile site or urine culture.

We retrospectively created a cohort of patients with CRE first identified in a urine culture from 1/1/2012–12/31/2017. We excluded patients with CRE identified in any sterile site prior to having CRE identified in urine. To account for the CDC CRE definition change in 2016, we used a single CRE definition for the study period: resistant to at least one non-ertapenem carbapenem (doripenem, imipenem, or meropenem MIC ≥ 4 μg/mL), and resistant to all tested third generation cephalosporins (Supplemental Figure 1). We defined subsequent bacteremia as a positive blood culture with the same CRE organism present in

the index urine culture, within one day to one year after the index CRE urine culture. We calculated the time to subsequent bacteremia as the difference in days between the first CRE urine culture and the first CRE blood culture.

Chart Review and Variable Definitions

EIP epidemiologists perform chart reviews for all cases of CRE and collect information on demographics, comorbidities including underlying urinary tract abnormalities, a patient's residence (inpatient facility, LTACH, long-term care facility (LTCF), or private residence), the location at time of culture collection (inpatient facility, LTACH, LTCF, or outpatient clinic), risk factors for CRE including the presence of medical devices, whether the patient was in the intensive care unit (ICU) in the week prior to the urine culture, specimen source, and antibiotic susceptibility results. We calculated and dichotomized the Charlson comorbidity index (CCI)[13] based on the median. The presence of a medical device was defined as having an indwelling urethral or suprapubic urinary catheter, central venous catheter or other indwelling device (e.g. endotracheal/nasotracheal tube, gastrostomy tube, nasogastric tube, tracheostomy, or nephrostomy tube) when the urine culture was obtained or in the two prior days. We captured 90-day mortality through Georgia Vital Statistics records.

Study Objectives

The primary objective was to describe the epidemiology of patients with CRE bacteriuria in Atlanta and determine if urinary catheters increase the risk of subsequent CRE bacteremia within one year. The secondary objective was to identify additional risk factors associated with developing CRE bacteremia. In an exploratory analysis we determined the proportion of patients with subsequent bacteremia that had similar CRE strains in both urine and blood cultures.

Pulsed Field Gel Electrophoresis

The Georgia EIP laboratory collects CRE urine and sterile site isolates from clinical laboratories in the catchment area when available. For patients with subsequent bacteremia where both the first urine and blood isolates were available (and in one case where a CRE urine isolate was available from four days after the initial isolate) we performed pulsed field gel electrophoresis (PFGE) to determine strain relatedness. We adapted the CDC PulseNet PFGE protocol for *E. coli*, *Salmonella* and *Shigella* spp.[14] and used Xbal as the restriction enzyme. The gels were run in 0.5X TBE (Tris-borate-EDTA) on a CHEF Mapper (Bio-Rad, Hercules, CA) with an initial switch time of 2.2 seconds and a final switch time of 54.2 seconds at 6 volts and an angle of 120 degrees. We used BioNumerics software v 7.6 (Applied Maths, Kortrijk, Belgium) to assess relatedness between paired isolates using an unweighted-pair group method of arithmetic averages and Dice coefficients with band position tolerance and optimization set at 1.5%.

Sample Size and Power Calculations

We anticipated that 50% of patients with CRE bacteriuria would have a urinary catheter, and 5% would develop subsequent bacteremia.[15] Medical devices can increase the risk of CRE acquisition with an odds ratio (OR) of 3.4–7.7 and patients with CRE rectal colonization

and a urinary catheter have almost 5 times the odds of developing a CRE infection than those without a catheter.[11,16] Here we used an OR of ~ 4 and estimated that 2.5% of patients without a urinary catheter and 9% of patients with a urinary catheter would develop subsequent bacteremia, requiring a sample size of 404 to achieve 80% power with an alpha of 0.05.

Statistical analysis

We calculated the yearly incidence of CRE bacteriuria in metropolitan Atlanta by dividing the number of new CRE bacteriuria cases by the U.S census bridged-race population estimates of the catchment area. For patients with a complete chart review, we compared patients with and without the presence of a urinary catheter using chi-square and Fisher's exact tests as appropriate for categorical variables, and Student's t-tests for continuous variables. We performed univariable and multivariable logistic regression to estimate the association between urinary catheter and subsequent bacteremia. A complete description of model development is described in supplementary materials.

Two sensitivity analyses were performed: 1) propensity score creation for the presence of a urinary catheter, with inverse probability weighting of this score in a logistic regression model to estimate the effect of urinary catheter on subsequent bacteremia and 2) cause-specific unadjusted proportional hazards model for subsequent bacteremia using death at 90 days as a competing risk; patients who died or did not develop bacteremia within 90 days were censored. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

Institutional Review Board Approval

The Georgia EIP surveillance, data collection and analysis are approved by the Emory University Institutional Review Board.

Results

Between 2012–2017 we identified 464 patients with their first episode of CRE bacteriuria in metropolitan Atlanta. The number of new CRE bacteriuria cases per year was relatively stable, although the annual incidence appeared to modestly decline over the study period (Table 1, Supplemental Figure 2). The mean (SD) annual incidence rate over the 6 years was 1.96 (0.19) and ranged from 1.68–2.20 cases per 100,000 people in Atlanta. Most patients with CRE bacteriuria (318, 69%) had *K. pneumoniae* (Table 2).

Among 464 patients, 425 (92%) had a complete chart review and were included in the final analysis. The mean (SD) age was 64.6 (17.0) years and 231 (54%) were female. Many patients were chronically ill with 159 (38%) having a CCI >3 and more than one-third with a decubitus ulcer. Medical devices were common: 238 (56%) had an indwelling urinary catheter (29 suprapubic and 209 urethral), 124 (29%) had a central venous catheter and 163 (39%) had another indwelling device. Almost half (48%) resided in a LTACH or LTCF prior to identification of CRE bacteriuria (Table 2).

Patients with urinary catheters were more likely to have central venous catheters (39% vs 17%, p <0.001) or other indwelling devices (49% vs 25%, p <0.001), have a decubitus

ulcer (45% vs 26%, p <0.001), and underlying urinary tract abnormalities (19% vs 11%, p = 0.01). Patients with urinary catheters more commonly had a CRE culture obtained in an inpatient facility (41% vs 28%, p = 0.02) and had been admitted to the ICU in the week prior (20% vs 4%, p <0.001) (Table 2).

Twenty-one (5%) patients developed CRE bacteremia within one year. The median (interquartile range [IQR]) time to subsequent bacteremia was 34 (20–110) days, with a minimum of 2 and a maximum of 300 days. All but one patient with subsequent bacteremia had *K. pneumoniae.* Compared to all other CRE species combined, *K. pneumoniae* was significantly associated with subsequent bacteremia (unadjusted OR 8.6, 95% CI 1.1–64.4).

The presence of a urinary catheter (OR 8.0, 95% CI 1.8–34.9), central venous catheter (OR 4.3, 95% CI 1.7–10.6), or other indwelling device (OR 4.3, 95% CI 1.6–11.4) were all significantly associated with subsequent bacteremia in univariable analyses. Additionally, the odds of bacteremia increased if the CRE urine culture was obtained while the patient was an inpatient (OR 5.7, 95% CI 1.3–25.9) or had been in the ICU in the week prior to the urine culture (OR 2.9, 95% CI 1.1–7.8) (Table 3). In the multivariable model, having a urinary catheter significantly increased the odds of subsequent bacteremia (OR 5.3 95% CI 1.2–23.6) after controlling for the presence of a central venous catheter, the presence of another indwelling device, and the location of culture collection (Table 3). This finding was confirmed in the first sensitivity analysis using inverse probability weighting (OR for urinary catheter was 7.1 [95% CI 1.7–29.6]). When accounting for death as a competing risk in the second sensitivity analysis, urinary catheters were also associated with subsequent bacteremia at 90 days (unadjusted hazard ratio 5.6, 95% CI 1.3–26.2).

Paired urine and blood CRE isolates were available for 8 patients. Seven (88%) patients had paired isolates that were > 90% similar on PFGE, and of those, five (63%) pairs appeared identical. The median (IQR) time to subsequent bacteremia was 31 (25–118) days in patients with highly related CRE strains (> 90% on PFGE). In the one patient with < 90% similarity on PFGE the time to bacteremia was 101 days (Supplemental Table 2).

Discussion

The presence of a urinary catheter increased the odds of developing CRE bacteremia within one year by at least five times in patients with CRE bacteriuria; an absolute risk increase of almost 7%. This is consistent with prior literature demonstrating that urinary catheters and central venous catheters increase the likelihood of invasive CRE infection in those with rectal colonization.[16,17] However, to our knowledge, this is the first study to investigate risk factors in patients with CRE bacteriuria, a common clinical scenario that does not involve obtaining rectal surveillance swabs. We did not differentiate urinary tract infections from colonization as this is challenging to do retrospectively and the mortality of patients with CRE urinary colonization is likely similar to that of patients with a urinary tract infection.[9]

We estimated that the average annual incidence of CRE bacteriuria in metropolitan Atlanta per 100,000 population was 1.96 cases, which remained stably within the range of 0.5–2.93 infections reported in a recent systematic review of CRE in the U.S.[18] This is similar to

national data showing a flat trend for CRE from all culture sites during our study period, despite increasing broad spectrum antibiotic use in U.S. hospitals.[1,19–22] Five percent of patients with CRE bacteriuria developed CRE bacteremia within one year. While relatively rare, this event is clinically important as CRE bacteremia is associated with up to a 40% increase in mortality.[8]

Similar to findings from national CRE surveillance,[4] our study showed that patients with CRE bacteriuria have high frequencies of chronic illness and indwelling devices. CRE infections most commonly occur in patients with prior healthcare exposure, and those residing in LTACHs may be at the highest risk.[18,23,24] Almost half of the patients in our study resided in an LTACH or LTCF four days prior to identification of CRE bacteriuria. However, only 34% had a culture obtained at an LTACH or LTCF, suggesting that patients may have been admitted to an inpatient facility prior to the culture being obtained. This finding highlights the interconnectedness of healthcare systems and demonstrates how multidrug-resistant organisms can easily be transferred between settings.

Both the Society for Hospital Medicine and the Society for Healthcare Epidemiology of America recommend minimizing the use of urinary catheters, daily assessments of necessity, and removing catheters when no longer needed as part of the Choosing Wisely campaign.[25,26] Our findings support this approach as a critical aspect of caring for patients with CRE bacteriuria. Unfortunately, we could not capture how often urinary catheters were removed or how long catheters remained in place. This area deserves future attention since prior studies have suggested that urinary catheters may be removed in less than a third of patients with CRE bacteriuria.[5] We suspect that the risk of subsequent bacteremia is related to how long a catheter remains in place, but how much risk each additional day confers is unknown. During a CRE outbreak in a South African hospital, each additional urinary catheter day was associated with a 7% increase in the odds of CRE acquisition.[27] Additional devices including central venous catheters or other indwelling devices also increased the risk of subsequent bacteremia in this study. Infection prevention strategies already employed at many hospitals to minimize medical devices should be particularly emphasized in patients with CRE bacteriuria as a means to decrease the risk of a future CRE bacteremia.

In an exploratory analysis, most patients with subsequent bacteremia had very similar strains of CRE in the blood and original urine culture. The small sample size limits our ability to draw conclusions, but this finding suggests that CRE bacteremia developing in patients with prior CRE bacteriuria may be related to the prior bacteriuria episode. Thus, subsequent bacteremia may be more likely from incomplete treatment or persistence of colonization rather than from acquisition of a new CRE infection. Alternatively, patients may be re-exposed to the same CRE strain multiple times, particularly if they return to the same living environment.

Unexpectedly we found that patients with carbapenem-resistant *K. pneumoniae* bacteriuria had a higher risk of subsequent bacteremia compared to patients with other species of CRE. To our knowledge *K. pneumoniae* has not been previously identified as a risk factor for subsequent bacteremia, but *in vitro* data suggests that multidrug-resistant *K. pneumoniae* may produce more biofilm than other drug-resistant Enterobacterales.[28] Biofilm production

on urinary catheters could be one reason patients with *K. pneumoniae* may be at increased risk bacteremia and this should be further investigated.

Strengths of this study include the use of active, population and laboratory-based surveillance data over six years, creating one of the largest cohorts of patients with CRE. This approach is advantegous over hospital-based surveillance studies, since we could identify patients with subsequent CRE infections after discharge as long as the culture was obtained within the 8-county metropolitan Atlanta area. This study is the first to examine factors that may increase a patient's risk for developing CRE bacteremia in an easily identifiable, high-risk group of patients—those with CRE bacteriuria—with urinary catheters, a potentially modifiable characteristic.

This study has limitations. First, we were not able to assess how long a urinary catheter remained in place after diagnosis of CRE or if the patient received antibiotics. Second, patients did not have routine surveillance cultures obtained nor were they prospectively followed. Instead, EIP data relies on automated laboratory queries to identify all patients with a CRE culture, and therefore case ascertainment can depend on clinical practice patterns that may vary across the spectrum of healthcare. While it is possible that we may have underestimated CRE bacteriuria, the generally low threshold for urinary cultures makes this less of a limitation than with cultures from other anatomic sites. Third, population-based surveillance may miss cases in non-residents or those who travelled outside of metropolitan Atlanta. Fourth, patients with and without urinary catheters were different, increasing the risk of confounding by indication. We attempted to account for this in a sensitivity analysis using inverse probability weighting and found that effect of urinary catheters on subsequent bacteremia remained. Fifth, in this fragile population, patients may die before the outcome of subsequent bacteremia. We adjusted for this using a Cox proportional hazard model with death as a competing risk. Finally, while the study was adequately powered to assess the effect of urinary catheters on subsequent bacteremia, the 95% CI was wide and the degree to which urinary catheters increase the risk of bacteremia is difficult to interpret.

In summary, patients with incident CRE bacteriuria in Atlanta are chronically ill, frequently reside in healthcare facilities, and have a high proportion of medical devices. Over half of the study cohort had a urinary catheter at the time of CRE bacteriuria and this increased the risk of developing subsequent CRE bacteremia within one year. Future studies are needed to evaluate how often urinary catheters are removed or exchanged in this high-risk group and interventions should focus on minimizing urinary catheter use whenever possible in patients with CRE. Urine cultures are frequently obtained in long-term care facilities, and targeted interventions in this setting may be particularly effective.[29] Lastly, additional research could assess whether biolfim burden, carbapenemase status or antibiotic therapy help explain our findings, and whther the risk of urinary catheters is consistent for patients with bacteriuria caused by other multidrug-resistant Gram-negative organisms such as *Pseudomonas aeruginosa*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Annual Number and Incidence Rates of Carbapenem-Resistant Enterobacterales Bacteriuria in Metropolitan Atlanta

Year	Number of New Cases of CRE Bacteriuria	Census Population	Annual Incidence Rate[a]
2012	84	3,821,534	2.20
2013	79	3,864,091	2.04
2014	77	3,925,130	1.96
2015	71	3,991,607	1.78
2016	84	4,036,982	2.08
2017	69	4,098,115	1.68

[a]Per 100,000 population

Abbreviations: CRE, carbapenem-resistant Enterobacterales

Table 2:

Demographics and Clinical Characteristics of Patients with Carbapenem-Resistant Enterobacterales Bacteriuria in Metropolitan Atlanta

	No Urinary Catheter (n = 187)	**Urinary Catheter[a] (n = 238)**	**Total (n = 425)**	**P-value[b]**
Age (mean years [SD])	67.0 (16.3)	62.7 (17.3)	64.6 (17.0)	0.01
Female	110 (59)	121 (51)	231 (54)	0.10
Race (n = 404)				0.26
Black	105 (59)	152 (67)	257 (64)	
White	66 (37)	70 (31)	136 (34)	
Other	6 (3)	5 (2)	11 (3)	
Charlson comorbidity index >3 (n = 424)	74 (40)	85 (36)	159 (38)	0.39
Hemi- or paraplegia	20 (11)	44 (18)	64 (15)	0.03
Central venous catheter[a]	32 (17)	92 (39)	124 (29)	<0.001
Other indwelling device[a]	47 (25)	116 (49)	163 (39)	<0.001
Decubitus ulcer	48 (26)	108 (45)	156 (37)	<0.001
Dementia	61 (33)	47 (20)	108 (25)	0.003
Underlying urinary tract abnormalities	20 (11)	46 (19)	66 (16)	0.01
Patient residence 4 days prior to culture (n = 420)				<0.001
Inpatient	27 (15)	63 (27)	90 (21)	
LTCF or LTACH	84 (46)	118 (50)	202 (48)	
Private residence	72 (39)	56 (24)	128 (30)	
Location where culture was obtained (n = 424)				0.02
Inpatient	53 (28)	96 (41)	149 (35)	
LTCF or LTACH	65 (35)	78 (33)	143 (34)	
Outpatient	69 (37)	63 (27)	132 (31)	
ICU prior to the culture[c] (n = 415)	7 (4)	47 (20)	54 (13)	<0.001
Organism				< 0.03
Klebsiella pneumoniae	121 (65)	182 (76)	303 (71)	
Escherichia coli	37 (20)	24 (10)	61 (14)	
Enterobacter cloacae	21 (11)	20 (8)	41 (10)	
Klebsiella aerogenes	4 (2)	8 (3)	12 (3)	
Klebsiella oxytoca	4 (2)	4 (2)	8 (2)	

All values are presented as number (%) unless otherwise stated

Abbreviations: SD, standard deviation; LTCF, long-term care facility; LTACH, long-term acute care hospital; ICU, intensive care unit

[a] At the time culture was obtained or in the prior 2 calendar days

[b] Comparison of patients with and without a urinary catheter

[c] Any time in the 7 calendar days prior to the culture

Table 3:

Univariable and Multivariable Logistic Regression Assessing Risk Factors for Subsequent Bacteremia in Patients with Carbapenem-Resistant Enterobacterales Bacteriuria

Variable	No Subsequent Bacteremia[a] (n = 404)	Subsequent Bacteremia [a] (n = 21)	Absolute Risk Increase[b]	Univariable OR (95% CI)	Multivariable OR (95% CI)[c]
Age (mean [SD])	64.6 (16.9)	64.8 (19.1)	N/A	1.0 (0.98–1.0)	--
Female	219 (54)	12 (57)	0.6%	1.1 (0.5–2.7)	--
Race (n = 404)					--
Black	240 (63)	17 (81)	3.90%	2.5 (0.8–7.7)[d]	--
White	132 (34)	4 (19)	Ref	Ref	--
Other	11 (3)	0 (0)	Ref	Ref	--
CCI >3 (n = 424)	147 (36)	12 (57)	4.2%	2.3 (0.96–5.6)	--
Urinary catheter[e]	219 (54)	19 (90)	6.9%	8.0 (1.8–34.9)	5.3 (1.2–23.6)
Central venous catheter[e]	111 (27)	13 (62)	7.8%	4.3 (1.7–10.6)	1.8 (0.6–5.1)
Other indwelling device[e]	148 (37)	15 (71)	6.9%	4.3 (1.6–11.4)	2.2 (0.7–6.5)
Decubitus ulcer	145 (36)	11 (52)	3.3%	2.0 (0.8–4.7)	--
Dementia	104 (26)	4 (19)	−1.7%	0.7 (0.2–2.1)	--
Hemi- or paraplegia	61 (15)	3 (14)	−0.3%	0.9 (0.3–3.3)	--
Underlying urinary tract abnormalities	64 (16)	2 (10)	−2.3%	0.6 (0.1–2.5)	--
Patient residence 4 days prior to culture (n = 420)					--
Inpatient	85 (21)	5 (24)	2.4%	1.8 (0.5–7.0)	--
LTCF or LTACH	190 (48)	12 (57)	2.8%	2.0 (0.6–6.2)	--
Private residence	124 (31)	4 (19)	Ref	Ref	--
Location where culture was obtained (n = 424)					--
Inpatient	137 (34)	12 (57)	6.5%	5.7 (1.3–25.9)	3.1 (0.6–15.0)
LTCF or LTACH	136 (34)	7 (33)	3.4%	3.3 (0.7–16.4)	2.1 (0.4–11.0)
Outpatient	130 (32)	2 (10)	Ref	Ref	Ref
ICU prior to the culture[f] (n = 415)	48 (12)	6 (29)	7.0%	2.9 (1.1–7.8)	--

All values are presented as number (%) unless otherwise stated

Abbreviations: OR, odds ratio; CI, confidence interval; SD, standard deviation; Ref, reference; CCI, Charlson comorbidity index; LTCF, long term care facility; LTACH, long term acute care hospital; ICU, intensive care unit

[a.] Subsequent bacteremia was defined as developing a blood culture with the same CRE organism present in the index urine culture, within one day to one year after the urine culture

[b.] Difference in risk of subsequent bacteremia between those with the variable of interest and those without the variable of interest

[c.] Final multivariable model created to estimate the association between urinary catheter and subsequent bacteremia. Blank cells indicate the term was not included in the model

[d] Odds ratio was calculated for black race versus any other race

[e] At the time culture was obtained or in the prior 2 calendar days

[f] Any time in the 7 calendar days prior to the culture