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Comparing the Outcomes of Adults With Enterobacteriaceae Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score–Matched Cohort

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Background. The recommended duration of antibiotic treatment for Enterobacteriaceae bloodstream infections is 7–14 days. We compared the outcomes of patients receiving short-course (6–10 days) vs prolonged-course (11–16 days) antibiotic therapy for Enterobacteriaceae bacteremia.

Methods. A retrospective cohort study was conducted at 3 medical centers and included patients with monomicrobial Enterobacteriaceae bacteremia treated with in vitro active therapy in the range of 6–16 days between 2008 and 2014. 1:1 nearest neighbor propensity score matching without replacement was performed prior to regression analysis to estimate the risk of all-cause mortality within 30 days after the end of antibiotic treatment comparing patients in the 2 treatment groups. Secondary outcomes included recurrent bloodstream infections, *Clostridium difficile* infections (CDI), and the emergence of multidrug-resistant gram-negative (MDRGN) bacteria, all within 30 days after the end of antibiotic therapy.

Results. There were 385 well-balanced matched pairs. The median duration of therapy in the short-course group and prolonged-course group was 8 days (interquartile range [IQR], 7–9 days) and 15 days (IQR, 13–15 days), respectively. No difference in mortality between the treatment groups was observed (adjusted hazard ratio [aHR], 1.00; 95% confidence interval [CI], .62–1.63). The odds of recurrent bloodstream infections and CDI were also similar. There was a trend toward a protective effect of short-course antibiotic therapy on the emergence of MDRGN bacteria (odds ratio, 0.59; 95% CI, .32–1.09; $P = .09$).

Conclusions. Short courses of antibiotic therapy yield similar clinical outcomes as prolonged courses of antibiotic therapy for Enterobacteriaceae bacteremia, and may protect against subsequent MDRGN bacteria.

Keywords. duration of therapy; gram-negative bacteremia; antibiotics; multidrug-resistant.

The incidence of gram-negative bacteremia continues to increase, particularly with advances in medical care, and remains a major contributor to morbidity and mortality for hospitalized patients [1]. Traditionally, gram-negative bacteremia is treated in the range of 7–14 days, but data for the optimal treatment duration within this range are limited. Prolonged antibiotic exposure has been associated with an increased likelihood of adverse drug events [2, 3], *Clostridium difficile* infections (CDI) [3] and antibacterial resistance [4]. The ideal duration of antibiotic therapy is one that optimizes clinical outcomes while minimizing adverse drug events.

Existing studies evaluating durations of therapy for gram-negative bacteremia have a number of limitations including small samples sizes, lack of comparator arms, and/or confounding by indication [5–7]. A meta-analysis of 24 randomized controlled trials including patients with bloodstream infections found that clinical cure and survival in patients receiving short courses of antibiotic treatment were similar to those in patients receiving prolonged courses of treatment [8]. However, approximately 80% of included patients had bacteremia as a consequence of community-acquired pneumonia or urinary tract infections and there were few included patients with healthcare-associated infections. Furthermore, there was significant heterogeneity between studies with regard to age (60% of patients were children), preexisting medical conditions, source of bacteremia,

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and severity of illness. To overcome some of these limitations, we sought to explore the optimal duration of therapy for gram-negative bacteremia by comparing the clinical outcomes of adult patients with Enterobacteriaceae bacteremia receiving short-course (6–10 days) vs prolonged-course (11–15 days) antibiotic therapy.

METHODS

Setting and Participants

Patients 18 years of age and older admitted to the Johns Hopkins Hospital, the University of Maryland Medical Center, and the Hospital of the University of Pennsylvania with Enterobacteriaceae bacteremia between 2008 and 2014 were retrospectively identified. In a given patient, only the initial episode of Enterobacteriaceae bacteremia during the study period was included.

The primary exposure was duration of antibiotic treatment, dichotomized to short-course (6–10 days) and prolonged-course (11–16 days) therapy, with the first day of therapy being the day that blood cultures were obtained. It was determined a priori to categorize duration of bacteremia into short-course and prolonged-course therapy to improve clinical applicability. Antibiotic duration included antibiotics continued after hospital discharge prescribed for bloodstream infections. The primary outcome was 30-day posttreatment mortality, defined as death from any cause within 30 days after the discontinuation of antibiotic therapy. For example, if a patient in the short-course group received 7 days of therapy, the observation time for the outcome would be days 8–37. Similarly, if a patient in the prolonged-course group received 14 days of therapy, the observation time for the outcome would be days 15–44. The time period of 30 days after discontinuation of antibiotics was selected so that the time period for which patients were "at risk" for the outcome would be similar between the 2 groups. All patients had to survive until at least 1 day after antibiotics were discontinued so that survival in the short-course group would not be artificially truncated. In addition, we performed a separate analysis comparing 30-day mortality between the short-course and prolonged-course groups, with day 1 being the first day positive blood cultures were obtained.

Secondary outcomes included (1) a recurrent bloodstream infection with the same organism, (2) CDI, and (3) emergence of multidrug-resistant gram-negative (MDRGN) colonization or infection that was not present within the year prior to the index blood culture date. All secondary outcomes were evaluated within 30 days of completing antibiotic therapy. Similar to the primary outcome, this time point was selected so the time at risk would be the same for both groups and differential exposure to antibiotics during the time at risk would be avoided.

Incident MDRGN colonization or infection was defined as Enterobacteriaceae, *Pseudomonas* species or *Acinetobacter* species recovered in subsequent clinical cultures resistant to at least 1 drug in 3 drug categories (piperacillin-tazobactam, extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, or [specifically for *Acinetobacter baumannii*] ampicillin-sulbactam) [9]. No active surveillance for MDRGNs was performed at any of the participating institutions. CDI was defined as a positive test for *C. difficile* in the setting of clinical criteria for infection [10].

Patients meeting any of the following criteria were excluded: (1) polymicrobial bacteremia, (2) duration of therapy outside of the 6- to 16-day range, (3) discontinuation of antibiotic therapy due to transition to hospice care, (4) death while receiving antibiotic therapy for Enterobacteriaceae bloodstream infection, (5) failure to receive at least 1 agent with in vitro activity against the isolated organism from the time of culture obtainment to the completion of antibiotic therapy, (6) treatment with aminoglycoside monotherapy, and (7) recipients of hematopoietic stem cell or solid organ transplantations. Transplant patients were excluded as it was observed that these patients almost exclusively received prolonged courses of antibiotic therapy for Enterobacteriaceae bacteremia on exploratory analysis and there were insufficient short-course patients to compare them to.

DATA COLLECTION

Demographic, preexisting medical conditions, source of bacteremia and source control measures, microbiological, treatment, and outcomes data for eligible patients were retrieved from electronic medical records from each of the institutions from medical record review and entered into a secure REDCap database. Source of infection and appropriateness of source control measures were determined by infectious diseases–trained physicians. Appropriate source control was defined as the removal of infected hardware, drainage of infected fluid collections, or resolution of obstruction for biliary or urinary sources during the time period of antibiotic therapy. To evaluate severity of illness, intensive care unit (ICU) admission and Pitt bacteremia score [11] were documented on day 1 of bacteremia. This study was approved by the institutional review boards of the 3 participating institutions, with a waiver of informed consent.

Statistical Analyses

Data analysis was performed using Stata version 12.0 software (StataCorp, College Station, Texas). The 2 treatment groups were compared on the basis of the duration of antibiotic treatment. Propensity scores were generated and propensity score matching was undertaken to account for treatment decisions influenced by confounding by indication (ie, the tendency for more ill-appearing or medically complex patients who would likely be at higher risk of mortality to receive prolonged courses of antibiotic therapy).

Propensity scores were calculated using a multivariable logistic regression model in which the dependent variable was a binary indicator of antibiotic duration. Covariates included in generating the propensity score included calendar year of bloodstream infection, hospital, age, preexisting conditions (end-stage liver disease, end-stage renal disease requiring dialysis, structural lung disease, congestive heart failure with an ejection fraction of <45%, diabetes, immunocompromising conditions (human immunodeficiency virus, chemotherapy within 6 months, absolute neutrophil count [ANC] <100 cells/μL at the time of positive blood culture obtainment, immunomodulatory therapy, or corticosteroids for ≥14 days), Pitt bacteremia score, ICU stay on day 1 of bacteremia, source of bacteremia, and source control measures. 1:1 nearest neighbor matching without replacement was performed with a caliper width of 0.20. Standardized mean biases were tested to ensure balance after propensity score matching between the short- and prolonged-course groups.

The χ^2 or Fisher exact test was used to compare baseline categorical variables, as appropriate, between matched pairs. Wilcoxon rank-sum test was used to compare baseline medians of continuous variables. Cox proportional hazards modeling was used to estimate the unadjusted hazard ratio (HR) and associated 95% confidence interval (CI) for potential risk factors associated with time to mortality. Prespecified potential confounders including immunocompromised status and variables yielding *P* values <.10 on univariable analysis of the propensity score–matched cohort were included in multivariable models. The proportional hazards assumption was examined by graphically inspecting complementary log–log plots for each variable. Logistic regression was used to estimate the odds ratios (ORs) and associated 95% CIs for recurrent bloodstream infections, subsequent CDI, and the emergence of MDRGN bacteria between the 2 groups. The Hosmer-Lemeshow test was used to assess the fit of regression models. A 2-sided *P* value <.05 was considered to be statistically significant for all tests.

RESULTS

A cohort of 4967 unique patients with Enterobacteriaceae bacteremia were identified during the study period, with 1769 patients meeting eligibility criteria (Figure 1). There were 385 propensity score–matched pairs in each treatment group. Baseline characteristics of these 2 groups were well-balanced when evaluating standardized biases. A comparison of baseline characteristics between short and prolonged-course antibiotic treatment groups before and after propensity score matching is shown in Table 1. The median duration of therapy in the short-course group and prolonged-course groups was 8 days (interquartile range [IQR], 7–9 days) and 15 days (IQR, 13–15 days), respectively. In accordance with the eligibility criteria, all patients received in vitro active antibiotic agents from the time blood cultures were obtained to the time antibiotics were discontinued. Additionally, all patients were initiated on β-lactam therapy at the time blood cultures were obtained. Approximately 30% of bloodstream infections occurred in ICU patients. The most common organisms identified from blood cultures in the matched cohort were *Escherichia coli* (46.9%) followed by *Klebsiella* species (32.6%), and *Enterobacter* species (11.7%) (Table 2).

Primary Outcome

After propensity score matching, there were 37 (9.6%) and 39 (10.1%) deaths within the 30-day follow-up period in the short-course and prolonged-course groups, respectively. In univariable analysis, shorter antibiotic durations were not associated with an increased risk of mortality (HR, 1.12; 95% CI, .70–1.80;

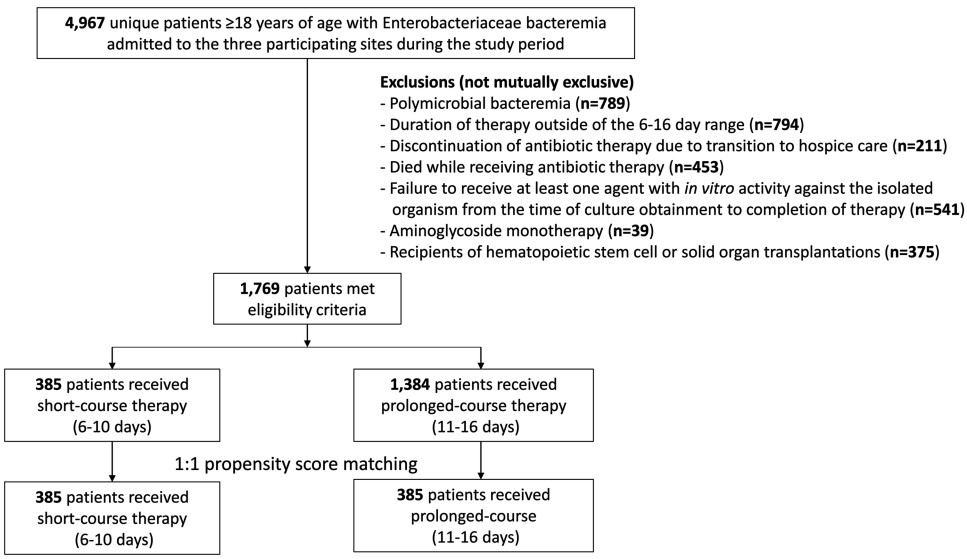

Figure 1. Study flowchart.

Table 1. Baseline Characteristics of Hospitalized Adult Patients With Enterobacteriaceae Bacteremia Receiving Short (6–10 Days) or Prolonged Courses (11–16 Days) of Antibiotic Therapy

Characteristic	Whole Cohort			Propensity Score–Matched Cohort		
	Short Course (n = 385)	Prolonged Course (n = 1384)	*P* Value	Short Course (n = 385)	Prolonged Course (n = 385)	*P* Value
Age, y, median (IQR)	60 (46–69)	58 (46–69)	.20	60 (49–69)	60 (49–70)	.73
Female sex	191 (49.6)	699 (50.5)	.76	191 (49.6)	174 (45.2)	.22
Race/ethnicity			.13			.15
White	196 (50.9)	647 (46.7)	.15	196 (50.9)	177 (46.0)	.17
Black or African American	154 (40.0)	584 (42.2)	.44	154 (40.0)	161 (41.8)	.61
Asian	11 (2.9)	62 (4.5)	.16	11 (2.9)	17 (4.4)	.25
Latino	8 (2.1)	51 (3.7)	.12	8 (2.1)	18 (4.7)	.05
Unknown or multiracial	16 (4.2)	40 (2.9)	.21	16 (4.2)	12 (3.1)	.44
Source of bacteremia						
Pneumonia	36 (9.4)	109 (7.9)	.35	36 (9.4)	33 (8.6)	.71
Skin and soft tissue	14 (3.6)	43 (3.1)	.60	14 (3.6)	17 (4.4)	.58
Urinary tract	134 (34.8)	566 (40.9)	.03	134 (34.8)	144 (37.4)	.45
Biliary	60 (15.6)	156 (11.3)	.02	60 (15.6)	65 (16.9)	.63
Gastrointestinal	87 (22.6)	261 (18.9)	.24	87 (22.6)	66 (17.1)	.12
Catheter-associated	54 (14.0)	240 (17.3)	.12	54 (14.0)	52 (13.5)	.83
Inadequate source control during antibiotic course	3 (0.8)	36 (2.6)	.48	3 (0.8)	4 (1.0)	.45
Pitt bacteremia score on day 1 of bacteremia, median (IQR)	2 (1–3)	2 (1–3)	.84	2 (1–3)	2 (1–3)	.59
Intensive care unit on day 1 of bacteremia	113 (29.4)	403 (29.1)	.93	113 (29.4)	122 (31.7)	.48
Preexisting medical conditions						
End-stage liver disease	35 (9.1)	87 (6.3)	.06	35 (9.1)	31 (8.1)	.61
ESRD requiring dialysis	18 (4.7)	59 (4.3)	.73	18 (4.7)	21 (5.5)	.62
Structural lung disease[a]	34 (8.8)	109 (7.9)	.54	34 (8.8)	24 (6.2)	.17
CHF with an ejection fraction <45%	46 (11.9)	131 (9.5)	.15	46 (11.9)	51 (13.2)	.59
Diabetes	96 (24.9)	325 (23.5)	.55	96 (24.9)	96 (24.9)	1.00
Immunocompromised[b]	127 (33.0)	523 (37.8)	.08	127 (33.0)	134 (34.8)	.59
HIV	14 (3.6)	63 (4.6)	.44	14 (3.6)	21 (5.5)	.23
Chemotherapy within 6 mo	93 (24.2)	419 (30.3)	.02	93 (24.2)	106 (27.5)	.29
Absolute neutrophil count ≤100 cells/μL	24 (6.2)	108 (7.8)	.30	24 (6.2)	22 (5.7)	.76
Immunomodulatory therapy or corticosteroids for ≥14 d	23 (6.0)	56 (4.0)	.01	23 (6.0)	16 (4.1)	.32

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CHF, congestive heart failure; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; IQR, interquartile range.

[a]Chronic obstructive pulmonary disease, emphysema, pulmonary fibrosis, tracheostomy dependency.

[b]Patients may have >1 immunocompromising condition.

Table 3). Similarly, there was no reduction in mortality for each additional day of antibiotic therapy for the 30 days after antibiotics were discontinued (HR, 0.97; 95% CI, .91–1.05). No difference in all-cause mortality was observed between short- and prolonged-course treatment groups after additional adjustment for immunocompromised status and for variables with *P* values <.10 on univariable analysis (adjusted HR [aHR], 1.00; 95% CI, .62–1.63). Additional factors that remained associated with

Table 2. Enterobacteriaceae Isolated in the Bloodstream of Hospitalized Adult Patients Between 2008 and 2014

Enterobacteriaceae	Entire Cohort (N = 1769)	Duration of Therapy in Matched Cohort	
		6–10 d (n = 385)	11–16 d (n = 385)
Escherichia coli	841 (47.5)	177 (46.0)	184 (47.8)
Klebsiella species	557 (31.5)	137 (35.6)	114 (29.6)
Enterobacter species	200 (11.3)	36 (9.4)	54 (14.0)
Serratia species	58 (3.3)	13 (3.4)	9 (2.3)
Proteus species	81 (4.6)	13 (3.4)	14 (3.6)
Citrobacter species	32 (1.8)	9 (2.3)	10 (2.6)

Data are presented as No. (%).

Table 3. Thirty-Day All-Cause Mortality for Hospitalized Adult Patients With Enterobacteriaceae Bacteremia in a Propensity Score–Matched Cohort

Variable	Unadjusted HR (95% CI)	*P* Value	Adjusted HR[a] (95% CI)	*P* Value
Short-course therapy (6–10 d)	1.12 (.70–1.80)	.64	1.00 (.62–1.63)	.97
Urinary source	0.36 (.19–.67)	.001	0.49 (.26–.94)	.03
Pneumonia	3.06 (1.73–5.42)	<.001	1.60 (.85–3.02)	.15
Pitt bacteremia score	1.31 (1.21–1.42)	<.001	1.29 (1.17–1.43)	<.001
ICU on day 1 of bacteremia	2.38 (1.48–3.81)	<.001	0.99 (.56–1.76)	.98
End-stage liver disease	3.58 (2.05–6.06)	<.001	4.12 (2.30–7.39)	<.001
Immunocompromised status	1.03 (.63–1.70)	.89	1.40 (.83–2.36)	.21

Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

[a]Adjusted for immunocompromised status and variables with $P < .10$ in univariable analysis.

30-day all-cause mortality in the multivariable model were urinary sources (protective), Pitt bacteremia score, and end-stage liver disease (Table 3). We also compared 30-day mortality in the propensity-matched cohort between the short-course and prolonged-course groups, with day 1 being the day the first positive blood culture was obtained, and found no difference between the 2 treatment groups (aHR, 0.92; 95% CI, .59–1.45).

Secondary Outcomes

There were 5 (1.3%) and 9 (2.3%) episodes of recurrent bloodstream infections with the same organism in the short- and prolonged-course treatment groups, respectively (OR, 1.32; 95% CI, .48–3.41). CDI occurred in 7 (1.8%) and 6 (1.6%) patients within 30 days of discontinuing antibiotics in the short- and longer-course treatment groups, respectively (OR, 1.16; 95% CI, .39–3.51). There were 17 (4.4%) reports of incident MDRGN resistance in the short-course and 28 (7.3%) in the prolonged-course treatment groups (OR, 0.59; 95% CI, .32–1.09; $P = .09$).

DISCUSSION

Our findings indicate that patients receiving 6–10 days of antibiotic therapy for uncomplicated Enterobacteriaceae bacteremia have a similar risk of survival in the ensuing 30 days as patients receiving longer courses of antibiotic therapy. Current Infectious Diseases Society of America guidelines for catheter-related gram-negative bloodstream infections suggest prescribing antibiotic therapy in the range of 7–14 days [12]. This recommendation is considered low-grade evidence (C-III) because of limitations with existing studies addressing this question. A 2001 multinational survey revealed that the durations of antibiotic therapy prescribed for gram-negative bacteremia range widely among clinicians [13]. The investigators concluded that the wide variability in antibiotic prescribing patterns suggests an urgent need to produce high-quality evidence to identify optimal antibiotic prescribing practices for bacteremia [13]. Unfortunately, little progress has been made since 2001 to refine treatment ranges and to standardize antibiotic administration practices for gram-negative bloodstream infections.

In the past, prolonged antibiotic treatment courses were prescribed for several reasons: lack of appreciation of the impact of antibiotic therapy on disturbances in the intestinal microbiome and associated downstream effects, limited comparative effectiveness studies exploring optimal durations of antibiotic therapy as prolonged durations of therapy were often used by default in infectious diseases trials, and a limited understanding that antibiotic resistance is a public health crisis [14, 15]. In recent years, however, there is mounting evidence of adverse events related to prolonged antibiotic use, encouraging the clinical community to reexamine common durations of therapy prescribed. Data from the treatment of several infectious processes, including results of a meta-analysis of urinary and respiratory outpatient conditions, suggest that antibiotic durations shorter than those traditionally prescribed yield comparable outcomes to more prolonged durations of therapy, but the risk of subsequent drug resistance is greater in the latter group [16–19].

In our propensity score–matched cohort of 770 patients, there were 45 (6%) patients with MDRGN organisms recovered on clinical cultures in the 30 days after discontinuing antibiotic therapy. Although not reaching statistical significance ($P = .09$), these odds were greater in patients receiving prolonged courses of antibiotic therapy. After conducting post hoc power calculations, as recovery of incident MDRGNs in subsequent clinical cultures was a relatively rare event, we determined that we only had 40% power to detect the difference in incidence of MDRGNs we observed in our cohort—indicating we were underpowered to detect a significant difference, if one existed.

There are a number of limitations that should be considered when interpreting our findings. First, evaluating treatment effects from observational data can be problematic because a number of prognostic factors may influence treatment decisions. We attempted to overcome this confounding by indication with the use of propensity score matching and derived 2 very well-matched groups with the sole difference between the groups being duration of antibiotic therapy. Although use of stringent propensity score matching led to the exclusion of large numbers of patients in the overall cohort, it ensured the 2 comparator groups were very similar with regard to demographic data, preexisting medical conditions, source control

measures, severity of illness, and the administration of in vitro active agents. However, we cannot exclude the possibility of additional, unmeasured confounding factors that could impact the association between duration of antibiotic therapy and mortality that we did not include in generating propensity scores. Second, our primary outcome was all-cause mortality within 30 days of discontinuing antibiotic therapy rather than mortality attributable to gram-negative bacteremia. Because many patients in our cohort had debilitating underlying medical conditions, differentiating between death related to gram-negative bacteremia and death from noninfectious causes was challenging. We limited the evaluation period to 30 days, rather than 90 days as used in some studies, to increase the likelihood that mortality was related to the bloodstream infection. Additionally, as virtually all patients with hematopoietic stem cell transplants or solid organ transplants with Enterobacteriaceae bacteremia that we reviewed received prolonged courses of antibiotic therapy, we were unable to include transplant patients in our propensity score–matched cohort because virtually no transplant patients received short-course therapy. However, we were able to include patients with a variety of other immunocompromising conditions in our cohort including HIV, receipt of chemotherapy within 6 months, ANC ≤100 cells/μL, and receipt of immunomodulatory therapy or corticosteroids for at least 14 days, and these conditions were well-balanced between the 2 treatment groups. In fact, approximately 34% of patients in our cohort were immunocompromised for other reasons. Finally, <1% of patients in our matched cohort had inadequate source control within 7 days, indicating that most patients had "uncomplicated" bacteremia. As most patients with retained hardware, large areas of devitalized bone, or infected fluid collections that we evaluated received >16 days of antibiotic therapy, the vast majority of patients with inadequate source control did not meet eligibility criteria for this study. Therefore, we are unable to make inferences on the optimal duration of therapy for Enterobacteriaceae bacteremia for patients with inadequate source control. Randomized controlled trials that are currently enrolling patients to evaluate this question further may shed more light on lingering issues (ClinicalTrials.gov identifiers NCT01737320, NCT03101072, NCT02400268).

These limitations notwithstanding, our study suggests that 6–10 days of antibiotic treatment is not associated with either an increased risk of mortality or an increased odds of recurrent bacteremia compared with longer antibiotic treatment courses for uncomplicated Enterobacteriaceae bacteremia. Furthermore, shorter durations of therapy for uncomplicated Enterobacteriaceae bacteremia may protect patients from subsequent antibiotic drug-resistant organisms.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH).

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