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Comparing the Outcomes Associated With Three Treatment Durations for Enterobacteriaceae Bloodstream Infection

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Abstract

Background: A proper duration for treating patients with Enterobacteriaceae bloodstream infection is not yet well defined; we attempt to find the appropriate course of treatment.

Methods: A retrospective multicenter study in Amman-Jordan. Medical records were reviewed for patients with blood cultures growth for Enterobacteriaceae. Information on blood cultures was extracted from the microbiology logbook and records. For adults >18 years, primary bacteremia and a known source were included. Patients who needed prolonged antibiotics treatment due to the nature of their infections and zoonotic infections, neutropenic cancer patients, organs with abscesses/empyema, CVC retention, polymicrobial septicemia, and expected survival ≤ 48 hours were excluded. Continuous variables were analyzed by (χ^2), ANOVA for means, and the Bonferroni for pairwise comparisons if P-value is <0.05.

Results: 323 Patients with Enterobacteriaceae growth on blood cultures were distributed as follows: patients with one-week treatment duration were 163, two-week 102, and three-week duration was 58. Characteristics were balanced among the three durations (P>0.05) except male gender; diabetes, steroids, CVC, and a few antibiotics were more in the three-week treatment (P<0.05). All-cause mortality, relapse, and reinfection did not differ significantly among the three treatment durations (P>0.05). The relapse rate in 90 days was 5.17%, and the reinfection rate was 4.3%.

Conclusion: There was no significant difference in the three antibiotics treatment durations in the 28-day, 90-day all-cause mortality rates, relapse, and reinfection rates.

Keywords: All-cause 28-day mortality; All-cause 90-day mortality; Bloodstream infection; Duration of antibiotic therapy; Enterobacteriaceae

Introduction

Mortality associated with Gram-negative bloodstream infections is high, in-hospital at about 20%, and the 28 days mortality may reach up to 30%. With multidrug-resistant gram-negative bacteria like Carbapenems-Resistant Enterobacteriaceae (CRE), Pseudomonas aeruginosa, Acinetobacter baumannii it may reach up to 60% [1-3]. Several studies focused on the treatment duration, reinfection, relapse of infection, and mortality. Some studies concluded that patients who received a short period of treatment for uncomplicated gram-negative sepsis did poorly and were advised 14 days of therapy [4]. In contrast, others demonstrated that a 7-day course or less of antimicrobials therapy was adequate if patients were wisely selected based on clinical resolution, biomarkers, clinical judgment, and microbiologic eradication [5]; Adrian Sousa et al. showed that a short duration of treatment was not different in the 30 days and 90 days mortality, but their patients included urinary tract as a source in 51% [6]. A narrative review of thirteen studies failed to conclude the best antimicrobial therapy duration in gram-negative sepsis. However, the reviewed studies were heterogeneous [7].

Hitherto, it is settled that treatment duration must be adequate to achieve the lowest rates of morbidity and mortality; in the meantime, not to overprescribe antimicrobials if less period is sufficient to avoid the potential effects of the increase in bacterial resistance or the unfavorable changes in human micro biota with longer durations. The current study aims to explore whether various durations of the antimicrobial therapy for Enterobacteriaceae bloodstream infection in the real-world influence the 28 days and 90 days of all-cause mortalities, relapse of the infections, and a new infection.

Materials and Methods

Study design

A multicenter retrospective study was conducted in three private hospitals in Amman-Jordan (Al Khalidi, the Specialty, and Jordan Hospital), all with about 700 beds, including about 65 ICU beds. Records for the patients with bloodstream infections caused by Enterobacteriaceae were reviewed. Patient records were identified through the microbiology laboratory logbook, blood cultures with growth for Enterobacteriaceae were included, and the medical records coding for bacteremia (ICD-10-CM. Code A41.50). The study included records for patients admitted between February 2016 and April 2022. The study was approved by each hospital Institutional Review Board (IRB), a consent was waived due to the nature of the study; however,

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on calling patients to obtain information on the patient health and survival, a verbal acceptance to answer a phone questionnaire on the patient health was requested from the patient or his family, if accepted the caller continued the phone questionnaire otherwise the phone call was courteously ended.

Cohorts included and their characteristics

This The main focus of the study is to review records for the septic patients admitted with documented monomicrobial Enterobacteriaceae bloodstream infection. Clinical criteria added to the judgment if the isolated bacteria are pathogens causing sepsis and treatment was commenced and not a contaminant. Included patients were those with an unknown source, i.e., primary bacteremia, and bacteremic patients with a known source: SSTI including pressure ulcers and surgical site infection, urinary tract including, abdomen, and pelvis, lower and upper respiratory passages, patients with community-associated or hospital-associated infections and were eighteen years or older. Excluded patients were those the nature of their sepsis or source may need prolonged therapy like CNS infections, infective endocarditis, osteomyelitis, solid organ recipients, cancer patients with neutropenia and hematopoietic stem cells recipients, necrotizing fasciitis and problematic source control, lung abscess, abdominal infection with the uncontrolled source with multiple surgeries, organs with abscesses/empyema, retention of CVC, polymicrobial septicemia including another gram-negative bacteria, gram-positive bacteria, and yeast, patients survival span is expected to be ≤ 48 hours, and zoonotic bacteria like salmonella or brucella.

Antimicrobials utilization protocol

Patients must have received antimicrobial therapy for at least three or more, and bacteria were sensitive to the prescribed antimicrobial(s), i.e., appropriate antimicrobial therapy. If the antibiotics were changed for some reason and bacteria were sensitive to the newly used antibiotic(s), then it was considered continuity of treatment. The date the first antibiotics started is the antibiotic(s) start day. If bacteria under treatment were resistant to the initially used antibiotic(s) and were switched to appropriate therapy, the switch day would be the treatment start day. Patients were followed up by phone calls 90 days after their hospital discharge, enquiring about health state, readmissions for reinfections or relapses, and if they died, the date of death. The three treatment durations for using antimicrobials on patients were divided arbitrarily: the one week included patients who were treated from 3 to seven days, the two weeks from 8 to 14 days, and the three weeks from day 15 and more prolonged. Antibiotics were administered in the short infusion time method in the three hospitals. Two hospitals have a clinical pharmacist division that assists in the antibiotic administration, dosing, and dose modification, and the third is through the treating medical and surgical teams.

Statistical analysis

Characteristics and features of the patients are described. Continuous variables among the three treatment durations were examined by (χ^2) and by ANOVA for multiple means; an Adjusted Bonferroni significance was calculated as a pairwise comparison if a difference was found, and outcomes were further analyzed by the Kruskal Wallis test due to low cell count. P-value was not significant. SPSS version 25 (IBM corporation) was used to analyze data; P-value is considered significant at<0.05. The Charlson Comorbidity Score examined mortality prediction. And severity was reviewed by Pitt Bacteremia.

Outcome measures

The treatment outcome is to evaluate all-cause mortality at 28-day mortality and 90-day after hospital discharge and to measure differences in the relapse of the infection and the reinfection.

Results

Records were reviewed for patients with Enterobacteriaceae bacteremia in 323 patients; 163 were in the one-week treatment duration, 102 in the two weeks, and 58 were in the three or more week's treatment duration. No significant difference in age (P=0.422). Gender distribution is significantly different; males were more in the three-week treatment duration versus the other two durations groups (Adjusted Bonferroni P=0.028). There were no significant differences among comorbidities among the three treatment durations except for diabetes mellitus (Adjusted Bonferroni P=0.020) and steroid use (Adjusted Bonferroni P=0.008), where the rate of diabetes was significantly lower in the three-week treatment duration than the other two durations (P=0.020). The rate of steroid use was substantially lower in the one-week treatment duration than in the other two treatment durations (P=0.008). Body Mass Index (BMI) was subdivided into six categories according to CDC (Table 1), there were no significant distribution differences in the six categories as distributed on the three treatment durations (P=0.219). Functional status on the sepsis day was subdivided into four arbitrary categories; they showed no significant differences in the general neurological condition among the three treatment durations (P=0.166). Patients who were on antibiotics before the onset of the admission sepsis within the last 90 days or in the hospital and were on some form of antibiotics before they developed sepsis showed no significant distribution difference among the three treatment durations (P=0.057). The appropriateness of the prescribed antibiotics after documentation of the bloodstream infection was similar among the three treatment durations (P=0.218). Patients who required endotracheal tube ventilation (P=0.170) and urinary catheters (P=0.328) were not significantly different for the three treatment durations. There was a significant increase in the ratio of CVC use in the three-week duration (P<0.05) compared with the one-week treatment group but similar to the two weeks treatment group (P>0.05). Both Pitt's bacteremia score (P=0.271) and Charlson's comorbidity score (P=0.631) were not significantly different among the three treatment durations. Antimicrobial families used in the treatment of patients were similar in distribution among the three treatment durations except for tigecycline (Adjusted Bonferroni P=0.004), and colistin (Adjusted Bonferroni P=0.001) were prescribed more in the two-week and the three-week treatments durations (Table 1). The various included Enterobacteriaceae (*E. coli*, *Klebsiella* species, *Enterobacter* species, and Proteus species) were not significantly different in the distribution of and the pattern of resistance (ESBL and CRE) among the three treatment groups (P=0.192). Bacterial sources of the bacteremia, whether primary bacteremia, abdomen, urinary, respiratory, skin, or soft tissue, did not significantly differ (P=0.629). The outcomes showed the 28-day and 90-day all-cause mortality was not significantly different among the three treatment durations (P>0.05), as well as relapse and new infections (P>0.05) (Table 2). No significant difference was demonstrated (P>0.05) among the three treatment durations for relapse of infection or a new infection. The outcomes were reanalyzed without bacteremia of urinary source (Table 3); again, there was no significant difference in the results (P>0.050). The total relapse was 24 (5.17%), and reinfection was 20 (4.3%).

Characteristics	Duration of antibacterial treatment in patients with enterobacteriaceae bloodstream infections			
	Patients N = 323			
	1 week n=163	**2 weeks n=102**	**≥ 3 weeks n= 58**	**P**
Age (Mean)	68.77	66.22	67.21	0.422
Gender				
Male	86	55	42	0.028#
Female	77	47	16	
Comorbidities				
Diabetes	90	55	20	0.020#
Hypertension	100	57	29	0.296
Steroids	30	32	21	0.008#
Malignancy	39	22	21	0.103
Tobacco	45	27	16	0.968
Chronic lung disease	17	14	8	0.682
Chronic liver disease	24	16	3	0.125
Chronic heart disease	66	42	23	0.98
Chronic gastrointestinal disease	30	9	8	0.089
CNS disease	31	16	10	0.757
Autoimmune disease	7	6	2	0.753
Body mass index				
<18.5 18.5 – 25 >25 – 30 >30 – 35 >35 – 40 >40	59 25 28 30 21	44 19 8 19 12	20 4 8 14 12	0.166
Functional status at the time of sepsis				
Fully alert conscious Some limitations include no assistance Partially disabled needs assistance Disabled bedridden Not available	59 25 28 30 21	44 19 8 19 12	20 4 8 14 12	0.166
Pre-admission Antimicrobials	19	13	14	0.057
Initially appropriate antimicrobial(s)	133	87	43	0.218
Endotracheal tube ventilation	18	16	12	0.17
Central line	27	17	19	0.019#
Urinary catheter	82	53	36	0.328
Bacterial Source	163	102	58	0.629
Pitt score	162	102	57	0.271
Charlson comorbidity score	162	102	58	0.631
Antimicrobials				
B-lactame β-lactamases inhbitor	33	26	23	0.014#
Cephalosporines	34	29	20	0.093
Carbapenems	126	88	43	0.111
Quinolones	40	22	13	0.845
Aminoglycosides	37	26	19	0.319
Tigecycline	11	10	13	0.004#
Colistin	6	8	11	0.001#
Enterobacteriaceae				
E. coli	2	2	1	0.192
Klebsiella	28	14	10	
Enterobacter spp.	11	5	2	
Proteus	3	1	1	
Total ESBL	66	54	27	
Total CRE*	5	6	5	
Bacterial source				
Primary bacteremia	35	28	12	0.629
Abdomen**	32	10	9	
Urinary tract	72	49	22	
Respiratory	18	9	9	
Skin and soft tissues	4	4	4	
Note: #The ratio is significantly higher for the ≥ 3 weeks; ¨Abdomen: intestines, peritoneal, pelvis, and hepatobiliary; *Including 11 KPC.				

Table 1: Characteristics and features of patients with Enterobacteriaceae bloodstream infections.

	The three durations of antibacterial therapy			
Outcomes	**One week n=163 (%)$**	**Two weeks n=102 (%)$**	**≥ 3 weeks n= 58 (%)$**	**P#**
28-day mortality*	8 (4.9)	6 (5.9)	8 (14.0)	0.059
90-day mortality*	46 (34.8)	32 (38.6)	26 (53.1)	0.082
Relapse of infection**	13	6	5	0.392
New infection**	11	3	6	0.381
Note: #Also was tested by kruskal wallis test due to low counts; P-value was not significant; *all-cause mortality. **Followed up to 90 days ; $(%) were entered for some cells to appreciate the ratio difference.				

Table 2: Outcomes associated with different durations of therapy for patients with Enterobacteriaceae bloodstream infections.

	The three durations of antibacterial therapy			
Outcomes	**One week n=163 (%)$**	**Two weeks n=102 (%)$**	**≥ 3 weeks n= 58 (%)$**	**P#**
28-day mortality*	5 (5.6)	4 (7.5)	4 11.4)	0.525
90-day mortality*	33 (44.6)	23 (57.5)	17 (58.6)	0.277
Relapse of infection**	7	3	4	0.358
New infection**	7	3	4	0.358
Note: #Also was tested by kruskal wallis test due to low counts; P-value was not significant; *all-cause mortality. **Followed up to 90 days ; $(%) were entered for some cells to appreciate the ratio difference.				

Table 3: Outcomes associated with different durations of therapy for patients with Enterobacteriaceae bloodstream infections excluding the urinary source.

Discussion

In our attempt to find an ideal duration of antibiotics treatment in Enterobacteriaceae bloodstream infection, a subdivision of the durations into three periods; one week, two weeks, and three weeks; unlike most of the previous studies that used two treatment durations, less/more than 14 days, less/more than seven days, less than seven days and more than 14 days, and less than versus ten days [8-10], the subdivision into the three treatment durations aim is to minimize neighboring values associated with two durations in an observational study. Several confounders and characteristics were included to adjust for the three treatment durations; the vast majority of confounders incorporated verified well-balanced cohorts (P>0.05), except for a few confounders (Table 1). Patients with Enterobacteriaceae bloodstream infection contained ESBL-producers and CRE, and their representations were well balanced among the three treatment durations. Earlier, the recommendation to incorporate important confounders in similar populations was described, including appropriateness of therapy, adjusting for severity by Pitt bacteremia score, and Charlson comorbidity score at the onset of therapy [11]; all were balanced here. Some measured characteristics may have affected the study outcome thru treatment choices like β-lactams β-lactamase inhibitors (P=0.014), tigecycline (P=0.004), and colistin (P=0.001) which were used more in the longer duration of treatment where a few patients had more drug-resistant bacteria (ESBL and CRE) requiring the use of more colistin and tigecycline; this may have affected the results thru bias due to confounding by indication [12]. Here, there were no statistically significant differences in the outcomes. Mortality on day 28 (P=0.059) and day 90 (P=0.082) were not statistically different for the three treatment durations. However, with a closer look at the ratios, the duration of therapy for the three-week duration was associated with higher 28-day and 90-day mortality; it may be said that the statistical significance for both was in the tendency range though not significant (Table 2). A single-center study focused on *E. coli* bloodstream infection, multivariate analysis for all-cause mortality at day 90. After adjusting the model by the propensity score, short therapy was not associated with a higher risk of mortality [13].

This study believes that short therapy duration suffices, especially in source-controlled bloodstream infected patients and those with minimal comorbidities. For the relapse of infection, there was no significant difference between the three durations of treatment (P=0.392) like in Giannella M et al. though their durations were less/more than ten days [13]. A sub-analysis (Table 3) excluding the urinary system as the source for the Enterobacteriaceae bloodstream infections and B-lactam Beta-lactamases inhibitors were under debate for being inferior to carbapenems in bloodstream infections of non-urinary sources [14,15]. In our study, 54 patients with bloodstream infections treated with B-lactam Beta-lactamases inhibitors were evenly distributed among the treatment durations (P=0.229). Still, there were no significant statistical differences between the three treatment groups in the measured outcomes, the 28-day mortality (P=0.525), the 90-day mortality (P=0.277), the relapse of infection (P=0.358), and a new infection within 90 days (p=0.358). In our study, the relapse rate was 5.17%, almost close to previous studies at about 3.4%-5% [16] our cohort reinfection rate was 4.3%.

It is well known now that a longer duration of antibiotics treatment for Enterobacteriaceae was not associated with a better outcome and was associated with decreased cost-effectiveness and increased resistance [17]. A bias toward better treatment success and reduced short-term mortality that may result from short versus prolonged antibiotics infusion times was not a concern; the three contributing hospitals do not use the prolonged antibiotics infusion protocol for all patients [18].

Conclusion

Subdividing the antibiotics treatment into one-week, two-week, and three-week treatment durations did not significantly differ in 28-day, 90-day all-cause mortality. The relapse and new infection rates did not show statistically significant differences. In our attempt to lower cost, increase antibiotics' cost-effectiveness and minimize resistance, it is conceivable to use the proper antibiotic treatment duration of seven days in well-selected patients with no complications, source control, and the nature of their infections does not need prolonged antibiotic treatment.

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Conflict of Interests

None

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