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Comparing the Outcomes Associated with Three Treatment Durations of *Pseudomonas* and *Acinetobacter* Bloodstream Infection

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Abstract

Background: The proper duration for treating patients with non-fermenting gram-negative bacteremia is not yet defined; we attempt to find an appropriate course of treatment.

Methods: A retrospective multicenter study in three hospitals, Amman-Jordan. Medical records were reviewed for patients with Lactose Non-Fermenting Gram-Negative (LNF) bacteremia. 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; neutropenic cancer patients, organs with abscesses/empyema, CVC retention, polymicrobial septicemia, and expected survival ≤ 48 hours. Continuous variables were analyzed by (χ^2), Mann-Whitney test, ANOVA for means, and the Bonferroni for pairwise comparisons for P-value <0.05. SPSS version-25 was used in the analysis.

Results: Included patients were 115 with LNF gram-negative growth on blood cultures, distributed as follows: patients with one-week treatment duration were 45, two-week 43, and three-week duration was 27. Characteristics were balanced (P>0.05) except for chronic lung disease, and a few antibiotics were more in the three-week duration (P<0.05). There was a significant difference for 28-day all-cause mortality (P=0.019), but relapse and reinfection did not significantly differ among the three treatment durations (P>0.05). The relapse rate was 3%, and a new infection was 7%.

Conclusion: There was no significant difference for one-week, two-week, and three-week antibiotics treatment durations in the 90-day all-cause mortality, relapse, and reinfection rates, but increased 28-day mortality in the three-week duration.

Keywords: Bloodstream infection; *Acinetobacter* relapse; Mortality; Antimicrobial therapy

Introduction

The treatment of LNF gram-negative bloodstream infections is challenging. Mortality associated with *Pseudomonas aeruginosa* and *Acinetobacter baumannii* may reach 60% [1,2]. Delaying effective anti pseudomonal antimicrobial therapy correlates with higher 30-day mortality; an initial 24 hours delay increases the mortality by about 28%, and every 24 hours delay is associated with a remarkable increase in mortality, and by delaying treatment for up to 120 hours, mortality becomes about 55% [3].

To reduce mortality and improve the outcome while keeping in mind antimicrobial stewardship, studies focused on the treatment duration in *Pseudomonas*, where it was recommended that a minimum of parenteral 14 days is necessary to reduce recurrence in allogeneic-Hematopoietic Cell Transplant (HCT) recipients [4], and in a study assessing colistin doses and nephrotoxicity, a longer duration of therapy for *Acinetobacter* was reported to be associated with increased survival (HR=0.86 P=0.002) [5]. There was a lack of comparative studies that compare different treatment durations in the treatment of NLF gram-negative bacteria but were dominated mainly by the Enterobacteriaceae [6]. An Inverted Probability Treatment Weight multivariate analysis (IPTW) concluded that 6-10 days of antimicrobials treatment for *Pseudomonas bacteremi*a was as effective as 14 days or more in 30-day mortality and recurrence and fewer discontinuation rates due to side effects [7]. Although the treatment duration for gram-negative NLF is not yet established, probing for an ideal course is needed to achieve the lowest morbidity and mortality rates. At the same time, to cut down on the long duration of antimicrobials treatment if less treatment duration is sufficient [8], with the associated known benefits of decreasing bacterial resistance, increasing cost-effectiveness, and minimizing the unfavorable effects on human microbiota with the longer durations.

The current study explores whether different durations of the antimicrobial therapy for LNF gram-negative bloodstream infections in the real world influence the 28-day and 90-day all-cause mortality, relapse of infection, and new infection.

Materials and Methods

Study design

A multicenter retrospective study reviews records for patients in three private hospitals in Amman-Jordan (Al Khalidi, the Specialty, and Jordan Hospitals) with around 700 beds, including 65 ICU beds. This is the second part of the study that started with evaluating the treatment durations for Enterobacteriaceae. The current study included three treatment durations for bloodstream infection caused

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by the LNF gram-negative bacteria, one-week, two-week, and three-week treatment durations. Patient records were identified through the microbiology laboratory logbook for blood cultures with the growth of non-fermenter gram-negative bacteria, namely *Pseudomonas* and *Acinetobacter*, and from the medical record coding for bacteremia (ICD-10-CM. Code A41.50). Records included 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, on calling patients by phone to obtain information on the patient health and survival, a verbal acceptance to answer a phone questionnaire on the patient health condition 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

The main focus of the study is to review records for the bacteremic patients admitted with mono microbial LNF gram-negative bloodstream infections. Clinical criteria judged the isolated bacteria as a pathogen causing the sepsis syndrome and not contamination, and treatment was commenced. The bloodstream infection source was 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, CAUTI, abdomen, and pelvis, lower and upper respiratory passages. Patients with community-associated or hospital-associated infections were included and were eighteen years or older. Excluded patients were those with the nature of their source or sepsis may need prolonged therapy like central nervous system infections, infective endocarditis, osteomyelitis, solid organ recipients, cancer patients with neutropenia and hematopoietic stem cells recipients, necrotizing fasciitis and difficult SSTI source control, lung abscess, abdominal infection with an uncontrolled source and multiple surgeries, organs with abscesses/empyema, retention of CVC, polymicrobial septicemia including another gram-negative bacteria, gram-positive bacteria, or yeast, patients survival span is expected to be ≤ 48 hours, and regional zoonotic bacteria like.

Antimicrobials utilization protocol

Patients must have received antimicrobial therapy for at least 72 hours, and bacteria were appropriately sensitive to the prescribed antimicrobial(s). If bacteria under treatment were resistant to the initially used antibiotic(s) and were switched to proper therapy, the switch day would be the day the treatment started. Patients were followed up by phone calls up to ninety days from their hospital discharge, questions related to health conditions were carried out, and readmissions for reinfections or relapses? And if they died, the date of death? The three treatment durations for using antimicrobials were divided arbitrarily; the one-week included patients who were treated for up to 7 days, the two-week from 8 to 14 days, and the three-week from days 15 and more extended. Antibiotics were administered in the short infusion time method in the three hospitals. Two hospitals have a clinical pharmacist who assists in the antibiotic choice, administration, dosing, and dose modification, and the third is through the treating medical and surgical attending teams.

Statistical analysis

The patients' characteristics and features are described. The subdivision into the three treatment durations aims to minimize neighboring values associated with two durations. Each of the duration values was explored, and all assumed a normal subgroup distribution except for the three weeks duration; it was adjusted by neighboring values to remove outliers and corrected skewness and kurtosis with a normalizing Q-Q plot and boxplot. The Chi-square test for categorical variables estimated statistical significance for a difference in a characteristic and with a post hoc analysis by adjusted Bonferroni when a chi-square calculated P-value was significant for the individual part. The Mann-Whitney Wilcoxon test examined outcome differences among the three treatment durations, and the P-value is considered significant at <0.05. SPSS version 25 was used in the data analysis. The Charlson Comorbidity Score examined mortality prediction found. And severity was reviewed by Pitt Bacteremia Score found. Outcome measures: All-cause mortality for 28-day and 90-day after hospital discharge and the relapse and new infections for the three treatment durations were evaluated.

Results

Records were reviewed for 115 patients with non-fermenter gram-negative bacteremia; 45 were in the one-week treatment duration, 43 in the two-week, and 27 were in the three-week or more treatment duration. No significant difference in age means (P=0.514), and gender (P=0.133). No significant differences among comorbidities among the three treatment durations except for chronic lung disease (Bonferroni adjusted P=0.028), with higher ratios in the three-week duration. Body Mass Index (BMI) was subdivided into six categories according to CDC; there were no significant differences among the six categories for the three treatment durations (P=0.723). Functional status on the sepsis day was subdivided into four categories; they showed no significant differences among the patients' general functional conditions (P=0.328). Patients who were on antibiotics before their admissions for sepsis or in the hospital and were on some form of antibiotics before they developed sepsis showed no significant distribution difference among the three treatment groups (P=0.084), and the appropriateness of the prescribed antibiotics (P=0.079). Patients who required endotracheal tube ventilation (P=0.425), urinary catheters (P=0.066), and CVC (P=0.551) were not significantly different for the three treatment durations. Sources of bacteremia like abdomen, urinary, respiratory, skin, soft tissue, and primary bacteremia did not demonstrate significant differences (P=0.676) in the three treatment groups. Both Pitt's bacteremia score (P=0.694) and Charlson's comorbidity score (P=0.959) were not significantly different among the three treatment groups. Antimicrobial families used in the treatment of patients were similar in distribution among the three treatment groups except for β-lactam β-lactamases inhibitor (Adjusted Bonferroni P=0.027) and aminoglycosides (Adjusted Bonferroni P=0.032) were prescribed more in the three-week treatment group. The total of *Pseudomonas* and *Acinetobacter* did not significantly differ (P=0.175) among the three treatment groups (Table 1).

Characteristics	Duration of antibacterial treatment in patients with *Pseudomonas* and *Acinetobacter* bloodstream infections			
	Patients N=115			
	1 week n=45	2 weeks n=43	≥ 3weeks n=27	P
Age (Mean)	67.44	63.67	67.11	0.514
Gender				
Male	27	32	14	0.133
Female	18	11	13	
Comorbidities				
Diabetes	22	24	12	0.629
Hypertension	30	22	14	0.272

Steroids	15	17	15	0.174
Malignancy	11	12	5	0.672
Tobacco	12	14	7	0.777
Chronic lung disease	6	13	11	0.028@
Chronic liver disease	6	11	2	0.105
Chronic heart disease	23	16	9	0.250
Chronic gastrointestinal disease	5	8	9	0.067
CNS disease	12	10	5	0.731
Autoimmune disease	1	4	1	0.302
Body mass index				
<18.5	5	1	2	0.723
18.5 – 25	15	21	12	
>25 – 30	18	12	9	
>30 – 35	4	5	1	
>35 – 40	1	2	2	
>40	2	2	1	
Functional status at the time of sepsis				
Fully alert conscious	9	10	6	0.328
Some limitations include no assistance	5	1	3	
Partially disabled needs assistance	9	7	2	
Disabled bedridden	7	15	6	
Not available	15	10	10	
Pre-admission Antimicrobials	6	14	8	0.084
Appropriate antimicrobial(s)	24	13	13	0.079
Endotracheal tube ventilation	17	22	13	0.425
Central line	16	20	12	0.551
Urinary catheter	31	33	25	0.066
Bacterial Source				
Primary bacteremia	18	18	10	0.676
Central nervous system	2	0	1	
Respiratory	10	10	7	
Abdomen**	4	6	3	
Skin and soft tissues	2	1	2	
Urinary tract	5	6	3	
Pitt score	45	43	27	0.694
Charlson comorbidity score	45	43	23	0.959
Prescribed antibiotics				
B-lactame β-lactamases inhibitor	8	17	12	0.027@
Cephalosporines	10	9	11	0.139
Carbapenems	31	26	19	0.611
Quinolones	10	13	8	0.656
Aminoglycosides	9	11	13	0.032@
Tigecycline	4	8	6	0.256
Colistin	16	16	13	0.541
Non-Lactose fermenters				
Pseudomonas *Acinetobacter*	20 25	11 32	9 18	0.175

Note: @: The ratio is significantly higher for the ≥ 3 weeks; **Abdomen: intestines, peritoneal, pelvis, and hepatobiliary.

Table 1: Patient demographics in percentage (%).

The outcomes (Table 2) showed the 28-day all-cause mortality was significantly higher in the three-week duration group (P=0.019); post hoc analysis demonstrated that the ratio of the three weeks duration is more than the other two durations of treatment. The 90-day all-cause mortality was not significantly different among the three treatment durations (P=0.801), as well as relapse and new infections (P=1.0). The relapse rate was 3 (2.6%), and the new infection rate was 7 (6.0%). No significant difference was demonstrated (P>0.05) among the three treatment durations for each relapse of infection or a new infection (Table 2). The outcomes were reanalyzed, including the respiratory and no known sources (Primary bacteremia); there was a significant difference in the 28-day mortality (P=0.013), with post hoc analysis showing that the ratio of death was more in the three-week duration of treatment, but not a significant difference for the 90-day mortality (Table 3).

Outcomes	Duration of antibacterial therapy			
	One week n=45 (%)$	Two weeks n=43 (%)$	≥ 3 weeks n=27 (%)$	P#
28-day mortality*	3 (6.7)	3 (7.0)	7 (26.9)	0.019
90-day mortality*	31	31	18	0.801
Relapse of infection**	0	3	0	1.0
New infection**	1	3	3	1.0

Note: #Mann whitney wilcoxon test; $(%) were entered for cells to appreciate the ration difference in case P-value <0.05; *all-cause mortality; **Followed up to 90 days; *Patients ratio in the ≥ 3 weeks is significantly higher than the other two durations.

Table 2: Outcomes associated with different durations of therapy for patients with *Pseudomonas* and *Acinetobacter* bloodstream infections.

Outcomes	Duration of antibacterial therapy			
	One week n=45 (%)$	Two weeks n=43 (%)$	≥ 3 weeks n=27 (%)$	P#
28-day mortality*	2 (6.6%)	3 (10.7%)	6 (33.3%)	0.013
90-day mortality*	22	21	15	0.416
Relapse of infection**	0	2	0	----
New infection**	0	3	3	----

Note: #Mann whitney wilcoxon test; *all-cause mortality; **Followed up to 90 days; *Patients ratio in the ≥ 3 weeks is significantly higher than the other two durations.

Table 3: Outcomes associated with different durations of therapy for patients with *Pseudomonas* and *Acinetobacter* bloodstream infections, including the respiratory and no known source for the bacteremia (Primary).

Discussion

It is customary to treat LNF gram-negative bloodstream infections with more prolonged therapy duration than Enterobacteriaceae. Still, data to support the shorter duration of treatment is not undoubtedly available, and the issue is not resolved. For less severe cases, early clinic stability, documentation of bloodstream sterilization, and the use of biomarkers propose a shorter course of antimicrobial treatment [9]. A published study demonstrated that the efficacy for seven days and 14 days of treatment was similar for all-cause mortality, but LNF *(Acinetobacter and Pseudomonas)* contributed with low numbers in both the long and short treatment arms, which may have affected the difference in the effect size [10]. Several confounders and characteristics of our cohort were balanced for the three treatment durations (P>0.05), except for chronic lung disease (P=0.028), *Pseudomonas* or *Acinetobacter* have comparable distribution among the three treatment durations despite the overall relatively low counts (P=0.175). Previously recommended confounders to be incorporated in such study, including appropriateness of therapy, adjusting for severity by Pitt bacteremia score, and Charlson comorbidity score at the onset of treatment, was incorporated in our study [11]. Some measured sub-characteristics may have affected the study outcome through treatment choices, i.e., confounding bias by indication, like β-lactams β-lactamase inhibitors (P=0.027), and aminoglycosides used in combination (P=0.032), both all were used more in the three-week duration of treatment, but this may have minimally affected the results, quite the opposite, the use of aminoglycosides in combination in the three-week treatment duration may have prevented excess mortality from *Pseudomonas* bloodstream infection as in ICU and hematological neutropenic patients [12,13]. A bias toward better treatment success and reduced short-term mortality resulting from short versus prolonged antibiotics infusion times was not a concern as the contributing hospitals do not use the prolonged antibiotics infusion protocol for all patients with gram-negative bloodstream infections in the three treatment durations [14].

There was a significant difference in the mortality in the day-28 mortality (P=0.019), where more death in the three-week duration occurred despite using aminoglycosides in combination, possibly causing bias toward better survival in this duration group. All three treatment durations were similar in the 90-day mortality, relapse (P=1.0) and new infections (P=1.0). A sub-analysis of 76 patients, including respiratory and primary bloodstream infections, again demonstrated an increase in mortality for the three-week treatment duration in the 28-day (P=0.013) but no difference for the 90-day (P=0.416). In our study, the relapse rate in the LNF gram-negative bloodstream infections was 3%, and a new infection rate was 7%. This study at least suggests that a longer duration of antibiotics treatment for LNF gram-negative bloodstream infections was not associated with a better outcome, adding to this the association of a longer duration of therapy with decreased cost-effectiveness and increased bacterial resistance [15,16].

Conclusion

Implementing antibiotics treatment duration for LNF gram-negative bloodstream infections into one-week, two-week, and three-week treatment durations, showed that treatment in the three-week duration significantly increased all-cause mortality by 28-day but not 90-day, and the rates for relapse of the same bacteria and the infection with new bacteria were similar. In our attempt to lower cost, increase antibiotics' cost-effectiveness and minimize resistance, it is conceivable to propose the shorter appropriate treatment duration after customizing patients, i.e., uncomplicated septic patients, source-controlled patients, first-time infection and a relapse, less severe cases, early clinical stability, documentation of bloodstream sterilization, and the use of the biomarker.

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Conflict of Interest

None

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