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ORIGINAL RESEARCH

Duration of Treatment for *Pseudomonas aeruginosa* Bacteremia: a Retrospective Study

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ABSTRACT

Introduction: There is no consensus regarding optimal duration of antibiotic therapy for *Pseudomonas aeruginosa* bacteremia. We aimed to evaluate the impact of short antibiotic course.

Methods: We present a retrospective multicenter study including patients with *P. aeruginosa* bacteremia during 2009–2015. We evaluated outcomes of patients treated with short (6–-10 days) versus long (11–15 days) antibiotic courses. The primary outcome was a composite of 30-day mortality or bacteremia recurrence and/or persistence. Univariate and inverse probability treatment-weighted (IPTW) adjusted multivariate analysis for the primary outcome

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was performed. To avoid immortal time bias, the landmark method was used.

Results: We included 657 patients; 273 received a short antibiotic course and 384 a long course. There was no significant difference in baseline characteristics of patients. The composite primary outcome occurred in 61/384 patients in the long-treatment group (16%) versus 32/273 in the short-treatment group (12%) ($p = 0.131$). Mortality accounted for 41/384 (11%) versus 25/273 (9%) of cases, respectively. Length of hospital stay was significantly shorter in the short group [median 13 days, interquartile range (IQR) 9–21 days, versus median 15 days, IQR 11–26 days, $p = 0.002$]. Ten patients in the long group discontinued antibiotic therapy owing to adverse events, compared with none in the short group. On univariate and multivariate analyses, duration of therapy was not associated with the primary outcome.

Conclusions: In this retrospective study, 6–-10 days of antibiotic course for *P. aeruginosa* bacteremia were as effective as longer courses in terms of survival and recurrence. Shorter therapy was associated with reduced length of stay and less drug discontinuation.

Keywords: *Pseudomonas aeruginosa*; Bacteremia; Antibiotics; Duration; Antimicrobial stewardship

Key Summary Points

Pseudomonas aeruginosa bacteremia is a severe infection, often treated with long-course (~ 14 days) antibiotics.

We aimed to assess whether 6–10 days of antibiotics would be as effective as 11–15 days for this infection.

Data from 657 patients with *P. aeruginosa* bacteremia collected retrospectively demonstrated no association between duration of therapy and mortality or bacteremia recurrence.

Short therapy was associated with less drug discontinuation and shorter length of stay.

Short course of antibiotics (6–10 days) may be considered for *P. aeruginosa* bacteremia.

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INTRODUCTION

In recent years, evidence has accumulated to support short duration of antibiotic therapy for Gram-negative bacteremia in general. Several nonrandomized studies have demonstrated no difference in mortality or other outcomes between short (6–10 days) and longer therapy for Gram-negative bacteremia [1–6]. Three randomized controlled trials have also demonstrated noninferiority of 7 days antibiotic treatment compared with 14 days. The vast majority of these studies, however, included Enterobacterales [7–9]

Patients with *Pseudomonas aeruginosa* bacteremia are more likely to be neutropenic or have another immunosuppressive condition, and more likely to have hospital-acquired bacteremia compared with those with Enterobacterales bacteremia. The most common sources of bacteremia are pulmonary, central line-associated, urinary tract, and unknown source, with pulmonary source carrying worse prognosis [10–12]. Intrinsic resistance to some antibiotics, enhanced by tremendous ability to acquire resistance to others, in addition to paucity of available oral agents, makes this pathogen difficult to treat [13]. Hence, some recommend to use prolonged (≥ 14 days) antibiotic course to treat *P. aeruginosa* bacteremia [14]. Few data are available to guide the duration of antibiotic treatment for *P. aeruginosa* bacteremia. Two previous retrospective studies including ~ 540 patients in total demonstrated no difference in mortality or recurrence using 7–11 days of antibiotics compared with longer treatment of 12–21 days [11, 15].

We aimed to further investigate whether short-duration antibiotics is non-inferior to longer duration in cases of *P. aeruginosa* bacteremia.

METHODS

Data Collection and Patient Inclusion

We used a large database of *P. aeruginosa* bacteremia collected during 2009–2015 from nine countries, 25 centers [16]. The collection of data was approved by the medical ethical committees of each participating center. STROBE guidelines for reporting in epidemiological studies were followed for the reporting of the current study.

We included consecutive adult patients

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(age ≥ 18 years) hospitalized with *P. aeruginosa* bacteremia. Further details on patients' identification and data collection are published elsewhere [12, 16, 17]. For the current analysis, and considering previous studies [11, 15], we included patients who received at least 6 days of antibiotics and less than 16 days, assuming that patients with prolonged treatments probably had a complicated course, with confirmed/suspected metastatic foci of infection, and endovascular or osteoarticular infection. Patients receiving either monotherapy or combination therapy were included, excluding monotherapy with aminoglycosides, polymyxins, antipseudomonal penicillin, or initial oral fluoroquinolone treatment. Patients with step-down to oral fluoroquinolones following any duration of initial intravenous therapy were also included. We dichotomized the comparison to short (6–10 days) and longer therapy (11–15 days), considering any in vitro antibiotic courses (as above), administered in hospital and post-discharge.

We documented baseline patients characteristics (demographics, comorbidities), infection-related parameters (source, severity, susceptibility data), and management data—the latter included documentation of appropriateness of empirical treatment. Appropriate was defined as in vitro antibiotic courses administered withing 24 or 48 h (both were documented). Type of main definitive antibiotic therapy (i.e., administered according to susceptibility testing) and duration were documented as well. Outcomes were also collected, as below.

Outcomes

The primary outcome was a composite of mortality or recurrence/persistence of bloodstream infection within 30 days of positive blood culture, defined as: recurrence—positive blood cultures for *Pseudomonas* after negative ones; and persistence—positive blood cultures for *Pseudomonas* after more than 72 h of treatment, as documented in patient records. Recurrence/persistence was considered an outcome if occurring upon completion of antibiotic treatment.

Secondary outcomes included individual components of the primary outcome: length of hospital stay, *Clostridioides difficile*-associated diarrhea, and discontinuation of antibiotics due to adverse events. Detailed definitions of these outcomes were previously described [16].

Statistical Analysis

Categorical data are expressed as numbers and percentages. Continuous data are expressed as means with standard deviation (SD) or medians with interquartile range (IQR), as appropriate. The *t*-test was used for comparison of normally distributed variables, and Mann–Whitney test for abnormally distributed variables. Comparison of categorical variables was conducted using χ^2 test or Fisher's exact test, as appropriate. A propensity score for duration of therapy was calculated for each patient by adjusting for all pretreatment variables potentially confounding the duration of treatment. Variables used to estimate the propensity score are detailed in Supplementary Material. Assuming baseline differences between groups, we used inverse probability weighting to control for these differences. Standardized mean difference was used to check whether balance between the baseline characteristics was achieved; less than 10% difference was considered a reasonable balance. Weighted subjects were entered in the generalized estimating equation (GEE) binary logistics. To avoid immortal time bias, the landmark method was used. Landmark was set at day 11 to ensure no deaths occurred in the short treatment group (6–10 days). Missing values of covariates were handled by multiple imputation. The center was introduced as a random effect variable using GEE models. For model selection, we used the quasi-likelihood under the independence model criterion (QIC). Six models with varied subset of covariates were tested, and the model with the lowest QIC was selected.

Variables in the analyses were considered statistically significant if they had a

Table 1 Patient characteristics by duration of treatment group (short/long)

Variables	Short treatment $N = 273$	Long treatment $N = 384$	All cohort $N = 657$	p value
Age (years), $N = 655$ (median, 25–75%)	68 (57.5–79)	67 (54–76)	67 (55–77)	0.094
Weight (kg), $N = 369$ (median, 25–75%)	72.5 (60–82.25)	71 (60–85)	72 (60–83.8)	0.984
Height (m), $N = 326$ (mean ± SD)	1.69 ± 0.09	1.68 ± 0.09	1.69 ± 0.09	0.556
Gender (female)	102 (37.4%)	133 (34.6%)	235 (35.8%)	0.472
Department of hospitalization	**$N = 273$**	**$N = 383$**	**$N = 656$**	0.727
Non-ICU	233 (85.3%)	318 (83%)	551 (84%)	
ICU	40 (14.7%)	65 (17%)	105 (16%)	
Daily living activities	**$N = 215$**	**$N = 339$**	**$N = 554$**	
Completely able	102 (18.4%)	189 (34.1%)	291 (52.5%)	0.221
Limited activities	56 (26%)	79 (23.3%)	135 (24.4%)	
Need help with activities of daily living	47 (21.9%)	55 (16.2%)	102 (18.4%)	
Bedridden	10 (4.7%)	16 (4.7%)	26 (4.7%)	
Arrival from	**$N = 272$**	**$N = 381$**	**$N = 653$**	0.226
Home	225 (82.7%)	330 (86.6%)	555 (85%)	
Nursing home/LTCF	20 (7.4%)	27 (7.1%)	47 (7.2%)	
Another hospital	27 (9.9%)	24 (6.3%)	51 (7.8%)	
Previous hospitalization (90 days)	155 (58.1%)	206 (55.4%)	361 (56.5%)	0.501
Endotracheal	36 (13.2%)	51 (13.3%)	87 (13.2%)	0.972
Arterial line	38 (13.9%)	62 (16.2%)	100 (15.3%)	0.418
Central venous line	127 (46.5%)	183/382 (47.9%)	310 (47.3%)	0.726
Urinary catheter	112/271 (41.3%)	142/382 (37.2%)	254/653 (38.9%)	0.283
Any foreign body	52/271 (19.2%)	88/382 (23%)	140/653 (21.4%)	0.238
Chemotherapy previous 30 days	79 (28.9%)	111 (28.9%)	190 (28.9%)	0.993
Corticosteroids	69/272 (25.4%)	75/384 (19.5%)	144/656 (22%)	0.075
Previous surgery (90 days)	68 (24.9%)	103 (26.8%)	171 (26%)	0.582
Chronic dialysis	9 (3.3%)	17 (4.4%)	26 (4%)	0.481
Intravenous drug use	5/271(1.8%)	3 (0.8%)	8/655 (1.2%)	0.286
Neutropenia	56 (20.5%)	86 (22.4%)	142 (21.6%)	0.563
Charlson score (median, 25–75%)	4 (1–6)	4 (1.25–6)	4 (1–6)	0.499

Table 1 continued

Variables	Short treatment $N = 273$	Long treatment $N = 384$	All cohort $N = 657$	p value
Charlson score				
CHF	40 (14.7%)	49 (12.8%)	89 (13.5%)	0.485
Solid metastatic	34 (12.5%)	58 (15.1%)	92 (14%)	0.335
Hemiplegia	14 (5.1%)	28 (7.3%)	42 (6.4%)	0.264
Diabetes with end organ damage	36 (13.2%)	37 (9.6%)	73 (11.1%)	0.153
Dementia	19 (7%)	21 (5.5%)	40 (6.1%)	0.431
Moderate-to-severe renal disease	25 (9.2%)	49 (12.8%)	74 (11.3%)	0.150
Chronic pulmonary disease	42 (15.4%)	73 (19%)	115 (17.5%)	0.228
Mild liver disease	12 (4.4%)	13 (3.4%)	25 (3.8%)	0.505
Moderate-to-severe liver disease	6 (2.2%)	12 (3.1%)	18 (2.9%)	0.473
Rheumatic	22 (8.1%)	36 (9.4%)	58 (8.8%)	0.558
Any malignancy	115 (42.1%)	162 (42.2%)	277 (42.2%)	0.987
Place of acquisition				0.532
Unknown	13 (4.8%)	12 (3.1%)	25 (3.8%)	
Community	35 (12.8%)	43 (11.2%)	78 (11.9%)	
Healthcare associated*	74 (27.1%)	118 (30.7%)	192 (29.2%)	
Nosocomial	151 (55.3%)	211 (54.9%)	362 (55.1%)	
MDR *Pseudomonas*	20 (7.3%)	39 (10.2%)	59 (9%)	0.211
Aminoglycoside resistance	33 (12.1%)	55 (14.3%)	88 (13.4%)	0.407
Fluoroquinolone resistance	63 (23.1%)	77 (20.1%)	140 (21.3%)	0.346
Sepsis presentation				
Source of bacteremia				0.277
Unknown	68 (24.9%)	79 (20.6%)	147 (22.4%)	
Abdominal	17 (6.2%)	28 (7.3%)	45 (6.8%)	
Line associated	64 (23.4%)	104 (27.1%)	168 (25.6%)	
Pulmonary	40 (14.7%)	62 (16.1%)	102 (15.5%)	
Skin, soft tissue, bone, and joints	16 (5.9%)	25 (6.5%)	41 (6.2%)	
Urinary	67 (24.5%)	78 (20.8%)	145 (22.1%)	
Other	1 (0.4%)	8 (2.1%)	9 (1.4%)	
SOFA score, $N = 571$ (median, 25–75%)	3 (1–5)	3 (1–5)	3 (1–5)	0.172
Temperature, $N = 634$ (mean ± SD)	38.5 ± 0.94	38.5 ± 0.94	38.5 ± 0.94	0.562
Systolic blood pressure, $N = 616$ (mean ± SD)	103.47 ± 24.3	104.37 ± 22.7	104 ± 23.4	0.637

Table 1 continued

Variables	Short treatment $N = 273$	Long treatment $N = 384$	All cohort $N = 657$	p value
Diastolic blood pressure, $N = 517$ (median, 25–75%)	55 (49–65)	58 (49–64)	56 (49–64.5)	0.382
Leukocytes, $N = 641$ (median, 25–75%)	11 (2.25–17.7)	8.7 (2–15.3)	9.5 (2.03–15.8)	0.170
Neutrophils, $N = 566$ (median, 25–75%)	8.34 (1.02–13.8)	6.8 (1.1–13)	7.6 (1.09–13.2)	0.385
Creatinine, $N = 633$ (median, 25–75%)	1.06 (0.71–1.6)	1.01 (0.72–1.6)	1.03 (0.71–1.6)	0.887
Sepsis management				
Main treatment				
Antipseudomonal cephalosporin	81 (29.7%)	116 (30.2%)	197 (30%)	0.331
Antipseudomonal penicillin	129 (47.3%)	162 (42.2%)	291 (44.3%)	
Carbapenem	63 (23.1%)	106 (27.6%)	169 (25.7%)	
Appropriate empirical treatment (< 48 h)	207/247 (83.8%)	313/360 (86.9%)	520/607 (85.7%)	0.278
Appropriate empirical treatment (< 24 h)	179/247 (72.5%)	97/360 (73.1%)	442/607 (72.8%)	0.873
Combination therapy	50 (18.3%)	69 (18%)	119 (18.1%)	0.910
Treatment duration (median, 25–75%)	8 (7–10)	13 (12–14)	11 (9–14)	< 0.001

ICU intensive care unit, *LTCF* long-term care facility, *CHF* congestive heart failure, *MDR* multidrug resistant
*Healthcare-associated bacteremia was defined as any patient coming from long-term care facility center, home intravenous or wound care previous 30 days, hemodialysis patients, previous ≥ 2 days hospitalization during last 90 days; nosocomial bacteremia was defined as onset after ≥ 48 h of hospitalization

p value < 0.05. All statistical analyses were conducted using SPSS program.

RESULTS

In the original database, 2396 patients were included. Of these, 657 patients were treated for 6–15 days with an in vitro course of antipseudomonal therapy that fulfilled our inclusion criteria above (see Supplemental Fig. 1 for flow chart of patient selection). Median age was 67 years [interquartile range (IQR) 55–77 years], and 234 (35.8%) were females. Of these patients, 273 received antipseudomonal regimen for 6–10 days (short course), and 384 received 11–15 days (long course). Overall, median treatment duration in the entire cohort was 11 days (IQR 9–14 days), with the short-arm median duration being 8 days (7–10 days) and the long arm 13 days (12–14 days, $p < 0.001$). Baseline characteristics of patients by duration of therapy are presented in Table 1. Variables included in the propensity score are detailed in Supplementary Material, with standardized mean difference of the original and weighted cohort.

No significant differences were documented in either demographic data, infection characteristics, or treatment between patients receiving short or long therapy. Sources of bacteremia were also similar between groups (Table 1). A trend for older age and more frequent use of corticosteroids was observed in the short-duration group, though nonsignificant [median age 68 years, interquartile range (IQR) 57.5–79 years versus 67 years (54–76 years), $p = 0.075$; corticosteroids 69/272, 25.4% versus 75/384, 19.5%,

Table 2 Outcomes by duration of treatment group (short/long)

Variable	Short treatment $N = 273$	Long treatment $N = 384$	All cohort $N = 657$	p value
30-Day mortality*	25 (9.2%)	41 (10.7%)	66 (10%)	0.523
Days of hospital stay—entire cohort, $N = 544$ (median, 25–75%)	13 (9–21)	15 (11–26)	15 (10–23)	**0.002**
Fever duration, $N = 562$ (median, 25–75%)	2 (1–3)	1 (1–3)	2 (1–3)	0.280
Recurrent/persistent bacteremia*	8/264 (3%)	21/375 (5.6%)	29/639 (4.5%)	0.124
Adverse events				0.398
Renal failure	$N = 265$	$N = 372$	$N = 637$	
No	240 (90.6%)	328 (88.2%)	568 (89.2%)	
Risk	12 (4.5%)	23 (6.2%)	35 (5.5%)	
Injury	4 (1.5%)	11 (3%)	15 (2.4%)	
Failure	6 (2.3%)	3 (0.8%)	9 (1.4%)	
Loss	2 (0.8%)	5 (1.3%)	7 (1.1%)	
End stage kidney disease	1 (0.4%)	2 (0.5%)	3 (0.5%)	
Clostridioides difficile	10/270 (3.7%)	9/379 (2.4%)	19/649 (2.9%)	0.322
Drug discontinuation d/t adverse events	0	10 (2.8%)	10 (1.6%)	0.006

GNR Gram-negative rods

*Mortality and recurrence/persistence do not sum up because one patient in each group died following a case of recurrence/persistence

$p = 0.094$]. Multidrug-resistant (MDR) *P. aeruginosa* rates were similar between groups (short 20 (7.3%) versus long 39 (10.2%), $p = 0.211$) (Table 1).

The primary outcome of mortality or recurrence/persistence occurred overall in 93 patients, 61/384 in the long-duration group (15.9%) and 32/273 in the short-duration group (11.7%) ($p = 0.131$). Components of the primary outcome were without significant difference between groups (Table 2). All-cause mortality at 30 days was 41 (10.7%) among those treated with longer duration, compared with 25 (9.2%) among patients treated with short antibiotic course ($p = 0.523$). Repeated blood cultures were obtained from 105 patients, 69/384 (18%) in the long treatment group and 36/273 (13.2%) in the short arm ($p = 0.11$). Positive repeated cultures, indicating recurrence/persistence, were demonstrated among 21/375 (5.6%) long-arm patients versus 8/264 (3%) short-arm patients ($p = 0.124$). Length of hospital stay was significantly shorter in the short-duration group (median 13 days, IQR 9–-21 days, versus 15 days, IQR 11–26 days, $p = 0.002$). Drug discontinuation due to adverse events was significantly more common in the long-duration group, with ten cases compared with none in the short treatment group ($p = 0.006$). These ten cases included five cases of discontinuation of β-lactams and five

quinolones. Similar rates of *C. difficile* were observed between the groups (Table 2).

Univariate analysis for risk factors for the composite outcome of mortality or recurrence is described in Table 3. Arrival to hospital from another institution (nursing home or another hospital); metastatic malignancy; previous hospitalization within 90 days; nasogastric tube or urinary catheter at bacteremia onset; higher sequential organ failure assessment (SOFA) score; and lower systolic blood pressure were significantly associated with the primary outcome. MDR *P. aeruginosa* rates, early appropriate empirical antibiotic therapy, and combination therapy rates were nonsignificantly different. Duration of therapy (short versus long) was not associated with this outcome (Table 3). Multivariate analysis demonstrated baseline metastatic malignancy [odds ratio (OR) 2.5, 95% confidence interval (CI) 1.36–4.6]; higher SOFA score (OR 1.1, 95% CI 1.01–1.2); and presence of nasogastric tube (OR 2.11, 95% CI 1.18–3.74) as predictors of mortality or recurrence. Duration of treatment was not significantly associated with the primary outcome in this analysis (OR 1.66, 95% CI 0.94–2.95) [Table 4; odds ratio > 1 represents higher risk for the composite outcome with long-duration therapy (not statistically significant)].

DISCUSSION

In this multinational, multicenter study including 657 patients with *P. aeruginosa* bacteremia, we did not find a strong association between duration of therapy and the composite outcome of mortality or recurrence/persistence of infection among patients treated with 6–-10 days antibiotic course compared with a longer course of 11–15 days. Mortality at 30 days was similar (9.2% with short antibiotic course and 10.7% with longer duration, $p = 0.523$). Duration of hospital stay was significantly shorter in the short-duration group, and discontinuation of antibiotics due to adverse events was significantly more common in the long-duration group. No significant differences were observed for *C. difficile*-associated diarrhea rates. Predictors of the composite outcome of mortality or recurrence in multivariate analysis included baseline metastatic malignancy, and a more severe clinical presentation of infection, represented by a higher SOFA score, and probably more severe baseline condition, represented by a nasogastric tube. Duration of treatment (short or long) was not a significant predictor.

These findings are in accordance with previous results of two smaller, retrospective, single-country studies from the USA and South Korea. Fabre et al. included 249 patients with *P. aeruginosa* bacteremia, 69 of whom received short-duration therapy of 7–11 days and 180 of whom received longer regimens of 12–21 days. No difference in rates of death or recurrent infection within 30 days were demonstrated between short and long therapy in this study. Length of hospital stay was significantly shorter in the short-duration group, similar to our findings. [11] Similarly, Bae et al. evaluated 290 patients with *P. aeruginosa* bacteremia, 97 of whom received short-course therapy (7–11 days) and 193 of whom received 12–21 days of therapy. This study also found no significant difference in mortality or recurrence between groups.

In recent years, shortening the duration of antibiotic therapy has become an important backbone of antibiotic stewardship. Potential benefits are reduction in adverse events, cost, superinfections including fungal infection and *C. difficile*, and prevention of resistance development. Shorter antibiotic courses have been demonstrated effective in randomized controlled trials for the treatment of various respiratory infections, urinary tract infections, intraabdominal infections, and others [18]. Specifically for uncomplicated Gram-negative bacteremia, three recent randomized controlled trials have demonstrated noninferiority of 7 days antibiotic course compared with 14 days [7–9]. However, only one of these trials included nonfermenters, with limited number of *P. aeruginosa* cases [7]; and immunocompromised patients were excluded from one trial [8] and constituted less than one-fourth of patients in the other trials [7, 9]. *P. aeruginosa* bacteremia is frequently hospital acquired, and occurs in patients who are immunocompromised, critically ill, or with chronic underlying medical

Table 3 Univariate analysis for risk factors for the primary outcome—mortality/recurrence

Variable	Mortality/recurrence (no) *N* = 552	Mortality/recurrence (yes) *N* = 105	*p* value
Age (years), *N* = 655 (median, 25–75%)	67 (55–78)	68 (55–76)	0.951
Weight (kg), *N* = 356 (median, 25–75%)	72 (60–84.1)	70 (61–82)	0.613
Height (m), *N* = 326 (mean ± SD)	1.68 ± 0.09	1.7 ± 0.08	0.272
Gender (female)	199 (36.1%)	36 (34.3%)	0.729
Department of hospitalization	N = 551	N = 105	0.931
Non-ICU	464 (84.2%)	87 (82.9%)	
ICU	87 (15.8%)	18 (17.1%)	
Daily living activities	N = 462	N = 92	0.337
Completely able	248 (53.7%)	43 (46.7%)	
Limited activities	113 (24.5%)	22 (23.9%)	
Need help with activities of daily living	82 (17.7%)	20 (21.7%)	
Bedridden	19 (4.1%)	7 (7.6%)	
Arrival from	N = 550	N = 103	0.141
Home	473 (86%)	82 (79.6%)	
Nursing home/LTCF	35 (6.4%)	12 (11.7%)	
Another hospital	42 (7.6%)	9 (8.7%)	
Residency—home	473 (85.7%)	82 (78.1%)	0.049
Previous hospitalization (90 days)	296/539 (54.9%)	65/100 (65%)	0.062
Endotracheal	69 (12.5%)	18 (17.1%)	0.198
Arterial line	84/550 (15.3%)	16 (15.2%)	0.993
Central venous line	251/550 (45.6%)	59 (56.2%)	0.047
Urinary catheter	205/549 (37.3%)	49/104 (47.1%)	0.061
Any foreign body	117/549 (21.3%)	23/104 (22.1%)	0.855
Chemotherapy previous 30 days	156 (28.3%)	34 (32.4%)	0.393
Steroids	120/551 (21.8%)	24 (22.9%)	0.807
Previous surgery (90 days)	139 (25.2%)	32 (30.5%)	0.257
Chronic dialysis	23 (4.2%)	3 (2.9%)	0.784
Intravenous drug use	5 (0.9%)	3 (2.9%)	0.119
Neutropenia	119 (21.6%)	23 (21.9%)	0.937
Charlson score (median, 25–75%)	4 (1–6)	4 (2–6)	0.328

Table 3 continued

Variable	Mortality/recurrence (no) $N = 552$	Mortality/recurrence (yes) $N = 105$	p value
Charlson score			
CHF	72 (13%)	17 (16.2%)	0.388
Solid metastatic	67 (12.1%)	25 (23.8%)	**0.002**
Hemiplegia	38 (6.9%)	4 (3.8%)	0.283
Diabetes with end organ damage	64 (11.6%)	9 (8.6%)	0.366
Dementia	32 (5.8%)	8 (7.6%)	0.474
Moderate-to-severe renal disease	63 (11.4%)	11 (10.5%)	0.781
Chronic pulmonary disease	101 (18.3%)	14 (13.3%)	0.220
Mild liver disease	19 (3.4%)	6 (5.7%)	0.265
Moderate-to-severe liver disease	15 (2.7%)	3 (2.9%)	1
Rheumatic	51 (9.2%)	7 (6.7%)	0.394
Any malignancy	229 (41.5%)	48 (45.7%)	0.421
Place of acquisition			0.239
Unknown	22 (4%)	3 (2.9%)	
Community	71 (12.9%)	7 (6.7%)	
Healthcare associated	162 (29.3%)	30 (28.6%)	
Nosocomial	297 (53.8%)	65 (61.9%)	
Place of acquisition—healthcare/nosocomial	459 (83.2%)	95 (90.5%)	0.058
MDR *Pseudomonas*	49 (8.9%)	10 (9.5%)	0.832
Aminoglycosides Resistance	72 (13%)	16 (15.2%)	0.545
Sepsis presentation			
Source of bacteremia			0.404
Unknown	120 (21.7%)	27 (25.7%)	
Abdominal	38 (6.9%)	7 (6.7%)	
Line associated	141 (25.5%)	27 (25.7%)	
Pulmonary	81 (14.7%)	21 (20%)	
Skin, soft tissue, bone, and joints	38 (6.9%)	3 (2.9%)	
Urinary	127 (23%)	18 (17.1%)	
Other	7 (1.3%)	2 (1.9%)	
SOFA score, $N = 571$ (median, 25–75%)	3 (1–5)	4 (2–6)	**0.002**
Temperature, $N = 634$ (mean ± SD)	38.5 ± 0.95	38.4 ± 0.86	0.758

Table 3 continued

Variable	Mortality/recurrence (no) $N = 552$	Mortality/recurrence (yes) $N = 105$	p value
Systolic blood pressure, $N = 616$ (mean ± SD)	105.2 ± 23.6	97.9 ± 21.6	0.004
Diastolic blood pressure, $N = 517$ (median, 25–75%)	58 (50–65)	53 (45–64)	0.129
Leukocytes, $N = 641$ (median, 25–75%)	9.5 (2.08–16.1)	9.2 (1.8–15.4)	0.913
Neutrophils, $N = 566$ (median, 25–75%)	7.6 (1.08–13.2)	7 (1.12–13.4)	0.898
Creatinine, $N = 633$ (median, 25–75%)	1.02 (0.71–1.6)	1.07 (0.74–1.76)	0.681
Treatment			
Duration of treatment—long	318 (57.6%)	66 (62.9%)	0.317
Appropriate empirical treatment (< 24 h)	365/505 (72.3%)	77/102 (75.5%)	0.506
Appropriate empirical treatment (< 48 h)	430/505 (85.1%)	90/102 (88.2%)	0.417
Combination therapy	104 (18.8%)	15 (14.3)	0.267

ICU intensive care unit, *LTCF* long-term care facility, *CHF* congestive heart failure, *MDR* multidrug resistant

Table 4 Risk factors for a composite outcome; multivariate generalized linear models (generalized estimating equation), adjusted by inverse propensity score weighting

Risk factor	Univariate analysis OR (95% CI)	Multivariate logistic regression analysis OR (95% CI)
Propensity score	–	0.33 (0.08–1.4)
Duration of treatment—long	1.42 (0.89–2.25)	1.66 (0.94–2.95)
Residency—home	0.62 (0.36–1.07)	0.67 (0.35–1.26)
Solid metastatic	2.35 (1.38–4.02)	2.5 (1.36–4.6)
Previous hospitalization	1.52 (0.95–2.43)	1.47 (0.86–2.5)
SOFA score	1.14 (1.05–1.23)	1.1 (1.01–1.2)
Nasogastric tube	2.26 (1.32–3.86)	2.11 (1.18–3.74)
Systolic blood pressure	1.14 (1.05–1.23)	0.99 (0.98–1.0)

$N = 657$, QIC 940.85, constant $\beta = 0.043$

As nasogastric tube and urinary catheter at presentation probably represent similarly baseline patient condition, only one was selected for multivariable analysis

Odds ratio > 1 correlates with higher risk for the composite outcome

OR odds ratio, *CI* confidence interval

conditions. Antibiotic resistance is common, and mortality is high [19]. Consequently, traditional duration of therapy is considered by some to be 14 days [11, 15]. Our results, accompanied by previous studies, support the use of shorter duration of therapy.

Rac et al. proposed using a combination of several vital signs and laboratory values at

72–96 h after Gram-negative bacteremia onset as early clinical failure criteria. These were suggested as a tool to guide treatment duration in a personalized approach [20]. Considering this, and our results, supporting the safety of shorter therapy, further studies may test this approach for *P. aeruginosa* bacteremia.

Limitations of our study are its retrospective design, with data collected until 2015. Though propensity score weighting was used to adjust for differences between groups, residual bias cannot be excluded. In addition, patients treated for more than 15 days were excluded, assuming a complicated infection, without detailed documentation of these complications, owing to the retrospective nature of this study. The comparison of duration ranges (6–10 days versus 11–15 days), rather than a fixed duration (e.g., 7 or 14 days), limits our ability to provide a specific recommended duration that is safe and effective. It also selects for a specific population, possibly limiting the generalizability of our results for any patient with *P. aeruginosa* bacteremia. Since the study was retrospective, the outcome of recurrent and/or persistent bacteremia was not based on a preplanned culture collection schedule, rather the practice used in each center according to the patient's clinical condition. In addition, data regarding source control are lacking. Since we excluded patients treated more than 15 days, we assume that most cases without appropriate source control were not included in this analysis, though this could not be verified. Another limitation lies in the use of the landmark method, which disregards patients who died/were censored before the landmark and restricts implementation of results to included patients. This inclusion only of patients who survived at least 11 days may produce a bias favoring the short therapy. The propensity score analysis for this study on duration may have better used variables of days 6–7, trying to mimic a randomized controlled trial recruiting at that point. However, these variables were missing for a considerable portion of patients as well as, when available, probably reflecting sicker patients still hospitalized and tested. Considering these limitations, randomized controlled trials are needed to test our findings, and are the optimal design to solve this clinical question.

CONCLUSIONS

In this retrospective study, for patients with *P. aeruginosa* bacteremia, we did not demonstrate a difference in clinical outcomes between patients treated with 6–10 days antibiotics compared with longer courses. Duration of hospital stay was shorter and adverse events leading to drug discontinuation were less common among patients treated with a shorter course. Prospective studies, ideally randomized controlled trials, should be designed to test shorter antibiotic therapy for *P. aeruginosa* bacteremia, and define subgroups of patients who would benefit most from this approach.

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Compliance with Ethics Guidelines. The study was approved by the local ethical committees of each participating center, which waved informed consent due to the retrospective nature of the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request, and with agreement of all contributing authors.

REFERENCES

1. Chotiprasitsakul D, Han JH, Cosgrove SE, Harris AD, Lautenbach E, Conley AT, et al. Comparing the outcomes of adults with Enterobacteriaceae bacteremia receiving short-course versus prolonged-course antibiotic therapy in a multicentre, propensity score-matched cohort. Clin Infect Dis. 2018;66:172–7. https://doi.org/10.1093/cid/cix767.

2. Sousa A, Pérez-Rodríguez MT, Suárez M, Val N, Martínez-Lamas L, Nodar A, et al. Short- versus long-course therapy in Gram-negative bacilli bloodstream infections. Eur J Clin Microbiol Infect Dis. 2019;38:851–7. https://doi.org/10.1007/s10096-019-03467-5.

3. Giannella M, Pascale R, Toschi A, Ferraro G, Graziano E, Furii F, et al. Treatment duration for *Escherichia coli* bloodstream infection and outcomes: retrospective single-centre study. Clin Microbiol Infect. 2018;24:1077–83. https://doi.org/10.1016/j.cmi.2018.01.013.

4. Doi A, Morimoto T, Iwata K. Shorter duration of antibiotic treatment for acute bacteraemic cholangitis with successful biliary drainage: a retrospective cohort study. Clin Microbiol Infect. 2018;24:1184–9. https://doi.org/10.1016/j.cmi.2018.01.021.

5. Uno S, Hase R, Kobayashi M, Shiratori T, Nakaji S, Hirata N, et al. Short-course antimicrobial treatment for acute cholangitis with Gram-negative bacillary bacteremia. Int J Infect Dis. 2017;55:81–5. https://doi.org/10.1016/j.ijid.2016.12.018.

6. Nelson AN, Justo JA, Bookstaver PB, Kohn J, Albrecht H, Al-Hasan MN. Optimal duration of antimicrobial therapy for uncomplicated Gram-negative bloodstream infections. Infection. 2017;45:613–20. https://doi.org/10.1007/s15010-017-1020-5.

7. Yahav D, Franceschini E, Koppel F, Turjeman A, Babich T, Bitterman R, et al. Seven versus fourteen days of antibiotic therapy for uncomplicated Gram-negative bacteremia: a non-inferiority randomized controlled trial. Clin Infect Dis. 2018. https://doi.org/10.1093/cid/ciy1054.

8. von Dach E, Albrich WC, Brunel A-S, Prendki V, Cuvelier C, Flury D, et al. Effect of C-reactive protein-guided antibiotic treatment duration, 7-day treatment, or 14-day treatment on 30-day clinical failure rate in patients with uncomplicated Gram-negative bacteremia: a randomized clinical trial. JAMA. 2020;323:2160–9. https://doi.org/10.1001/jama.2020.6348.

9. Molina J, Montero-Mateos E, Praena-Segovia J, León-Jiménez E, Natera C, López-Cortés LE, et al.

Seven-versus 14-day course of antibiotics for the treatment of bloodstream infections by Enterobacterales: a randomized, controlled trial. Clin Microbiol Infect. 2021. https://doi.org/10.1016/j.cmi.2021.09.001.

10. Choi Y, Paik JH, Kim JH, Han SB, Durey A. Clinical predictors of *Pseudomonas aeruginosa* bacteremia in emergency department. Emerg Med Int. 2018;2018:7581036. https://doi.org/10.1155/2018/7581036.

11. Fabre V, Amoah J, Cosgrove SE, Tamma PD. Antibiotic therapy for *Pseudomonas aeruginosa* bloodstream infections: how long is long enough? Clin Infect Dis. 2019. https://doi.org/10.1093/cid/ciz223.

12. Babich T, Naucler P, Valik JK, Giske CG, Benito N, Cardona R, et al. Risk factors for mortality among patients with *Pseudomonas aeruginosa* bacteraemia: a retrospective multicentre study. Int J Antimicrob Agents. 2019. https://doi.org/10.1016/j.ijantimicag.2019.11.004.

13. Herrera S, Bodro M, Soriano A. Predictors of multidrug resistant *Pseudomonas aeruginosa* involvement in bloodstream infections. Curr Opin Infect Dis. 2021;34:686–92. https://doi.org/10.1097/QCO.0000000000000768.

14 Kanj S, Sexston D. *Pseudomonas aeruginosa* bacteremia and endocarditis. Waltham: Up To Date; 2021.

15. Bae M, Jeong Y, Bae S, Kim MJ, Chong YP, Kim S-H, et al. Short versus prolonged courses of antimicrobial therapy for patients with uncomplicated *Pseudomonas aeruginosa* bloodstream infection: a retrospective study. J Antimicrob Chemother. 2021. https://doi.org/10.1093/jac/dkab358.

16. Babich T, Naucler P, Valik JK, Giske CG, Benito N, Cardona R, et al. Ceftazidime, carbapenems, or piperacillin–tazobactam as single definitive therapy for *Pseudomonas aeruginosa* bloodstream infection—a multi-site retrospective study. Clin Infect Dis. 2019. https://doi.org/10.1093/cid/ciz668.

17. Babich T, Naucler P, Valik JK, Giske CG, Benito N, Cardona R, et al. Combination versus monotherapy as definitive treatment for *Pseudomonas aeruginosa* bacteraemia: a multicentre retrospective observational cohort study. J Antimicrob Chemother. 2021;76:2172–81. https://doi.org/10.1093/jac/dkab134.

18. Spellberg B, Rice LB. Duration of antibiotic therapy: shorter is better. Ann Intern Med. 2019;171:210–1. https://doi.org/10.7326/M19-1509.

19. Bassetti M, Vena A, Croxatto A, Righi E, Guery B. How to manage *Pseudomonas aeruginosa* infections. Drugs Context. 2018;7: 212527. https://doi.org/10.7573/dic.212527.

20. Rac H, Gould AP, Bookstaver PB, Justo JA, Kohn J, Al-Hasan MN. Evaluation of early clinical failure criteria for Gram-negative bloodstream infections. Clin Microbiol Infect. 2020;26:73–7. https://doi.org/10.1016/j.cmi.2019.05.017.

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