Clinical Infectious Diseases

BRIEF REPORT

Antibiotic Therapy for *Pseudomonas aeruginosa* Bloodstream Infections: How Long Is Long Enough?

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In a multicenter, observational, propensity-score–weighted cohort of 249 adults with uncomplicated *Pseudomonas aeruginosa* bacteremia, patients receiving short-course (median, 9 days; interquartile range [IQR], 8–10) therapy had a similar odds of recurrent infection or death within 30 days as those receiving longer courses (median, 16 days; IQR, 14–17).

Keywords. gram-negative bacteremia; treatment duration; *Pseudomonas aeruginosa*; piperacillin-tazobactam; cefepime.

Rising rates of antibiotic resistance, impacts on the intestinal microbiome, and antibiotic-associated adverse events [1] have stimulated an interest in reevaluating frequently prescribed durations of antibiotic therapy for bacterial infections. A growing body of evidence suggests durations of therapy that are shorter than those commonly prescribed are as effective as longer durations of antibiotic therapy for infections such as community-acquired pneumonia [2, 3], ventilator-associated pneumonia [4, 5], urinary tract infections [6], cellulitis [7], and intra-abdominal infections [8].

In a randomized, controlled trial that included 604 patients with gram-negative bloodstream infections (BSI), including both *Enterobacteriaceae* and glucose nonfermenting gram-negative organisms (eg, *Pseudomonas aeruginosa*), it was found that patients treated with 7 days of antibiotics, in the setting of appropriate source control, had outcomes comparable to those who received 14 days of therapy [9]. In the aforementioned trial, it was not possible to determine if the findings are generalizable to patients with pseudomonal BSI as there were few patients infected with *P. aeruginosa* (28 patients in the 7-day group and 20 patients in the 14-day group). Additionally, patients infected with *P. aeruginosa* often have underlying medical conditions, sources of infection, and severity of illness that are different from those in patients infected with *Enterobacteriaceae*, leading clinicians to frequently treat *P. aeruginosa* infections more aggressively [10]. Our objective was to determine if short courses of antibiotic therapy are associated with similar clinical outcomes as found in prolonged courses of therapy for adults with uncomplicated pseudomonal BSI.

METHODS

Study Population

All patients aged ≥18 years with a positive blood culture for *P. aeruginosa* admitted to 5 hospitals in the Johns Hopkins Health System between 1 July 2016 and 30 October 2018 were evaluated for inclusion. The primary exposure was a short course of therapy. After visual inspection of the durations of therapy prescribed, short course was defined as 7–11 days of antibiotics (Supplementary Figure 1).

Patients who met any of the following conditions were excluded: BSI complicated by osteoarticular infections, endocarditis/endovascular infections, or central nervous system infections; receipt of less than 7 days of antibiotic therapy; failure to receive an agent with in vitro activity (ie, susceptible using the Clinical and Laboratory Standards Institute criteria [11]) against the isolated organism for all consecutive days of the treatment course (ie, the day of blood culture collection to the completion of antibiotic therapy); receipt of aminoglycoside monotherapy during any portion of the treatment course; or inability to complete the planned course of therapy due to death or transition to hospice care. Furthermore, any patient who received more than 21 days of antibiotic therapy was excluded in the event that there was a metastatic foci of infection that might not have been identified or well documented in the medical records, warranting a prolonged treatment course.

Outcomes

The primary outcome was a composite outcome that included recurrent *P. aeruginosa* infection or death, both within 30 days of discontinuing antibiotic therapy. The day after discontinuation of antibiotic therapy was selected as the first day for which the evaluation of clinical outcomes occurred to ensure a similar observation period for both treatment groups. As an example, for a patient who received 8 days of therapy, the period for observation of the primary outcome was day 9 to day 39. For a patient who received 15 days of therapy, the period of observation for the primary outcome was day 16 to day 46. Two physicians, blinded to the duration of therapy prescribed, independently determined whether any subsequent *P. aeruginosa* cultures represented true infection or colonization.

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Data Collection

Information regarding demographics, preexisting medical conditions, source of BSI and source control measures, severity of illness, microbiology data, and antibiotic treatment was collected by chart review for all patients. Adequate source control, defined as the removal of any infected hardware or devices, drainage of infected fluid collections, or resolution of biliary or urinary obstruction during the course of antibiotic therapy, was independently adjudicated by 2 infectious diseases physicians. The Epic Care Everywhere network that includes inpatient and outpatient records from a large number of healthcare facilities in the United States was reviewed for all patients to identify relevant postdischarge data.

Statistical Analyses

Baseline categorical data were compared using the χ^2 test, and continuous data were compared using the Wilcoxon rank sum test. To balance differences with respect to baseline characteristics between the 2 groups, inverse probability of treatment weighting was performed [12]. Using multivariable logistic regression, propensity scores were created for each patient with the dependent variable being a binary outcome of duration of therapy. Covariates used for generating propensity scores included age, gender, chemotherapy within the previous 6 months, hematologic stem-cell transplantation (HSCT) within the previous 12 months, absolute neutrophil count (ANC) <500/μL on day 1 of BSI, AIDS, ≥10 mg per day of corticosteroids for longer than 2 weeks or immunomodulatory therapy, source of BSI, appropriate source control, Pitt bacteremia score on day 1 of BSI, intensive care unit status on day 1 of BSI, combination therapy longer than 48 hours, and transition to oral step-down therapy.

Patients who received short-course antibiotic treatment were weighted by the inverse of the propensity score, and those who received prolonged courses were weighted by the inverse of 1 minus the propensity score. A new weighted pseudopopulation was created in which individuals who received a duration of therapy outside of the anticipated range were given an increased weight, whereas individuals who received an expected duration of therapy were given a decreased weight as they were already adequately represented in their exposure group. Weights were stabilized to increase precision by reducing the influence of extreme weights (ie, patients who were significantly "upweighted" or "downweighted"). Baseline characteristics were considered balanced if standardized difference values were less than 10%. In the final analysis, odds ratios (ORs) and 95% confidence intervals (CIs) for the composite outcome were estimated using weighted regression, adjusting for variables with standardized differences greater than 10%. A 2-sided P value < .05 was considered statistically significant for all tests. Statistical analysis was completed using STATA version 13.0 (StataCorp, College Station, TX).

RESULTS

Overall, 366 patients with *P. aeruginosa* BSI were evaluated (Supplementary Figure 2). Of the 249 patients who met eligibility criteria, 69 (28%) received short-course therapy (median, 9 days; interquartile range [IQR], 8–10) and 180 (72%) received prolonged therapy (median, 16 days; IQR, 14–17). Clinical characteristics of the unweighted and weighted cohorts are shown in Table 1. Baseline clinical characteristics of the weighted cohort were well balanced, with the exception of pulmonary source of infection, which had greater representation in the short-course therapy group (Supplementary Figure 3). Appropriate source control was achieved in approximately 94% of patients in both treatment groups. All cases without source control consisted of retained central venous catheters. The median duration of bacteremia was 1 day (IQR, 1-1) for both the short-course and prolonged-course groups.

Antibiotics prescribed as culture-directed therapy included piperacillin/tazobactam (31%), cefepime (29%), ciprofloxacin (24%), meropenem (12%), and ceftazidime (4%). Overall, 27 (37%) patients in the short-course and 63 (35%) in the prolonged-course groups transitioned to an oral fluoroquinolone during their treatment course, with the median day of transition being 5 days for the short-course group and 6 days for the prolonged-course group. For both groups, 36% of patients completed the recommended treatment course as an outpatient.

In the weighted cohort, the primary outcome of recurrent *P. aeruginosa* infection at any site or mortality within 30 days of completing therapy occurred in 10 (14%) patients in the short-course group and in 24 (13%) in the prolonged-course group (OR, 1.06; 95% CI, 0.42–2.68; P = .91). More specifically, 5 (7%) patients in the short-course group and 20 (11%) in the prolonged-course group had a recurrent infection within 30 days of discontinuing antibiotics, and 5 (7%) patients in the short-course group and 6 (4%) in the prolonged-course group died within 30 days of discontinuing antibiotics (P > .05 for both). On average, patients who received short-course therapy spent 4 fewer days in the hospital (from the time of blood culture collection to hospital discharge) compared to patients who received longer courses (4.04 days; 95% CI, 1.25–6.83 days; P = .005).

DISCUSSION

In this multicenter, observational, propensity-score–weighted cohort of 249 adults with *P. aeruginosa* BSI, there was no difference in death or recurrent infection within 30 days of completing antibiotic therapy regardless of whether patients were treated with a short course (median, 9 days) or prolonged course (median, 16 days) of antibiotics. Moreover, patients treated with shorter courses were discharged from the hospital approximately 4 days sooner than those who remained on longer courses of intravenous therapy. Similar to what has been

Table 1. Demographic and Clinical Features of 249 Patients Who Received Short-course (7–11 Days) or Prolonged-course (12–21 Days) Antibiotic Therapy for *Pseudomonas aeruginosa* Bloodstream Infections Before and After Inverse Probability of Treatment Weighting

	Full Cohort				Weighted Cohort[a]			
Characteristic	Short Course (n = 69; 28%)	Prolonged Course (n = 180; 72%)	*P* Value	Standardized Differences	Short Course Weighted (n = 72; 28.6%)	Prolonged Course Weighted (n = 179; 71.4%)	*P* Value	Standardized Differences
Age, median (IQR), y	61 (48–76)	66 (52–76)	.208	–0.172	61 (50–79)	66 (52–76)	.836	–0.032
Female sex	26 (37.7)	68 (37.8)	.989	–0.002	24 (33.9)	68.0 (38.0)	.599	–0.084
Weight, median (IQR), kg	74 (59.0–93.0)	75 (62.5–86.9)	.354	0.115	70 (50.3–91.0)	75 (64.0–87.0)	.894	–0.023
Source of bacteremia								
Biliary	5 (7.3)	5 (2.8)	.108	0.205	3 (3.6)	7 (3.8)	.938	–0.010
Central venous catheter	19 (27.5)	57 (31.7)	.526	–0.090	20 (28.3)	54 (30.3)	.777	–0.045
Intra-abdominal	7 (10.1)	15 (8.3)	.652	0.062	6 (7.7)	15 (8.6)	.818	–0.032
Pulmonary	7 (10.1)	25 (13.9)	.429	–0.115	12 (16.8)	23 (13.1)	.563	0.105
Skin or soft tissue	15 (21.7)	18 (10.0)	.014	0.324	9 (12.9)	24 (13.6)	.881	–0.021
Urinary tract	16 (23.2)	59 (32.8)	.140	–0.214	22 (30.4)	54 (30.3)	.949	0.011
Source control achieved	65 (94.2)	168 (93.3)	.802	0.036	67 (94.0)	167 (93.4)	.868	0.025
Intensive care unit, day 1	21 (30.4)	54 (30.0)	.947	0.009	24 (33.4)	54 (30.3)	.696	0.067
Pitt bacteremia score, median (IQR); day 1	2 (2–3)	2 (1–3)	.298	0.085	2 (1–3)	2 (1–3)	.855	–0.025
AIDS	5 (7.3)	3 (1.7)	.025	0.271	2 (3.1)	5 (2.7)	.860	–0.023
Chemotherapy, past 6 months	16 (23.2)	36 (20.0)	.580	0.077	13 (18.2)	37 (20.8)	.661	–0.065
Immunosuppressive therapy[b]	4 (5.8)	23 (12.8)	.113	–0.241	9 (11.9)	20 (11.2)	.911	0.023
Hematologic stem cell transplantation, past 12 months	6 (8.7)	27 (15.0)	.189	–0.195	12 (17.0)	25 (13.7)	.619	0.091
Day 1 absolute neutrophil count 0–500 cells/mL	14 (20.3)	27 (15.0)	.314	0.138	13 (17.7)	30 (16.6)	.850	0.030
End stage liver disease	4 (5.8)	3 (1.67)	.078	0.218	2 (2.9)	6 (3.5)	.826	–0.032
End stage renal disease, dialysis dependent	12 (17.4)	38 (21.1)	.512	–0.094	16 (22.1)	36 (19.9)	.750	0.055
Diabetes	9 (13.0)	32 (17.8)	.367	–0.131	10 (14.0)	29 (16.2)	.698	–0.061
Combination antibiotic therapy[c]	3 (4.4)	10 (5.6)	.701	–0.055	3 (4.7)	9 (5.3)	.858	–0.027
Transitioned to oral therapy	17 (24.6)	68 (37.8)	.050	–0.285	27 (37.4)	62 (34.9)	.760	0.053

Abbreviation: IQR, interquartile range.

[a]As weighting reduces or increases the representation (ie, weight) of each patient to create a contrived population of patients receiving short-course therapy who look similar to those in the prolonged-course group, weighted tabulate and summarize commands were used to obtain the counts and proportions as well as median and IQRs for the new weighted cohort.

[b]Immunosuppressive therapy included ≥10 mg per day of corticosteroids for longer than 2 weeks, biologic agents, or immune modulator therapy (including those used for solid organ transplant recipients).

[c]Combination antibiotic therapy included 48 hours or more of an antibiotic agent with in vitro activity against *Pseudomonas aeruginosa*.

observed with *Enterobacteriaceae* BSI [13, 14], conversion to oral therapy after an appropriate clinical response is observed and source control is achieved appears effective for pseudomonal bacteremia.

Due to *P. aeruginosa*'s propensity to develop resistance and affect patients who are immunocompromised, have indwelling hardware, or have chronic underlying medical conditions [10], there has been a general acceptance that patients with *P. aeruginosa* BSI require more aggressive management than those with BSI due to most other gram-negative organisms. To ensure our findings were generalizable to patient populations at greatest risk for *P. aeruginosa* BSI, we elected to include high-risk patients who are frequently excluded from comparative effectiveness antibiotic studies; 65% of the cohort consisted of severely immunosuppressed patients (ie, AIDS, solid organ transplant recipients, chemotherapy within the past 6 months, HSCT within the past 12 months, ANC <500 cells/mL).

Although our primary intent in this study was to focus on treatment duration, 36% of patients in both the short-course and prolonged-course groups were transitioned to an oral fluoroquinolone at a median of 5 days after initiating therapy. All patients transitioned to oral step-down therapy had source control. Patients who transitioned to oral therapy did not have differences in the composite outcome vs those who remained on intravenous therapy (13% for both groups).

Our study was retrospective, and imbalances between the groups may have persisted despite applying propensity-score weighting to reduce selection bias. We limited the evaluation period to 30 days, rather than 90 days as used in other studies, in order to increase the likelihood that outcomes were related to the original BSI. Because of the small number of patients who did not have source control (less than 7% of the weighted cohort), we are unable to make inferences regarding the optimal duration of therapy for *P. aeruginosa* BSI for patients with inadequate source control.

We found that patients with *Pseudomonas* BSI who received approximately 10 days of antibiotic therapy had outcomes similar to those of patients who received a prolonged course of therapy, with the potential added benefit of earlier hospital discharge if treated with a shorter course. Further interventional studies are necessary to evaluate the reproducibility of our findings.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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