Diagnostic Microbiology and Infectious Disease 93 (2019) 346–348

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Clinical Studies

Outcomes of empiric aminoglycoside monotherapy for *Pseudomonas aeruginosa* bacteremia

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ARTICLE INFO

Article history:
Received 20 March 2018
Received in revised form 23 October 2018
Accepted 27 October 2018
Available online 9 November 2018

Keywords:
30-Day mortality
Functional monotherapy
Inappropriate therapy

ABSTRACT

We evaluated 30-day mortality in patients with *Pseudomonas aeruginosa* bacteremia. There was no significant difference in mortality among patients who received functional aminoglycoside monotherapy versus inappropriate empiric therapy. Among patients given appropriate empiric therapy, functional aminoglycoside monotherapy was associated with less favorable outcomes compared to beta-lactam monotherapy.

As aminoglycosides remain one of the few classes of antibiotics that retain susceptibility against multidrug-resistant *Pseudomonas aeruginosa*, they are often used as empiric therapy and may be the only active agents when used in a combination (i.e., functional monotherapy). However, data from randomized controlled trials do not support the use of aminoglycoside monotherapy, with the exception of urinary tract infections (Vidal et al., 2007). The objective of our study was to assess the outcomes of patients treated with functional aminoglycoside monotherapy for the empiric treatment of *P. aeruginosa* bacteremia.

This was a single-center, retrospective, cohort study conducted from January 2002 through December 2015 in an 850-bed academic teaching hospital in Houston, Texas. Adult patients with a positive blood culture for *P. aeruginosa* and hospitalized for at least 48 h after the index culture were eligible for inclusion. Included patients were stratified by receipt of appropriate versus inappropriate empiric therapy; patients who received appropriate empiric therapy were further stratified based on class of antibiotics given (functional aminoglycoside monotherapy versus beta-lactam monotherapy). Patients who received more than 1 active antibiotic were excluded. The primary endpoint was 30-day all-cause hospital mortality from the day of index blood culture. Appropriate empiric antibiotic therapy was defined as administration of antipseudomonal antibiotic(s) within 24 h of positive index blood culture, which was shown to be active against the isolate. Functional aminoglycoside monotherapy was defined as administration of an aminoglycoside as the only active agent given empirically for >1 dose and a minimum of 48 h of therapy. Inappropriate empiric antibiotic therapy was defined as no active agent given empirically. Patient characteristics were initially compared based on 30-day all-cause hospital mortality. Continuous variables were compared using the Student *t* test or the Kruskal–Wallis test, while categorical variables were compared using Fisher's exact test. To identify independent risk factors for 30-day mortality, univariate logistic regression analysis was performed to determine the odds ratios (ORs) and 95% confidence intervals (CIs) of different variables. Variables found to have *P* values < 0.2 on the univariate analysis were entered into a multivariate analysis using both forward and backward stepwise selection processes. *P* values of ≤ 0.05 were considered statistically significant. Statistical analyses were performed using SYSTAT, version 12 (SYSTAT Software, Inc., Chicago, IL).

A total of 103 patients were evaluated during the study period. The overall 30-day mortality rate was 20.4%. Among the patients evaluated, 45 patients (43.7%) received inappropriate empiric therapy, and 58 patients (56.3%) received appropriate empiric (functional) monotherapy. Overall, 30-day mortality was not different in patients who received inappropriate compared to appropriate empiric therapy (24.4% versus 17.2%; $P = 0.46$). Thirty-day mortality was stratified to different demographic and clinical variables (Table 1). Patients who expired had a longer length of hospital stay before index culture and higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. Twelve patients were given aminoglycosides as functional monotherapy (5 for amikacin, dose range: 4.3–7.3 mg/kg; 6 for tobramycin, dose range:

Abbreviations: OR, odds ratio; COPD, chronic obstructive pulmonary disease; ESRD, end stage renal disease; APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval.

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https://doi.org/10.1016/j.diagmicrobio.2018.10.019
0732-8893/

Table 1
Thirty-day mortality stratified to different demographic/clinical variables ($n = 103$).

Variable	30-Day mortality n/N (%)	P value
Age, years		
<= 63 (median)	10/53 (18.9)	0.81
> 63	11/50 (22.0)	
Sex		
Female	8/39 (20.5)	1.00
Male	13/64 (20.3)	
Race[a]		
Non-Caucasian	10/43 (23.3)	0.63
Caucasian	11/58 (19.0)	
Length of hospital stay, days		
<= 20, median	6/54 (11.1)	0.03
> 20	15/49 (30.6)	
Length of hospital stay before cultures, days		
<= 4, median	6/52 (11.5)	0.03
> 4	15/51 (29.4)	
APACHE II		
<= 15, median	6/54 (11.1)	0.03
> 15	15/49 (30.6)	
Hypertension		
Yes	13/70 (18.6)	0.60
No	8/33 (24.2)	
Congestive heart failure		
Yes	10/30 (33.3)	0.06
No	11/73 (15.1)	
Asthma		
Yes	1/8 (12.5)	1.00
No	20/95 (21.1)	
COPD		
Yes	7/21 (33.3)	0.13
No	14/82 (17.1)	
Stroke		
Yes	3/19 (15.8)	0.76
No	18/84 (21.4)	
ESRD		
Yes	7/21 (33.3)	0.13
No	14/82 (17.1)	
Diabetes mellitus		
Yes	13/43 (30.2)	0.05
No	8/60 (13.3)	
Cirrhosis		
Yes	3/6 (50.0)	0.10
No	18/97 (18.6)	
Hepatitis		
Yes	2/10 (20.0)	1.00
No	19/93 (20.4)	
HIV		
Yes	0/2 (0.0)	1.00
No	21/101 (20.8)	
Posttransplant		
Yes	3/15 (20.0)	1.00
No	18/88 (20.5)	
Source of bacteremia		
Line		
Yes	2/8 (25.0)	0.66
No	19/95 (20.0)	
Lungs		
Yes	5/23 (21.7)	1.00
No	16/80 (20.0)	
Urinary tract		
Yes	1/19 (5.3)	0.11
No	20/84 (23.8)	
Wound		
Yes	2/11 (18.2)	1.00
No	19/92 (20.7)	
Abdomen		
Yes	6/15 (40.0)	0.08
No	15/88 (17.0)	
Inappropriate empiric therapy		
Yes	11/45 (24.4)	0.46
No	10/58 (17.2)	

[a] No ethnicity information in 2 patients.

1.9–4.2 mg/kg; and 1 for gentamicin, dose: 1.5 mg/kg). Among these 12 patients, 3 received extended-interval dosing and 9 received traditional dosing. Of the patients who received traditional dosing, 5 out of 9 had end stage renal disease (ESRD). There was no significant difference in 30-day mortality among patients who received functional aminoglycoside monotherapy versus inappropriate empiric therapy (33.3% versus 24.4%; $P = 0.71$). The rate of 30-day mortality in the functional aminoglycoside monotherapy group was more than double the mortality rate of the beta-lactam monotherapy group, although this was not found to be statistically significant (33.3% versus 13.0%; $P = 0.19$).

As there is considerable literature supporting the benefits of appropriate empiric therapy, including the numerically lower mortality rate found in our study, we further explored the risk factor(s) for 30-day mortality in patients who received appropriate therapy. Univariate analyses revealed variables to be potential risk factors; these variables were subsequently entered into a multivariate analysis. In the multivariate analysis, age (OR, 1.11; 95% CI, 1.02 to 1.20; $P = 0.02$) and functional aminoglycoside monotherapy (OR, 12.54; 95% CI, 1.51 to 103.99; $P = 0.02$) remained in the final model and were found to be independent risk factors for 30-day mortality (Table 2).

In this study, we evaluated the outcomes of patients with *P. aeruginosa* bacteremia, with a specific focus on the outcomes of patients who received appropriate therapy during the first 72 h of treatment. Several studies have demonstrated the importance of appropriate empiric therapy in achieving favorable outcomes (Hyle et al., 2005; Kang et al., 2003; Micek et al., 2005). Micek et al. found that among patients who received appropriate empiric antibiotics, there was no significant difference in hospital mortality between the type of antibiotic therapy received (e.g., beta-lactam monotherapy versus aminoglycoside monotherapy versus fluoroquinolone monotherapy versus combination therapy) (Micek et al., 2005). In contrast, our study found that despite being considered appropriate empiric therapy, patients who received an aminoglycoside had a significantly higher risk of 30-day hospital mortality when compared to patients who received an appropriate beta-lactam. Previous studies have demonstrated worse outcomes in patients treated with aminoglycosides versus comparators (Bailey et al., 2002; Crabtree et al., 1999; Leibovici et al., 1997; Paul et al., 2004). In a prospective, observational study, patients with Gram-negative bacteremia who were treated with appropriate empiric aminoglycoside monotherapy had a higher mortality rate than those given an appropriate beta-lactam (24% versus 17%, respectively, $P < 0.01$). However, the difference was not significant after adjusting for potential confounders (Leibovici et al., 1997). An observational study of hospitalized surgical patients who had Gram-negative infections demonstrated a significantly higher mortality rate in patients who received a regimen containing an aminoglycoside compared to a nonaminoglycoside (25.8% versus 13.5%; $P < 0.02$) (Crabtree et al., 1999). The authors of this study specifically evaluated mortality in patients with pneumonia due to a Gram-negative organism and found a significantly higher rate of mortality in patients who received an aminoglycoside compared to those who did not (36.7% versus 17.9%; $P < 0.04$). A possible explanation for the higher mortality rate in our study may be that there was a higher proportion of patients with lung as the source of bacteremia in the aminoglycoside group compared to the beta-lactam group (33.3% versus 13.0%). Aminoglycosides generally exhibit poor penetration into the lung tissues with significantly lower lung epithelial lining fluid concentrations compared to plasma concentrations (Rodvold et al., 2011).

There were several limitations to our study. First, as with any retrospective, observational study design, we were unable to control for antimicrobial prescribing practices stratified for the source of bacteremia. Patients who received aminoglycosides may have been perceived to be more critically ill. Second, we did not stratify patients based on infections due to multidrug-resistant phenotypes, and we did not specifically assess definitive therapy once antimicrobial susceptibilities were known. Studies have demonstrated worse outcomes in patients infected with multidrug-resistant *P. aeruginosa* (Aloush et al., 2006; Lautenbach

Table 2
Risk factors associated with 30-day mortality in patients given appropriate empiric therapy (n=58).

Variable	Univariate analysis OR (95% CI)	*P* value	Multivariate analysis[a] OR (95% CI)	*P* value
Age	1.05 (1.00–1.12)	0.06	1.11 (1.02–1.20)	0.02
Total length of hospital stay	1.00 (0.99–1.02)	0.62		
Length of hospital stay before culture	1.01 (0.99–1.03)	0.24[b]		
Comorbidities				
Congestive heart failure	3.00 (0.74–12.18)	0.12		
COPD	2.51 (0.52–12.09)	0.25		
Diabetes mellitus	1.53 (0.39–5.99)	0.55		
APACHE II	1.09 (0.99–1.19)	0.07		
Functional aminoglycoside monotherapy[c]	3.33 (0.76–14.58)	0.11	12.54 (1.51–103.99)	0.02
Source of bacteremia				
Line	1.22 (0.12–12.26)	0.87		
Urinary tract	0.30 (0.03–2.60)	0.27		
Abdomen	4.67 (1.01–21.49)	0.05		

[a] Receiver operating characteristic area under the curve = 0.784.
[b] *P* value = 0.17 with the variable log-transformed (0 day assigned a value of 1).
[c] Compared to beta-lactams.

et al., 2010; Tam et al., 2010). The limited sample size in our study precluded further categorization and assessments. Of note, functional aminoglycoside monotherapy was continued as definitive therapy in 11 of 12 patients; 1 patient was switched to colistimethate sodium. Third, we did not specifically evaluate the impact of dosing and duration of empiric aminoglycoside therapy on outcomes. In our center, therapeutic drug monitoring of aminoglycoside serum concentrations is not routinely performed if aminoglycosides are used empirically (typically for 2–3 days until susceptibility results are available). The clinical response to aminoglycosides is best predicted by the peak-to-minimum inhibitory concentration ratio, with a ratio of at least 10-to-1 associated with clinical efficacy (Moore et al., 1987). Depending on the dosing modality utilized (traditional, multiple daily dosing versus high-dose, extended-interval dosing), considerable intersubject variability in pharmacokinetics could be encountered, and patients may not have achieved an optimal dosing exposure (Marik et al., 1991; Roger et al., 2015). Furthermore, in a recent report released by the National Antimicrobial Susceptibility Testing Committee for the United States, the recommended breakpoint thresholds for susceptibility for amikacin and tobramycin against *P. aeruginosa* would be ≤2 μg/mL and ≤1 μg/mL, respectively (Bhavnani et al., 2018). These recommended breakpoint thresholds are 4–8-fold lower than the current recommended breakpoint threshold from Clinical and Laboratory Standards Institute (≤16 μg/mL and ≤4 μg/mL, respectively). Consequently, patients in our study who received an aminoglycoside might not have received appropriate empiric therapy, which could have some implications on the outcomes of our study.

In conclusion, patients who received functional aminoglycoside monotherapy had less favorable outcomes compared to patients who received beta-lactam monotherapy for the empiric treatment of *P. aeruginosa* bacteremia. This poses a significant therapeutic challenge as aminoglycosides remain one of our last-line agents for multidrug-resistant *P. aeruginosa* infections. The best evidence-based approach to advance medical care of patients should consider an optimal balance of clinical benefits and potential risk of nephrotoxicity associated with aminoglycosides.

Funding

The study was supported by Merck under an investigator-sponsored clinical trial research agreement.

Declarations of interest

V.H.T. is a consultant on the Advisory Board of Achaogen; other authors: none to declare.

Ethics

Institutional Review Board approval was obtained prior to initiation of the study. Due to the retrospective nature of this study, the need for patient consent was waived.

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