

# Effectiveness of oral antibiotics for definitive therapy of non-Staphylococcal Gram-positive bacterial bloodstream infections

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## Abstract

**Background:** Data on the effectiveness of definitive oral (PO) antibiotics for BSIs in preparation for discharge from hospital are lacking, particularly for Gram-positive bacterial BSIs (GP-BSI). The objective of this study was to determine rates of treatment failure based on bioavailability of PO antimicrobial agents used for GP-BSI.

**Methods:** This was a single-center, retrospective cohort study of adult inpatients admitted to an academic medical center over a three-year period. Patients with a non-staphylococcal GP-BSI who received intravenous antibiotics and were then switched to PO antibiotics for at least a third of their treatment course were included. The cohort was stratified into high ( $\geq 90\%$ ) and low ( $< 90\%$ ) bioavailability groups. The primary endpoint was the proportion of patients experiencing clinical failure in each group. Secondary endpoints included clinical failure stratified by antibiotic group, bactericidal versus bacteriostatic PO agents, and organism.

**Results:** A total of 103 patients met criteria for inclusion, which failed to reach the a priori power calculation. Of the patients included, 26 received high bioavailability agents and 77 received low bioavailability agents. Infections originated largely from a pulmonary source (30%) and were caused primarily by streptococcal species (75%). Treatment failure rates were 19.2% in the high bioavailability group and 23.4% in the low bioavailability group ( $p = 0.66$ ). Clinical failure stratified by subgroups also did not yield statistically significant differences.

**Conclusions:** Clinical failure rates were similar among patients definitively treated with high or low bioavailability agents for GP-BSI, though the study was underpowered to detect such a difference.

**Keywords:** bacteremia, bioavailability, Gram-positive, oral antibiotics

Received: 27 January 2019; revised manuscript accepted: 21 June 2019.

## Introduction

Bloodstream infections (BSIs) are associated with significant morbidity and mortality, and are the 11th leading cause of death in the United States (US).<sup>1</sup> In an epidemiological study of nosocomial BSIs in the US, 65% of episodes were caused by Gram-positive bacterial organisms.<sup>2</sup> Treatment of Gram-positive bacterial BSIs typically involves a course of intravenous (IV) therapy, requiring

administration *via* IV lines, prolonged hospitalization, increased treatment costs, and increased risk of line-related infections.<sup>3,4</sup> There is a paucity of evidence-based data on the effectiveness of definitive antimicrobial regimens, specifically oral (PO) options, for Gram-positive bacterial BSIs in preparation for discharge from hospital. The 2007 Infectious Diseases Society for America (IDSA) guideline for community acquired

*Ther Adv Infectious Dis*

2019, Vol. 6: 1–12

DOI: 10.1177/  
2049936119863013

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pneumonia (CAP) suggests that a switch to PO therapy is reasonable, even in patients with bacteremia, once clinical stability is achieved<sup>5</sup>; however, this recommendation is based on a small study in which only 9% of patients had concomitant bacteremia, with no information about which PO antibiotics were used.<sup>6</sup> A similar, randomized study by Oosterheert and colleagues assessing the effectiveness of early PO antibiotic use in severe CAP showed the majority of patients received amoxicillin/clavulanic acid. However, the specific agents used in the 9% of patients with concomitant bacteremia was not specifically mentioned.<sup>7</sup>

The practice of transitioning from IV to PO antimicrobial agents with high bioavailability for the completion of treatment of BSI is largely based on expert opinion. Providers often analyze patient-specific factors in clinical context to determine agent selection and appropriate timing of PO antibiotics, due to the lack of conclusive data demonstrating efficacy of one PO agent over another. In an evidence-based review by Hale and colleagues, the authors point to susceptibility data, source control, stable hemodynamics, and the use of highly bioavailable agents as important considerations prior to switching to PO therapy in Gram-positive bacterial BSI.<sup>8</sup> More data for the transition from IV to PO antibiotics in Gram-negative bacterial BSIs have been published than in Gram-positive bacterial BSI, but with conflicting results. A study by Kutob and colleagues examined treatment failure rates based on bioavailability of PO antimicrobial agents prescribed for definitive therapy of Gram-negative bacterial BSI, and found that the risk of treatment failure increased as bioavailability of the PO regimen declined.<sup>9</sup> In contrast, a study published by Mercurio and colleagues found no difference in clinical success between PO stepdown therapy with beta-lactams or fluoroquinolones for Gram-negative bacterial BSI.<sup>10</sup>

The purpose of this study was to examine the rate of clinical treatment failure based on bioavailability of PO agents and to determine risk factors for failure. This study was designed to help guide selection of the most optimal antimicrobial agents in solely Gram-positive bacterial BSIs, due to the gap in literature on this topic. We hypothesized that patients treated with agents with lower bioavailability would be more likely to experience clinical failure than those treated with higher bioavailability agents.

## Methods

### Study design and setting

This was a single-center, retrospective cohort study of adult inpatients admitted to an academic medical center in Charlotte, NC, between 1 September 2014 and 31 August 2017. Patients with a Gram-positive bacterial BSI caused by a prespecified list of organisms who received IV antibiotics and were then switched to PO antibiotics for discharge were included. Patients were identified through a Theradoc® information systems (Premier, Inc., Charlotte, NC, USA) generated report. The electronic medical record was used to gather and collect all necessary data, and approval for the study was obtained through the institutional review board. The data were entered and managed in a secure Research Electronic Data Capture (REDCap™) database.<sup>11</sup>

### Patient selection

Adult patients (>18 years old) were included in the study if they had a positive blood culture for *Streptococcus* spp., *Enterococcus* spp., *Peptostreptococcus*, or *Clostridium* spp.; if they received appropriate antibiotic therapy; and if at least one-third of their total course of antibiotics received were PO, including both inpatient and upon discharge. Appropriate antibiotic therapy was defined as antibiotics adequately dosed for the patient's creatinine clearance (CrCl) with *in vitro* activity against the isolate based on the Clinical and Laboratory Standards Institute criteria. CrCl and dose were assessed at the initiation of IV and PO antibiotics, and again at hospital discharge. Patients were excluded if they had bacteremia caused by *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, or had a prior episode of bacteremia due to the same organism within the past 90 days. Patients were also excluded if the organism identified was determined by a treating clinician to be a contaminant; if the patient had a polymicrobial infection with an organism not listed previously; if the patient was never admitted for IV treatment; if the patient had a catheter-related BSI, concomitant meningitis, osteomyelitis, or endocarditis; or if they expired during hospitalization.

### Study objectives

The primary outcome of this study was clinical failure in patients receiving high *versus* low

bioavailability agents. High bioavailability agents were defined as those with >90% bioavailability and included clindamycin, doxycycline, fluoroquinolones, linezolid, metronidazole, and trimethoprim/sulfamethoxazole. Low bioavailability agents were <90% bioavailable, including the aminopenicillins, penicillins, and cephalosporins. Clinical failure was defined as all-cause mortality within 90 days of diagnosis of BSI, 90-day hospital readmission from date of previous discharge due to infectious process, switch back to IV therapy due to lack of improvement on PO therapy, or recurrent BSI due to the original organism within 90 days of switch to PO therapy. To determine all-cause mortality, both medical records and death certificate databases were searched. Secondary endpoints assessed included clinical failure stratified by antibiotic group, organism, and bactericidal *versus* bacteriostatic agents. Bacteriostatic agents were defined as clindamycin, doxycycline, and linezolid. Duration of hospitalization, clinical failure in patients who had documented microbiological clearance *versus* those who did not, and source of infection were also assessed.

### Statistical analysis

Descriptive statistics including means and standard deviations, or counts and percentages, were calculated for all variables. The primary analysis was a chi-squared test comparing the proportion of patients experiencing clinical failure in those receiving high *versus* low bioavailability agents. To assess potential risk factors of treatment failure, univariate logistic regression models were used to calculate odds ratios and 95% confidence intervals. To compare baseline characteristics and other secondary outcomes between study groups, Student's *t* test was used for normally distributed data, the Wilcoxon rank sum test was used for ordinal data or continuous data that were not normally distributed, and the chi-square test or Fisher's exact test was used for categorical data. A two-tailed *p* value of less than 0.05 was considered statistically significant. SAS Enterprise Guide®, version 6.1, was used for all analyses (SAS Institute Inc., Cary, NC, USA).

Sample size was based on a chi-square test comparing the proportion of patients experiencing clinical failure in those receiving high *versus* low bioavailability agents. To detect a proportional

difference of 10%, and assuming a 4% rate of clinical failure for patients treated with agents known to have higher bioavailability, 128 patients were required per treatment group for a power of 80% and alpha of 0.05. These failure rates were based on earlier studies in Gram-negative bacteremia as well as clinical expertise.<sup>9</sup>

### Results

Over the 3-year study period, 597 adult patients with non-Staphylococcal Gram-positive bacterial BSIs were identified, with 103 patients being eligible for inclusion (Figure 1). The median patient age was 59, with 51% being female, and 47% and 43% being White and African American, respectively (Table 1). Out of 103 included patients, 26 received PO treatment with highly bioavailable agents, whereas 77 patients received low bioavailability agents. In this study, 19% of the patients were actively immunocompromised, defined as an absolute neutrophil count <500/mm<sup>3</sup>, chemotherapy within 30 days of BSI, human immunodeficiency virus and CD4 count <200/mm<sup>3</sup>, transplant recipients, receiving immunosuppressive medications, or receipt of prednisone >20 mg or equivalent for at least 7 days. Baseline characteristics between groups

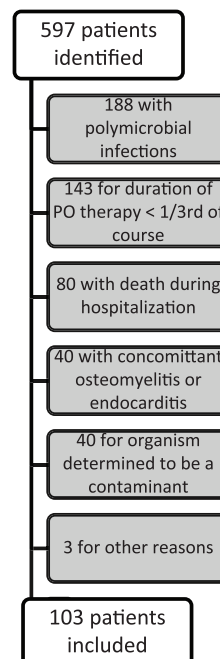


Figure 1. Summary of patient exclusion.

**Table 1.** Baseline demographics.

<b>Clinical characteristics of patients with Gram-positive bloodstream infection by bioavailability group</b>				
<b>Variable</b>	<b>Bioavailability</b>			<b>p-value</b>
	<b>Total (n = 103)</b>	<b>High (n = 26)</b>	<b>Low (n = 77)</b>	
Age (years) [median (IQR)]	59 (43–72)	62 (46–70)	57 (41–73)	0.516
Weight (kg) [median (IQR)]	75 (68–90)	78 (68–86)	75 (66–90)	0.846
Female sex [n (%)]	52 (50.5)	12 (46.2)	40 (51.9)	0.609
Race [n (%)]	–	–	–	0.308
White	48 (46.6)	15 (57.7)	33 (42.9)	
African American	44 (42.7)	9 (34.6)	35 (45.5)	
Asian	3 (2.9)	2 (7.7)	1 (1.3)	
American Indian	2 (1.9)	–	2 (2.6)	
Other	4 (3.9)	–	4 (5.2)	
Unknown	2 (1.9)	–	2 (2.6)	
Immunocompromised [n (%)]	20 (19.4)	4 (15.4)	16 (20.8)	0.548
Pitt bacteremia score [median (IQR)]	1 (0–2)	1 (0–2)	1 (1–2)	0.059
Charlson Comorbidity index [median (IQR)]	4 (2–7)	4.5 (3–7)	4 (2–6)	0.258
Diabetes mellitus [n (%)]	24 (23.3)	5 (19.2)	19 (24.7)	0.570
Moderate-severe renal disease [n (%)]	19 (18.4)	4 (15.4)	15 (19.5)	0.775
Moderate-severe liver disease [n (%)]	9 (8.7)	3 (11.5)	6 (7.8)	0.689
Cancer [n (%)]	27 (26.2)	12 (46.2)	15 (19.5)	0.008
Source of infection [n (%)]				0.132
Urinary	10 (9.7)	2 (7.7)	8 (10.4)	
Pulmonary	31 (30.1)	8 (30.8)	23 (29.9)	
Intra-abdominal	9 (8.7)	4 (15.4)	5 (6.5)	
Skin/soft tissue	20 (19.4)	1 (3.8)	19 (24.7)	
Other	9 (8.7)	3 (11.5)	6 (7.8)	
Unknown	24 (23.3)	8 (30.8)	16 (20.8)	
Appropriate antibiotic duration (days) [median (IQR)]	–	–	–	–
IV	5 (4–7)	4 (3–6)	5 (4–7)	0.117
PO	9 (7–12)	9.5 (7–14)	9 (8–11)	1.000
Total	15 (13–17)	14 (11–16)	15 (14–17)	0.183
Confirmed negative blood cultures [n (%)]	77 (74.8)	22 (84.6)	55 (71.4)	0.181
Days to blood culture clearance [median (IQR)]	2.6 (1.8–2.9)	2.4 (1.5–2.8)	2.6 (1.8–3.0)	0.495
ID consult involvement [n (%)]	53 (51.5)	14 (53.8)	39 (50.6)	0.778
Length of stay (days) [median (IQR)]	7 (5–10)	8 (5–10)	6 (5–9)	0.534
ID, infectious diseases; IQR, interquartile range.				

were well balanced, apart from 46% of the high bioavailability group having a history of cancer compared with 20% of the low bioavailability group ( $p=0.008$ ). The predominant source of infection was pulmonary (30%) with the predominant organism being a streptococcal species (75%) (Table 2). Patients were treated for a median of 15 days with 9 days administered orally and 7 days administered in the hospital.

Overall, 23 out of the 103 patients experienced clinical failure (Table 3). In the high bioavailability group, 4 of the 26 patients were readmitted due to an infectious process, and 1 patient in the group expired for a total of five failures. In the low bioavailability group, 15 of the 77 were readmitted due to infection, with 1 of the 15 expiring, 5 requiring a switch back to IV therapy due to lack of improvement, and 2 having recurrent bacteremia due to the original organism. An additional three patients in the low bioavailability group died within 90 days of diagnosis for a total of 18 failures. Upon stratifying failure rates based on bioavailability, 19.2% of the high bioavailability group failed, while 23.4% of the low bioavailability group failed ( $p=0.66$ ). When assessing for risk factors for failure between bacteriostatic *versus* bactericidal agents, high *versus* low bioavailability agents, medication class, and organism, there were no statistically significant associations identified (Table 4).

## Discussion

In this study, no difference in rates of clinical failure between the high (19.2%) and low (23.4%) bioavailability groups were observed. Additionally, there were no statistically significant differences in secondary endpoints. Failure rates in this study were higher than those seen in prior studies for the treatment of Gram-negative bacteremia. Kutob examined 362 cases of Gram-negative bacteremia treated with PO antibiotics and reported failure rates of 2%, 12%, and 14% for high, moderate, and low bioavailability agents respectively ( $p=0.02$ ).<sup>9</sup> Similar to Kutob, Mercurio studied PO treatment of Gram-negative bacteremia with beta-lactams compared with fluoroquinolones in 224 patients. This resulted in failure rates of 13% for each group ( $p=0.96$ ).<sup>10</sup> Apart from focusing on Gram-negative as opposed to Gram-positive organisms, these studies also had dissimilar stratifications of bioavailability,

different definitions of clinical failure, and unique patient populations. In our study, 19% of patients were immunocompromised, with 9% having moderate-to-severe liver disease. In the Kutob study, these were the only two statistically significant risk factors for failure seen outside of bioavailability, and, in their study, only 9% were immunocompromised, with 3% having liver cirrhosis.<sup>9</sup> This could indicate that our patient population had a higher burden of illness and may have been more infection prone. In the study by Mercurio, 5% of patients had cirrhosis, and the number of immunocompromised patients was not stated.<sup>10</sup> Mercurio found diabetes with complications as their largest risk factor for treatment failure, which entailed 23% of their population, a similar proportion to our study.<sup>10</sup>

Infections in our study were largely from a pulmonary source and caused by a streptococcal species, whereas prior studies had high rates of urinary sources of infection due to *Escherichia coli*.<sup>9,10</sup> It is important to note differences in treatment of these organisms, especially when considering use of low bioavailability agents. In general, streptococcal species have much lower minimum inhibitory concentrations for beta-lactam antibiotics when compared with the Enterobacteriaceae, making pharmacodynamic targets more easily achievable, even with use of agents with lower bioavailability.<sup>12</sup> With the majority of patients in this study having a streptococcal pneumonia as their source of BSI, these results could be taken into consideration when recommending treatment options in conjunction with clinical experience, microbiological data, and previous literature. Ramirez found that, in patients with *Streptococcus pneumoniae* bacteremia from a pulmonary source, there was no difference in clinical outcomes between patients who received PO switch therapy *versus* those who completed a course of IV only therapy after showing clinical improvement.<sup>6</sup> Although the specific antibiotics used were not mentioned, together these studies provide rationale for treating highly susceptible organisms such as *Streptococcus pneumoniae* with targeted antimicrobial agents such as beta-lactams.

In this study, median length of therapy was approximately 2 weeks in both groups, similar to other studies in Gram-negative bacterial infections, and which recent literature suggests may not be needed in lower inoculum infections with

**Table 2.** Microbiology.

Microbiology and treatment of Gram-positive bloodstream infection					
Bacteria	Total (n = 103)	Bioavailability		Pharmacodynamic property	
		High (n = 26) n (%)	Low (n = 77) n (%)	Bactericidal (n = 96) n (%)	Bacteriostatic (n = 7) n (%)
<i>Streptococcus</i> species	77 (75)	17 (65)	60 (78)	72 (75)	5 (71)
Group A <i>Streptococcus</i>	7 (6.8)	1 (3.8)	6 (7.8)	6 (6.3)	1 (14.3)
Group B <i>Streptococcus</i>	16 (15.5)	3 (11.5)	13 (16.9)	15 (15.6)	1 (14.3)
Group C <i>Streptococcus</i>	1 (1)	–	1 (1.3)	1 (1)	–
Group G <i>Streptococcus</i>	3 (2.9)	–	3 (3.9)	3 (3.1)	–
Viridans group <i>Streptococcus</i>	17 (16.5)	2 (7.7)	15 (19.5)	15 (15.6)	2 (28.6)
<i>S. pneumoniae</i>	27 (26.2)	9 (34.6)	18 (23.4)	27 (28.1)	–
<i>S. bovis</i>	1 (1)	–	1 (1.3)	1 (1)	–
<i>S. anginosus</i>	2 (1.9)	2 (7.7)	–	1 (1)	1 (14.3)
<i>S. constellatus</i>	1 (1)	–	1 (1.3)	1 (1)	–
<i>S. intermedius</i>	1 (1)	–	1 (1.3)	1 (1)	–
<i>S. mitis</i>	1 (1)	–	1 (1.3)	1 (1)	–
<i>Enterococcus</i> species	10 (10)	1 (4)	9 (12)	9 (9)	1 (14)
<i>E. faecalis</i>	9 (8.7)	–	9 (11.7)	9 (9.4)	–
<i>E. faecium</i>	1 (1)	1 (3.8)	–	–	1 (14.3)
<i>Peptostreptococcus</i> species	8 (8)	2 (8)	6 (8)	8 (8)	–
<i>Clostridium</i> species	8 (8)	6 (23)	2 (3)	7 (7)	1 (14)
<i>C. perfringens</i>	1 (1)	1 (3.8)	–	1 (1)	–
<i>C. sordelli</i>	1 (1)	–	1 (1.3)	1 (1)	–
<i>C. septicum</i>	2 (1.9)	2 (7.7)	–	1 (1)	1 (14.3)
<i>C. ramosum</i>	1 (1)	1 (1)	–	1 (1)	–
Individual species not specified	3 (2.9)	2 (7.7)	1 (1.3)	3 (3.1)	–

absence of a deep seeded source.<sup>9–10,13,14</sup> However, to our knowledge, there are no published studies in Gram-positive bacterial infections to support this extrapolation. Due to the prolonged duration in both groups, it is unknown how a shorter duration of therapy would affect failure rates between groups, or if the similar failure rates were due to the 2-week course. With most patients receiving low bioavailability

agents, it is clear that use of these agents was common practice at our institution for treatment of Gram-positive bacterial BSI after initial IV antibiotics.

To our knowledge, this is the first study of IV to PO switch therapy for the completion of treatment of Gram-positive bacteremia. Similar studies are available in Gram-negative bacteremia;

**Table 3.** Primary outcomes.

Outcomes	Bioavailability			p-value
	Total (n = 103)	High (n = 26) n (%)	Low (n = 77) n (%)	
Clinical Failure	23 (22.3)	5 (19.2)	18 (23.4)	0.661
90-day readmission	47 (45.6)	13 (50)	34 (44.2)	0.605
Infection related	19 (18.4)	4 (15.4)	15 (19.5)	0.775
90-day all-cause mortality	5 (4.9)	1 (3.8)	4 (5.2)	1.000
Switch from PO back to IV therapy	5 (4.9)	–	5 (6.5)	0.327
Recurrent bloodstream infection within 90 days of switch to PO therapy	2 (1.9)	–	2 (2.6)	1.000

however, there are conflicting results regarding whether high bioavailability agents are more successful in treating BSI.<sup>9,10,15</sup> This study adds to the literature in an area of uncertainty, but must be interpreted with its limitations.

Due to the retrospective nature of this study, the medical record was relied upon and the data extracted were dependent upon documentation accuracy. There was no randomization of the treatment groups and the groups were unevenly split, with 25% receiving high bioavailability agents and 75% receiving low bioavailability agents. We were also unable to confirm adherence to the treatment regimen upon discharge due to the study design and had to rely on discharge medication reconciliations with the assumption of adherence. Although death certificate databases were searched and medical records postdischarge were examined, some clinical failures may have gone undetected if they were admitted to a hospital outside of the center's healthcare system. For the five patients who were confirmed to have expired during the study period, cause of death (e.g. whether or not infection-related) was unable to be determined. Due to the strict exclusion criteria and the unexpectedly small sample size, power was not met, making the validity of these results uncertain. To power our study to detect the 4% difference in clinical failure that was seen, over 300 patients in each group would have been required. As our data set was run through a Theradoc® generated report in conjunction with our rapid diagnostic blood culture testing,

our data set was able to go back only as far as September of 2014 when these processes were implemented.

Despite these limitations, this study is the first of its kind in Gram-positive bacterial BSI. The patients in this trial did receive a long duration of PO therapy, with a median of 9 out of 15 (60%) days of therapy being PO, and patients were followed for 90 days postdiagnosis. As the primary objective of this trial was to determine the effectiveness of PO antibiotics, this is a major strength of the data. All patients received appropriately dosed and active antibiotics for the duration of their course. Despite no statistically significant differences, relevant risk factors were chosen to determine their effects on treatment outcomes, including bioavailability and pharmacodynamic properties. This study is hypothesis-generating for future, large-scale studies.

### Conclusion

There were no differences in outcomes between the use of high or low bioavailability agents for the treatment of Gram-positive bacterial BSI. There were also no risk factors observed that increased the risk of failure based on the type of agent used or the organism and source that were being treated. Due to its limitations, conclusions cannot be drawn solely from this study; however, it is hypothesis-generating in an area where there is a paucity of data. These results set the stage for future, large-scale studies to validate the results of this study.

**Table 4.** Univariate analysis for risk factors of treatment failure.

Variable	OR (95% CI)	p-value
Medication class	–	–
Penicillin VK	1.429 (0.259–7.897)	0.683
Aminopenicillins	0.643 (0.25–1.654)	0.360
Cephalosporins	2.063 (0.715–5.947)	0.180
Fluoroquinolones	0.285 (0.035–2.335)	0.242
SMX/TMP	N/A*	N/A*
Clindamycin	0.864 (0.092–8.129)	0.898
Doxycycline	N/A*	N/A*
Linezolid	N/A*	N/A*
Metronidazole	1.429 (0.259–7.897)	0.683
Organism	–	–
<i>Streptococcus</i> species	1.281 (0.423–3.884)	0.661
<i>Enterococcus</i> species	0.857 (0.169–4.348)	0.852
<i>Peptostreptococcus</i> species	1.175 (0.221–6.253)	0.850
<i>Clostridium</i> species	0.474 (0.055–4.065)	0.496
Source	–	–
Urinary	1.565 (0.371–6.605)	0.542
Pulmonary	0.577 (0.193–1.726)	0.325
Intra-abdominal	0.993 (0.192–5.144)	0.994
Skin/Soft Tissue	1.204 (0.385–3.759)	0.750
Other	N/A*	0.968
Unknown	1.75 (0.616–4.969)	0.293
Length of hospital stay $\geq 5$ versus $< 5$ days	6.852 (0.865–54.249)	0.068
Bacteriostatic vs bactericidal	1.429 (0.259–7.897)	0.683
Bioavailability high vs low	0.78 (0.257–2.366)	0.661
Blood culture clearance yes versus no	0.712 (0.255–1.987)	0.517
*Unable to be calculated due to small sample size SMX/TMP, sulfamethoxazole/trimethoprim.		

**Acknowledgment**

The authors would like to thank Jing Zhao, MD, PhD from the Center for Outcomes Research and Evaluation (CORE) for help with statistical analysis.

**Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.



**Conflict of interest statement**

The authors declare that there is no conflict of interest.

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**Appendix A.** Oral bioavailability of various antimicrobial agents per package insert.

Agent	% Bioavailable
Penicillin VK	25–60
Aminopenicillins	
Ampicillin	50
Amoxicillin	70–77
Amoxicillin/clavulanate	70–77
Cephalosporins	
First-generation	
Cephalexin	80
Third-generation	
Cefpodoxime	41–64
Cefdinir	16–25
Cefixime	40–52
TMP/SMX	90
Clindamycin	90
Doxycycline	100
Linezolid	100
Metronidazole	100
Fluoroquinolones*	
Levofloxacin	100
Moxifloxacin	90
*Ciprofloxacin not included given lack of reliable activity against Gram-positive organisms.	

**Appendix B.** Appropriate renal dose adjustments.

Package insert, American Journal of Kidney Diseases, and institution specific recommendations		
Drug	Normal dose	Renal adjustment (CrCl in mL/min)
Penicillin VK	250–500 mg Q6–8H	None
Ampicillin	500 mg Q6H	10–50: 500 mg Q6–12H <10: 500 mg Q12–24H
Amoxicillin	500 mg Q8H 875 mg Q12H	10–30: 500 mg Q12H <10: 500 mg Q24H Should not use 875 mg tablet if CrCl <30
Amoxicillin/clavulanate	500 mg Q8 875 mg Q12H 2000 mg ER Q12H	10–30: 500 mg Q12H <10: 500 mg Q24H ER tab should not be used if CrCl <30
Cephalexin	500 mg Q6H	15–29: 500 mg Q8–12H 1–14: 500 mg Q24H
Cefadroxil	1–2 g daily divided	25–50: 500 mg Q12H 10–25: 500 mg Q24H <10: 500 mg Q36H
Cefpodoxime	200–400 mg Q12H	<30: 200–400 mg Q24H HD: 3x week after HD OR 200 mg once, 100 mg 12 h later, then 100 mg q24h
Cefixime	200 mg Q12H 400 mg Q24H	<20: 200 mg Q24H HD: use not recommended
TMP/SMX	10–15 mg/kg Q6–8H	15–30: 50% reduction <15: use not recommended
Clindamycin	300–450 Q6H	None
Doxycycline	100 mg Q12H	None
Linezolid	600 mg Q12H	None
Metronidazole	500 mg Q6–8H	None
Levofloxacin	500–750 mg Q24H	750 mg 20–49: 750 mg Q48H 10–19: 750 × 1, 500 mg Q48H 500 mg 20–49: 500 × 1, 250 mg Q24H 10–19: 500 × 1, 250 mg Q48H
Moxifloxacin	400 mg Q24H	None

**Appendix C.** Oral antibiotics prescribed.

Agent	<i>n</i>	Most common dosing regimen	<i>n</i> (%)
High bioavailability		–	
Fluoroquinolones		–	
Moxifloxacin	1	400 mg Q24H	1 (100)
Levofloxacin	11	750 mg Q24H	7 (64)
Linezolid	1	600 mg Q12H	1 (100)
Doxycycline	1	100 mg Q12H	1 (100)
Metronidazole	7	500 mg Q8H	7 (100)
Clindamycin	5	450 mg Q6H	2 (40)
TMP/SMX	1	160/800 mg Q12H	1 (100)
Low bioavailability		–	
Penicillins		–	
Penicillin VK	7	500 mg Q6H	6 (87)
Ampicillin	2	500 mg Q6H	2 (100)
Amoxicillin	24	500 mg Q8H	16 (67)
Amoxicillin/Clav	23	875 mg Q12H	19 (83)
Cephalosporins		–	
Cephalexin	12	500 mg Q6H	9 (75)
Cefpodoxime	6	200 mg Q12H	5 (83)
Cefdinir	2	300 mg Q12H	2 (100)
Cefixime	1	200 mg Q12H	1 (100)