

Original Research

Clinical Impact of Oral Step-Down Therapy for Gram-Negative Bacteremia: A Retrospective Study

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Abstract

Background

In recent years, there has been a growing body of evidence that supports oral step-down therapy for the treatment of gram-negative bacteremia. The purpose of this study was to compare outcomes for hospitalized patients who received intravenous-only (IV-only) therapy versus oral step-down therapy with low, moderate, and highly bioavailable antimicrobials for the treatment of gram-negative bacteremia.

Methods

In this retrospective, single-center, observational study, we examined data from adult patients hospitalized with gram-negative bacteremia in a 1-year period. Data analysis was performed using information collected from electronic medical records and a clinical surveillance system.

Results

A total of 199 patients were included in this study. Patients in the IV-only group had higher Charlson comorbidity index scores at baseline and higher rates of intensive care unit admission while bacteremic ($P = .0096$ and $.0026$, respectively). The primary outcome of 30-day all-cause mortality was significantly lower in the oral step-down group ($P < .0001$). Secondary outcomes of 30-day bacteremia recurrence, line-associated complications, and hospital length of stay were similar between groups. The total duration of antibiotic therapy was one day longer for oral step-down patients ($P = .0015$) and the estimated cost of antibiotic therapy was significantly lower in this group ($P < .00001$).

Conclusion

In this retrospective study, oral step-down therapy was not associated with increased 30-day all-cause mortality. Oral step-down therapy was also more cost-effective than IV-only therapy, while both groups had similar bacteremia recurrence within 30 days.

Keywords

gram-negative bacterial infections/drug therapy; bacteremia; infectious diseases; bacteremia/drug therapy; anti-bacterial agents/administration & dosage; oral administration; intravenous administration; mortality

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Background

Gram-negative bacteremia (GNB) is a significant cause of morbidity and mortality in the hospital setting,¹ with around 300 000 cases occurring annually in North America.² The most common sources of GNB include the urinary and gastrointestinal tracts,¹ with *Escherichia*

coli and *Klebsiella pneumoniae* being the most commonly isolated pathogens.³ Currently, there are no guidelines specifically dedicated to GNB. Available data are provided by the Infectious Diseases Society of America guidelines for the diagnosis and management of intravascular catheter-related infection and primary literature sources.⁴

Intravenous (IV) antimicrobial therapy is commonly used for the treatment of GNB.² However, prolonged usage of IV antimicrobials has been associated with line-related adverse events and extended hospital length of stay (LOS).² In recent years, there are more data supporting the use of oral step-down therapy for GNB treatment following adequate source control and clinical stability. For example, there is evidence that oral step-down antimicrobial regimens resulted in non-inferior outcomes and fewer hospital days compared to IV-only regimens for the treatment of GNB.^{3,5} Furthermore, oral step-down therapy is considered a more cost-effective alternative to IV-only therapy to alleviate healthcare expenditures.^{2,6} Oral agents with high and moderate bioavailability such as fluoroquinolones (FQs) and sulfamethoxazole-trimethoprim (SMX-TMP) have been preferred for treating GNB, due to concerns that oral agents with lower bioavailability may lead to treatment failure.⁷ However, recent studies demonstrated similar clinical outcomes in hospitalized patients transitioned to oral step-down therapy with lower bioavailability, such as beta-lactams (BLs).^{2,8}

At our facility, oral step-down antimicrobial therapy, particularly with BLs, is commonly prescribed for the treatment of GNB. The purpose of this study was to evaluate the current oral step-down practices at our institution and compare clinical outcomes between patients who received IV-only versus oral step-down antimicrobial therapy for GNB. We hypothesized that patients in the 2 treatment arms would have similar clinical outcomes.

Methods

This study was deemed exempt from oversight by HCA Healthcare's Institutional Review Board and the requirement for informed consent was waived. We conducted a retrospective, single-center, observational study of adult patients hospitalized with GNB between August 1, 2019, and August 1, 2020. Patients were included if they were at least 18 years of age and either received IV antibiotics for the full treatment duration or were transitioned to oral therapy at any point. Patients were excluded if they were less than 18 years of age, had blood cultures that turned positive after discharge or death, had polymicrobial bacteremia or com-

plicated bacteremia including central nervous system involvement, bone and joint infection, or endocarditis, or were discharged from the emergency department without readmission. Pertinent patient data were collected from electronic medical records and a clinical surveillance system, a tool used to conduct prospective audit and feedback activities, and readmission data were available across multiple hospitals for the local health system. The primary outcome was 30-day all-cause mortality from the last day of inpatient antibiotic therapy. Survival was assumed for all patients without any documentation of death or acute transition to hospice within 30 days. Secondary outcomes included 30-day bacteremia recurrence, escalation to IV therapy in the oral step-down group, line-associated adverse events as evident by ultrasound-confirmed deep venous thrombosis or line-associated infections, duration of IV and oral antibiotic therapy from the first positive gram stain, hospital LOS from the first positive gram stain, and estimated cost of antibiotic therapy based on average wholesale pricing data. Additional data points of interest included the culture-confirmed or provider-suspected source of bacteremia, achievement of source control, duration of IV therapy prior to oral step-down, isolation of organisms with inducible or confirmed resistance to third-generation cephalosporin or carbapenems, Charlson comorbidity index (CCI) scores at baseline, intensive care unit (ICU) admission at any point while bacteremic, and bioavailability of oral antibiotics. Fisher's exact test and Mann-Whitney U test were utilized to perform statistical analysis.

Results

A total of 256 unique patients with GNB were screened for potential inclusion in this study, with 199 patients meeting the criteria for inclusion. The IV-only group had 114 patients and the oral step-down group had 85 patients (**Figure 1**).

As presented in **Table 1**, patients in the IV-only group had higher CCI scores and rates of ICU admission while bacteremic at baseline ($P = .0096$ and $.0026$, respectively). The most common sources of bacteremia were the urinary and gastrointestinal tracts in both groups, and the achievement of source control was similar between groups ($P = .87$). *E coli* and *K pneumo-*

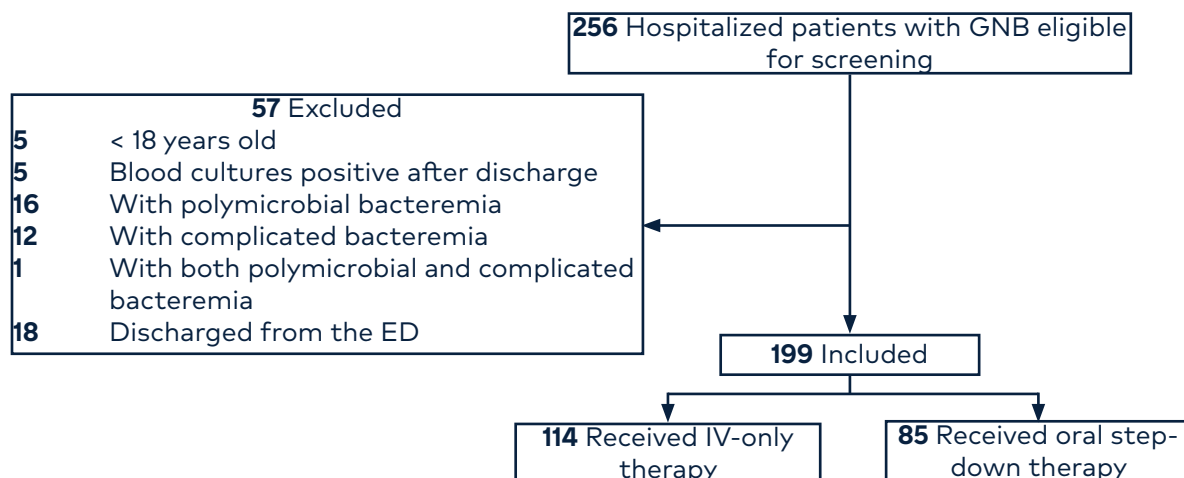


Figure 1. The flow chart shows the inclusion and exclusion criteria and study groups. Abbreviations: GNB = gram-negative bacteremia, ED = emergency department, IV = intravenous

niae were the most commonly isolated organisms in both groups, with a higher prevalence of isolates with inducible or confirmed resistance to third-generation cephalosporins in the IV-only group ($P < .0001$).

The primary outcome of 30-day all-cause mortality was significantly lower in the oral step-down group compared to the IV-only group (4.7% vs 26.3%, $P < .0001$). Both groups had similar rates of 30-day bacteremia recurrence, line-associated complications, and hospital LOS ($P = .51, .51, \text{ and } .11$, respectively) (Table 2). The total duration of antibiotic therapy was shorter in the IV-only group by one day (13 vs 14 days, $P = .0015$), and the median duration of IV therapy prior to oral step-down was 3 days (IQR 2-5 days). The estimated cost of antibiotic therapy was significantly lower in the oral step-down

group ($P < .00001$), and a single patient in the oral step-down group was transitioned back to IV antimicrobial therapy (Table 2).

At our facility, oral BLs with low bioavailability were the most frequently prescribed oral step-down therapy for GNB (Table 3).

Discussion

In this study of 199 patients with GNB, oral step-down therapy was associated with a significantly lower 30-day mortality compared to IV-only therapy. The frequent isolation of *E coli* from urinary and intra-abdominal sources in this study was consistent with existing literature for GNB, as was the median duration of 3 days of IV antibiotic therapy prior to oral step-down.^{3,8} Previous studies have shown increased

Table 1. Characteristics of Hospitalized Adult Patients With Intravenous-Only Versus Oral Step-Down Antimicrobial Regimens

Characteristic	IV-only (n = 114)	Oral step-down (n = 85)	P value
CCI: median score (IQR)	5 (3-7)	4 (2-6)	.0096
ICU admission: n (%)	43 (37.7)	15 (17.7)	.0026
Organism: name (%)	<i>E coli</i> (53.5) <i>K pneumoniae</i> (16.7) Other (29.8)	<i>E coli</i> (62.4) <i>K pneumoniae</i> (15.3) Other (22.3)	N/A
MDROs isolated: n (%)	50 (43.86)	6 (7.06)	< .0001
Source: source name (%)	UTI (57.0) IAI (20.2) Other (22.8)	UTI (51.8) IAI (22.4) Other (25.8)	N/A
Source control: n (%)	85 (74.7)	65 (76.5)	.87

Abbreviations: IV = intravenous, CCI = Charlson comorbidity index, IQR = interquartile range, ICU = intensive care unit, MDRO = multi-drug resistant organism, UTI = urinary tract infection, IAI = intra-abdominal infection

Table 2. Study Outcomes in Intravenous-Only Versus Oral Step-Down Groups

Outcome	IV-only (n = 114)	Oral step-down (n = 85)	P value
30-day all-cause mortality: n (%)	30 (26.3)	4 (4.7)	< .0001
30-day bacteremia recurrence: n (%)	2 (1.8)	0 (0)	.51
Escalation from oral to IV therapy: n (%)	N/A	1 (1.2)	N/A
Line-associated complications: n (%)	2 (1.8)	0 (0)	.51
Duration of therapy: median days (IQR)	13 (5-15)	14 (12-16)	.0015
Cost of antibiotic therapy: median dollars (IQR)	67.73 (26.03-118.05)	23.90 (15.68-34.47)	< .00001
LOS: median days (IQR)	5 (3-10.8)	5 (3-7)	.11

Abbreviations: LOS = length of stay, IV = intravenous, IQR = interquartile range

line-associated adverse events and a prolonged hospital LOS in patients who are maintained on IV-only therapy compared to oral step-down therapy, but there was no significant difference in these outcomes noted in this study. However, information on line-associated complications was not available after patients were discharged on IV antibiotics. Thus, there could have been adverse events associated with extended IV antibiotic usage that were not documented in the inpatient electronic medical records.

There were significantly fewer deaths in the oral step-down group. The majority of deaths in our study occurred during hospitalization while patients were receiving IV antibiotic therapy, which may have driven this mortality difference. Patients in the IV-only group also had higher CCI scores and rates of ICU admission, suggesting these patients were more critically ill at baseline. The increased severity of illness for patients in the IV-only group potentially explains why these patients remained on IV antibiotic therapy for the full treatment duration. Additionally, organisms with inducible or confirmed resistance to third-generation

cephalosporins were more frequently isolated in the IV-only group, leaving fewer oral step-down therapy options for these patients. During the study period, minimum inhibitory concentrations (MIC) and associated susceptibility interpretations for FQs were suppressed on all culture results due to breakpoint changes, though manual susceptibility testing was available upon request. This suppression of susceptibility results for FQs may have impacted the overall step-down therapy prescribing patterns in this study. However, MIC and susceptibility interpretive data were routinely available for SMX-TMP, a moderately bioavailable oral agent of choice for GNB, yet it was not commonly prescribed as step-down therapy.

Historically, oral BLs have not been preferred agents for GNB due to risks of clinical failure associated with subtherapeutic serum levels.^{9,10} However, oral BLs are associated with better tolerability and less collateral damage than FQs and SMX-TMP,^{2,8} rendering them appealing step-down options for GNB. With a bioavailability of only 16-25%,¹¹ cefdinir was, surprisingly, the most frequently prescribed oral step-down therapy in this study. As a result, it could

Table 3. Bioavailability of Oral Step-Down Antimicrobials

	Bioavailability		
	Low (< 75%)	Moderate (75-94%)	High (≥ 95%)
Distribution of individual antibiotics: drug name, n (%)	Cefuroxime, 4 (4.6) Cefpodoxime, 4 (4.6) Cefdinir, 41 (47.1) Amoxicillin/ clavulanate, 5 (5.7)	SMX-TMP, 2 (2.3) Ciprofloxacin, 5 (5.7) Cephalexin, 18 (20.7)	Levofloxacin, 7 (8) Metronidazole, 1 (1.1)
Total distribution of antibiotics in each category: n (%)	54 (62.1%)	25 (28.7%)	8 (9.2%)

Abbreviation: SMX-TMP = sulfamethoxazole-trimethoprim

be inferred that oral step-down therapy using agents with low bioavailability, such as oral BLs, could be a reasonable treatment option for GNB once clinical stability is achieved.

As recent literature has demonstrated that a shorter antibiotic duration of 7 days is non-inferior to 14 days for uncomplicated, source-controlled GNB,¹ there is an opportunity to optimize the duration of therapy at our facility since most of our patients received 14 days of antibiotics. This opportunity can encourage a reduction in antibiotic usage and subsequently the cost of therapy for both the patients and the institution.

Our study was not without limitations. The retrospective nature of this study made it challenging to collect complete data. Since the study was conducted at only 1 institution with a small sample size, extrapolation of the results should be done with caution. Another major limitation of this study was the lack of access to mortality and bacteremia recurrence data from other health systems.

Conclusion

The majority of the findings in this study were consistent with previous literature on the management of GNB. Our patients who received oral step-down therapy had lower mortality rates, and had reduced antimicrobial costs without a clinically significant difference in hospital LOS or duration of antibiotic therapy. Based on the results of this study, oral step-down antibiotic therapy, including agents with lower bioavailability, may be a reasonable treatment option in patients hospitalized with GNB following source control and clinical stability. Due to the small sample size and single-center nature of this study, further research is needed to confirm the validity of oral step-down antimicrobial therapy, especially of oral BLs, in the treatment of GNB.

Authors' Contributions

NN was involved in project development, data collection, data analysis, and writing of the abstract and manuscript. KO was involved in formulating the project idea, project development, data collection methods, data analysis guidance, and writing of the abstract and manuscript. AJ and MM were involved in the project

development and writing of the abstract and manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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