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Intravenous-only or intravenous transitioned to oral antimicrobials for Enterobacteriaceae-associated bacteremic urinary tract infection

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Abstract

Limited evidence supports use of oral antibiotics for Enterobacteriaceae-associated bacteremic urinary tract infection. This retrospective cohort study found no statistically significant difference in the composite outcome of treatment failure in patients who received exclusively intravenous versus intravenous/oral antibiotics for the treatment of bacteremic urinary tract infections.

Keywords

urinary tract infection; Enterobacteriaceae; bacteremia; oral antibiotic; antibiotic; fluoroquinolone

Background

Bacteremia is typically treated with intravenous (IV) antibiotics for a duration determined by the nidus of infection. In some cases, such as pneumonia, there is sufficient evidence for guidelines to recommend oral (PO) antibiotics.[1] In other situations, clinicians must use judgment based on factors such as persistence of bacteremia, likely susceptibility of potential pathogens to appropriate antibiotics, predicted adequacy of drug absorption and

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penetration at the site of infection, host immune status, anticipated adherence, and reliability of follow-up.

Some evidence supports the use of PO fluoroquinolones for bacteremic urinary tract infections (UTIs). One study showed that patients treated with ciprofloxacin or levofloxacin, whether administered IV or PO, had negative cultures at the test of cure.[2] Another investigation of the treatment of pyelonephritis with ciprofloxacin demonstrated the effectiveness of PO therapy despite 42% of patients having positive blood cultures.[3] Additionally, a study examining the cost savings of an IV-to-PO transition for bacteremia found that length of hospital stay (LOS) decreased by 6 days, and hospital days on antibiotics decreased by 2 days in the IV-to-PO transition group.[4] When assessed, the common predictors for not de-escalating were documented fluoroquinolone resistance, bacteria other than *Escherichia coli*, and discharge to a long-term care facility.[5]

The purpose of the current study was to examine failure rates among patients receiving exclusively IV antibiotics (IV-only) compared with partial or complete treatment with PO (referred to as IV/PO) antibiotics for Enterobacteriaceae bacteremic UTIs.

Methods

Following approval by the Institutional Review Board at the Medical University of South Carolina (MUSC), a retrospective cohort study of patients with Enterobacteriaceae bacteremic UTI was conducted. Patients ≥ 18 years old hospitalized between July 1, 2010, and June 30, 2015 were included. Enterobacteriaceae bacteremic UTI was defined as those with positive urine and blood cultures, collected within a 24-hour period, with the same pathogen (i.e., *Enterobacter* spp., *E. coli*, *Klebsiella* spp., *Proteus* spp., *Serratia marcescens*, *Citrobacter* spp., *Morganella morganii, or Providencia* spp). Exclusion criteria were inability to receive PO therapy (e.g., pathogen not susceptible to any PO antibiotic; allergy to PO antibiotics to which organism was susceptible), ongoing receipt of total parenteral nutrition, and patients with long-term vascular access such as a port or tunneled central venous catheter. Eligible patients were identified, and baseline characteristics were extracted from an internal database. ICD codes were used to calculate the Charlson comorbidity index (CCI).[6–8] The medical record (EPIC starting in July 2014 and McKesson-Horizon Meds Manager from July 2010 to July 2014) was also reviewed for relevant study data including antibiotics, pathogen susceptibilities, and information related to treatment course. The two treatment groups, IV-only and IV/PO, were compared for the composite primary outcome of documented failure of therapy, defined as escalation to IV from PO antibiotic, change in antibiotic due to worsening clinical status, or readmission for the same infection and pathogen (either UTI and/or bacteremia) within 30 days of discharge. At our institution, patients admitted with bacteremic UTI often are started on IV antibiotics initially and then transitioned to PO antibiotics on the day before discharge. Secondary outcomes of LOS and hospital days on antibiotics were also evaluated. Outcomes were assessed between groups using Fisher's exact test or Wilcoxon rank sum tests, as appropriate, due to the low failure rates and relatively small sample size. Continuous data is represented as median (interquartile range [IQR]) in the results. In order to account for differences in severity of

illness, generalized linear models were also used to compare group (IV-only vs. IV/PO) differences while accounting for CCI scores.

Results

Two hundred forty one patients met the inclusion criteria. The median age of the patients was 64 (54 to 74) years, 46% were male, and were predominantly African American (53%) or Caucasian (46%)(Table1). CCI was 7 (4 to 10), and most patients had diabetes, often with comorbid renal disease. LOS was 5.2 (3.7 to 10.9) days, with 25.7% of patients being admitted directly to the ICU. ICU LOS was 93 (38 to 349) hours for IV-only and 65 (46 to 109) hours for IV/PO. Overall, 42 (39.6%) of IV-only were admitted to the ICU versus 37 (27.4%) of IV/PO (p=0.045). Bacteremia was identified within 72 hours of admission in 88.8% of patients. One hundred six patients (44%) were treated with IV-only and 135 patients (56%) with IV/PO, 5 of who received PO antibiotics only. Pathogens isolated from blood and urine cultures were predominately *E. coli* (56.8%) and *K. pneumoniae* (22.8%). *E. coli* was the pathogen in 50% (95% CI: 40 to 60%) of the IV-only and 62% (95% CI: 53 to 70%) of the IV/PO (p=0.07). Polymicrobial infections (≥ 2 pathogens) with the same Enterobacteriaceae isolates in blood and urine were found in 1% of patients. Multidrug resistant (MDR) pathogens, which are defined as resistance to three or more antimicrobial classes, were found in 39% (95% CI: 29 to 49%) of IV-only and 23% (95% CI: 16 to 31%) of IV/PO (p=0.01). Discharge antibiotics were predominantly ciprofloxacin (65.3%), various β-lactam antibiotics (19%), and trimethoprim-sulfamethoxazole (TMP-SMX; 9.1%) if PO (n=121) and ceftriaxone (73.9%), cefepime (5.8%), and ertapenem (5.8%) if IV (n=69).

There was not a significant difference in the primary outcome of documented treatment failure in IV-only (3.8% [95% CI: 1.0 to 9.4%] failure) compared with IV/PO (8.2% [95% CI: 4.1 to 14.1%] failure; p=0.19). IV-only had 14.2% (95% CI: 8.1 to 22.3%) all-cause mortality during hospitalization versus 2.2% (95% CI: 0.5 to 6.4%) of IV/PO (p<0.001). Hospital days on antibiotics were fewer in the group treated with PO antibiotics (5 [3 to 7] days vs. 6 [4 to 10] days; p<0.001). For the IV/PO group, median number of days of IV prior to switching to PO was 4 days (IQR 2 to 5; range 0 to 15). The IV/PO group includes 5 patients that exclusively received PO antibiotics and therefore no days of IV antibiotics. LOS was less in the group treated with PO antibiotics (4.6 [3.1 to 7.8] days vs. 7.1 [4.0 to 17.5] days; p<0.001). CCI was 8 (5 to 11) in IV-only vs. 6 (4 to 9) in IV/PO (p=0.03). Since CCI was different between IV-only and IV/PO, all outcomes were re-evaluated using CCI as a covariate in generalized linear models. Following adjustment for CCI, LOS remained significantly related to the group with IV-only having longer hospital stays (p=0.004). CCI was not found to be significantly related to LOS (p=0.2), death during hospitalization (p=0.4), nor MDR pathogen (p=0.9). Also, the hospital days on antibiotics were still different between groups after adjustment for CCI (p<0.001). Neither CCI nor treatment group was related to failure in multivariate analysis.

Failures in the IV-only group (n=4) occurred in patients with *E. cloacae*, *P. mirabilis*, *E. coli*, and *M. morganii*. Three IV-only failures were admitted to the ICU, and of those admitted to the ICU all 3 had MDR pathogens. Failures in the IV/PO group (n=11) occurred in patients with *E. coli* (n=5), *K. pneumoniae* (n=3), *S. marcescens* (n=2), and *P. mirabilis* (n=1). MDR

pathogens were present in 4 of 11 patients in the IV/PO failure subgroup. Overall, reasons for failure were readmission within 30 days with same infections (5 total = 1 IV-only + 4 IV/PO), escalation from PO to IV antibiotic (5 total = 5 IV/PO; note that this cannot be detected in IV-only group), and change in antibiotics due to declining clinical status (6 total = 3 IV/PO + 3 IV-only).

For 5 of the 11 treatment failures in the IV/PO group, the criterion for failure was escalation from PO to IV therapy, an outcome that cannot, by definition, be detected in the IV-only group and may be secondary to clinical reasons other than treatment failure, which may bias to detect more failure in the IV/PO group. The rationale for antibiotic changes was not always clearly documented, so if the patient could have been worsening clinically, this was assumed to be a failure. Adverse events associated with IV therapy, such as extravasation or catheter-associated infections or complications, were not addressed in the study. Patient adherence to any therapy after discharge was not assessed. However, 4 of the 6 IV/PO patients prescribed a PO fluoroquinolone at discharge who experienced treatment failure were also discharged on a scheduled polyvalent cation that may have contributed to treatment failure. None of the 5 patients receiving only PO antibiotics (included in the IV/PO group for analysis) experienced treatment failure, and 2 of the 5 patients treated with only PO antibiotics had MDR pathogens.

Discussion

This study included patients treated with PO antibiotics for bacteremic UTI and involved a variety of pathogens and antibiotic regimens. Overall, there was no difference in treatment failure between IV-only and IV/PO. However, shorter LOS and fewer hospital days on antibiotics were observed for the IV/PO versus the IV-only group. While this study was not designed to examine whether patients remained hospitalized to complete a course of IV antibiotics, it might be inferred from the lower frequency of discharge on IV antibiotics. Typical practice at our institution is to initiate patients admitted for bacteremic UTI with IV antibiotics and transition to PO the day before discharge which is reflected in the median 4 days of IV prior to transitioning to PO antibiotics for the IV/PO group. Facilitating discharge by using PO antibiotics may potentially reduce hospitalization costs or improve patient satisfaction scores. LOS was calculated from admission to discharge and not from time of documented infection to discharge. However, because 88.8% of patients were found to be bacteremic within 72 hours of admission, LOS is a decent surrogate marker for the impact of the infection on LOS. Critically ill patients with longer ICU admissions were included in the study limit the generalizability of LOS as an outcome given their complex illness and multifactorial reason for longer LOS. Additionally, in this study 46% of the population was male and urologic abnormalities were not quantified, which could have led to more failure from complicated UTI.

It appears that the IV-only group included more severely ill patients in aspects beyond the CCI (Table). These patients had a higher incidence of infection with MDR organisms, longer ICU LOS, and were more often admitted to the ICU. Nonetheless, accounting for CCI did not impact the results for primary or secondary outcomes. However, CCI is calculated from ICD-9 and ICD-10 codes and therefore there is potential for coding errors.

One factor unique to this institution that might have influenced prescribing is a formulary restriction of ciprofloxacin to a documented susceptible pathogen and non-formulary status of levofloxacin. Historically, relatively low susceptibilities of typical target pathogens, namely *P. aeruginosa* and *E. coli*, led to this restriction. Because these drugs exhibit many desirable characteristics including high concentrations in the genitourinary system, similar concentrations with PO and IV dosing, and low cost, higher use may have yielded different results, possibly improving the favorability of IV/PO treatment.

In light of these limitations, similar results in a larger study population to corroborate the findings of this study and elucidate risk factors for failure would further enhance clinical decision-making. A publication on the effectiveness of PO antibiotics in the treatment of gram-negative bloodstream infections included 70.2% patients with bacteremia from a urinary source and found that antibiotics with high bioavailability had a lower rate of failure than antibiotics of moderate or low bioavailability.[9] However, the evidence that PO therapy can be used successfully to complete the treatment course for Enterobacteriaceae bacteremic UTI, coupled with the potential for reducing costs with shorter lengths of stay and fewer hospital days on antibiotics, provides a foundation for utilization of PO antibiotics in this situation.

Conclusion

IV/PO treatment was associated with a shorter length of stay and fewer hospital antibiotic days compared with IV-only therapy. No statistically significant differences in treatment failures were observed between groups. Transitioning from IV to PO antibiotic therapy is a viable treatment option to consider for patients with bacteremic Enterobacteriaceae UTI.

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Table 1

Baseline characteristics

Characteristic	Treatment group, No. (%)		
	IV-only (n=106)	IV/PO (n=135)	Overall (n=241)
Age, years[a]	64 (54–75)	64 (55–72)	64 (54–74)
Male	56 (53)	56 (41)	112 (46)
Race			
Caucasian	45 (42)	66 (49)	110 (46)
African American	59 (56)	68 (50)	128 (53)
Charlson comorbidity index[a]	8 (5–11)	6 (4–9)	7 (4–10)
Myocardial infarction	17 (16)	7 (5)	24 (10)
Congestive heart failure	31 (29)	35 (26)	66 (27)
Peripheral vascular disease	24 (23)	32 (24)	56 (23)
Cerebrovascular disease	32 (30)	33 (24)	65 (27)
Dementia	7 (7)	8 (6)	15 (6)
Chronic pulmonary disease	36 (34)	48 (36)	84 (35)
Rheumatic disease	7 (7)	14 (10)	21 (9)
Peptic ulcer disease	11 (10)	11 (8)	22 (9)
Mild liver disease	30 (28)	24 (18)	54 (22)
Diabetes without chronic complication	64 (60)	72 (53)	136 (56)
Diabetes with chronic complication	21 (20)	35 (26)	56 (23)
Hemiplegia or paraplegia	21 (20)	17 (13)	38 (16)
Renal disease	39 (37)	66 (49)	105 (44)
Any malignancy (except skin)	50 (47)	44 (33)	94 (39)
Moderate or severe liver disease	6 (6)	1 (1)	7 (3)
Metastatic solid tumor	19 (18)	10 (7)	29 (12)
HIV/AIDS	0 (0)	0 (0)	0 (0)

HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; IV = intravenous; PO = oral.

[a]Data presented as median (interquartile range: 25th percentile to 75th percentile).