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Comparison of intravenous and oral definitive antibiotic regimens in hospitalised patients with Gram-negative bacteraemia from a urinary tract infection

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ABSTRACT

Objectives: Transitioning patients from intravenous (IV) to oral antibiotic therapy has been shown to be a successful approach for several infections. However, minimal data exist evaluating outcomes following transition from to oral antibiotics for patients with bacteraemia secondary to a urinary tract infection (UTI). This study compared treatment failures between patients treated exclusively with IV antibiotics and those transitioned from IV to oral antibiotics for bacteraemia secondary to UTI.

Methods: This single-centre, retrospective cohort study included hospitalised, non-critically ill adult patients treated with culture-susceptible antibiotic therapy for 7–21 days. Patients were divided into two cohorts based on the route of definitive antibiotic administration. Treatment failure was a composite outcome of death and recurrence of the index micro-organism within 21 days following negative blood cultures.

Results and discussion: Among the 346 patients enrolled, 82 (23.7%) were in the IV cohort and 264 (76.3%) were in the IV-to-oral cohort. A total of six treatment failures occurred; 2 (2.4%) in the IV cohort and 4 (1.5%) in the oral transition cohort (hazard ratio = 0.62, 95% confidence interval 0.11–3.39; $P = 0.58$). All failures were due to recurrence of the index organism. Secondary outcomes demonstrated a significantly higher rate of IV line-associated complications in the IV cohort ($P = 0.03$) and a favourable hospital length of stay in the oral cohort ($P < 0.001$). Patients transitioned from IV to oral antibiotics based on culture-susceptibility data experienced similarly low rates of treatment failure as those who received exclusive IV therapy.

1. Introduction

The urinary tract is implicated as a common source of infection among hospitalised patients with Gram-negative bacteraemia [1]. Epidemiologic data demonstrate that *Escherichia coli* is typically the most common organism isolated in these infections, particularly in community-acquired infections [2]. Empirical therapy is often intravenous (IV) and directed towards this organism, with agent selection based on resistance trends and patient-specific factors [3]. Once microbiological data become available, clinicians may have an array of agents to select for definitive therapy, including the possibility of an oral agent.

There is a paucity of literature describing optimal definitive management of Gram-negative bacteraemia from a urinary tract infection (UTI). When available, transition to a highly bioavailable and susceptible oral antibiotic to complete therapy may be reasonable, although there is minimal data examining this approach. To date, two studies have compared oral step-down antibiotic regimens among patients with Gram-negative bloodstream infections (BSIs), with variable results [4,5]. One study demonstrated non-inferiority between β-lactams and fluoroquinolones [5], whereas the other showed a significant difference in treatment failure among antibiotics with high, moderate and low bioavailability [4]. Both studies included variable sources of

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infection and did not utilise a cohort of patients treated exclusively with IV antibiotics to serve as a control. In a small retrospective cohort study of patients with Gram-negative bacteraemia originating from a UTI, low failure rates were observed among patients treated exclusively with IV management compared with step-down therapy to an oral antibiotic [6]. To date, there are no additional data describing definitive management strategies or transition to oral antibiotics in this patient population.

The purpose of this study was to compare the rate of treatment failure between patients treated exclusively with IV antibiotics and those transitioned from IV to oral antibiotics for Gram-negative bacteraemia secondary to UTI. Secondary objectives were to describe the rate of complications from IV line use (i.e. line-associated infection, thrombosis, device dysfunction) and hospital length of stay (LoS) after the start of therapy between groups.

2. Methods

2.1. Subjects

This was a single-centre, retrospective cohort study conducted at a large tertiary academic medical centre (Mayo Clinic, Rochester, MN). To be eligible for inclusion, patients had to be ≥18 years of age at the time of hospitalisation, less severely ill [treated in an intensive care unit (ICU) for <48 h], have a diagnosis of bacteraemia secondary to UTI, and treated with culture-susceptible antibiotic therapy for a minimum of 7 and maximum of 21 days. All patients required at least one dose of IV antibiotic therapy and a positive blood culture with reported antimicrobial susceptibilities. Patients were excluded if: their medical records were unauthorised for research; they had documented non-compliance to therapy listed in the medical record related to the index infection; the index organism was resistant to all oral antimicrobial options (could not be transitioned to oral); blood cultures grew *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus* spp. or any fungal species; cultures demonstrated polymicrobial growth; or they were on concurrent antibiotic therapy for other indications. This study was approved by the Institutional Review Board of Mayo Clinic (Rochester, MN).

2.2. Procedures

A data report from 1 January 2008 to 30 June 2016 was generated from an internal infection control database for all patients with documented bacteraemia considered secondary to UTI, defined as a positive urine culture for the same index organism within 48 h of positive blood culture. Individuals from this report were then screened based on the aforementioned inclusion and exclusion criteria and were divided into two cohorts based on definitive treatment of their bacteraemia: (i) IV antibiotics only for the entire duration; or (ii) transition (at any point in therapy) from IV to oral antibiotics. During chart review, the source of infection was confirmed to be from the urinary tract. Dosing of antibiotics was not retrospectively assessed but was assumed to be appropriate as all antibiotics were evaluated by a clinical pharmacist at the time of initial dispensing. Definitive antibiotic (oral or IV) and duration were selected at the discretion of the prescriber.

2.3. Data collection

For each included patient, demographic data (age, sex, race) and pertinent past medical history [urinary procedure within 30 days prior to positive blood culture, indwelling urinary device at the time of positive blood culture (including urinary catheter insertion within 72 h), immunocompromised condition] were collected. Patients were considered immunocompromised if they had a diagnosis of human immunodeficiency virus (HIV) or active malignancy or were receiving chronic immunosuppressant therapy (prednisone 20 mg/day or equivalent, anti-rejection therapy, tumour necrosis factor-alpha inhibitors or chemotherapy) at the time of study inclusion. Clinical data (hospital admission/discharge dates, Charlson comorbidity index, maximum body temperature within 24 h if transitioned from IV to oral therapy), pharmacological data (definitive antibiotic selection, duration of therapy) and microbiology data [dates of positive and first negative blood culture (if available), organism identified, antimicrobial susceptibilities] were also collected. The severity and age-weighted Charlson comorbidity index was computed based on the date of first positive blood culture for all included patients to assess the severity of illness [7]. Study data were collected and managed using Microsoft Excel (Microsoft Corp., Redmond, WA) and REDCap (Research Electronic Data Capture), a secure, Web-based application designed to support data capture for research studies [8].

2.4. Objectives

The primary objective was to compare the rates of treatment failure between treatment groups. Treatment failure was a composite outcome defined as either of the following: (i) death as a consequence of bacteraemia secondary to UTI; or (ii) positive blood culture for the same index organism requiring initiation of new antibiotic therapy. This composite outcome was assessed for a 21-day period starting from either the date of first negative blood culture or the first date of culture-susceptible antibiotics if there was no repeat culture. The decision to assess the primary outcome at 21 days was determined by the investigators given the lack of a validated or widely accepted definition of antibiotic failure. Extension of this time frame may increase the risk of other external factors influencing the success or failure of the chosen therapy. The secondary objectives were to compare the rate complications from IV line use (line-associated infection, thrombosis, device dysfunction) and hospital LoS following the start date of antibiotics between both cohorts using the same time frame as the primary objective.

2.5. Statistical analysis

Patient demographic data were compared using the Wilcoxon rank-sum test and Pearson's χ^2 test for continuous and discrete variables, respectively. Univariate Cox regression models were used to measure the association between therapy group and the outcomes of treatment failure, IV line-associated complications, hospital LoS after antibiotic start, and antibiotic duration. These models compared rates of daily failure, complication, hospital discharge and therapy completion when on oral therapy compared with IV therapy, respectively, and are reported as hazard ratios (HRs) with their 95% confidence intervals (CIs). Group membership was treated as a time-dependent covariate in these models, allowing patients to change from the IV to oral group at the appropriate follow-up time. Multivariable modelling was not performed owing to the limited number of treatment failures and IV line-associated complications. Landmark summaries of duration of therapy and hospital LoS, whereby therapy group membership was defined based on a fixed day of therapy, were performed to create unbiased comparisons between therapy groups. All analyses were conducted using SAS v.9.4 and JMP v.13.0 (SAS Institute Inc., Cary, NC).

3. Results

A total of 499 patients were screened for study eligibility. Applying the inclusion and exclusion criteria, 346 patients were

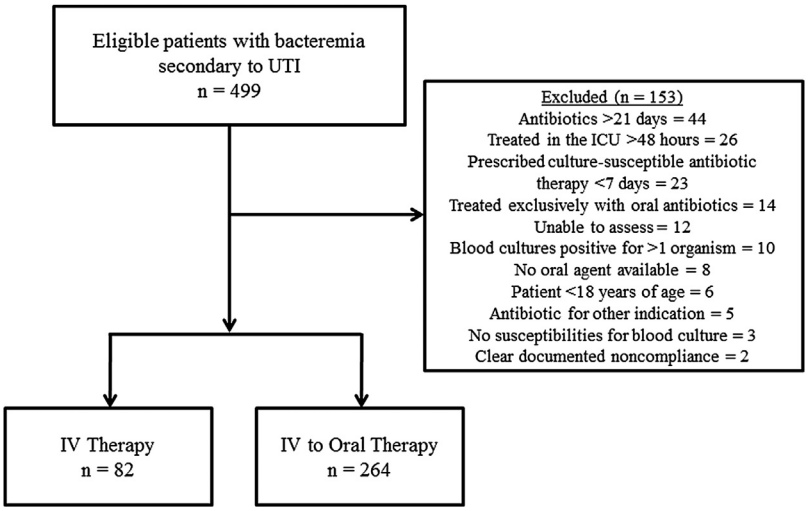

Fig. 1. Consort flow diagram illustrating patient exclusion and group assignment. UTI, urinary tract infection; IV, intravenous; ICU, intensive care unit.

eligible for review (82 patients in the IV cohort and 264 patients in the transition cohort) (Fig. 1). The most common reasons for exclusion were antibiotic duration >21 days and ICU stay >48 h.

The patient characteristics are summarised in Table 1. In the IV cohort, there were significantly more males (54% vs. 40%; $P = 0.03$), immunocompromised patients (41% vs. 21%; $P < 0.001$) and patients who underwent a urinary procedure or had an indwelling urinary device (50% vs. 31%; $P = 0.001$) prior to positive blood cultures. The causative micro-organisms also differed between cohorts, with a larger proportion of patients in the transition cohort infected with *E. coli*.

The most common definitive antibiotics utilised in the IV cohort were ceftriaxone, ertapenem and cefepime. The most common definitive antibiotics utilised in the transition cohort were ciprofloxacin, levofloxacin and trimethoprim/sulfamethoxazole (SXT). The median time to receipt of culture-susceptible antibiotics was longer in the IV cohort (Table 1). Duration of therapy was compared as a daily therapy completion rate and was similar between cohorts (oral versus IV HR = 1.18, 95% CI 0.92–1.51; $P = 0.20$). A landmark analysis on Day 7 of therapy demonstrated that patients receiving oral antibiotics had a median duration of therapy of 14 days [interquartile range (IQR) 13–15 days; $N = 254$ on Day 7] and patients receiving IV antibiotics had a mediation duration of therapy of 15 days (IQR 14–15.5 days; $N = 92$ on Day 7).

For the primary outcome of treatment failure, a total of six events were observed during the study period (Table 2). Treatment failure rates were similar between both cohorts [2/82 (2.4%) in the IV cohort vs. 4/264 (1.5%) in the transition cohort; oral vs. IV HR = 0.62, 95% CI 0.11–3.39; $P = 0.58$]. There were no deaths as a consequence of the original infection. All clinical failures were due to positive microbiology for the same index organism requiring initiation of new antibiotic therapy. No patients were transitioned from oral therapy back to IV therapy to treat the original infection.

Secondary outcomes demonstrated a significantly higher rate of IV line-associated complications in the IV cohort (6.1% vs. 0.4%; oral vs. IV HR = 0.08, 95% CI 0.01–0.74; $P = 0.03$) (Table 2). Hospital LoS after the start of antibiotic therapy was compared as a daily risk of discharge and favoured the oral cohort (oral vs. IV HR = 4.0, 95% CI 3.2–5.1; $P < 0.001$). A landmark analysis on Day 4 of therapy demonstrated that patients receiving oral antibiotics had a median length of stay of 4 days (IQR 4–5 days; $N = 100$ on Day 4) and patients receiving IV had a median length of stay of 6 days (IQR 5–9 days; $N = 109$ on Day 4) (Fig. 2).

Among the transition cohort, patients were changed to oral therapy after a median of 3 days of IV antibiotics (IQR 2–4 days). In this group, a total of 238 patients (90.2%) were afebrile (maximum temperature <38 °C) on the day of transition. Among all of the patients included, 280 patients (80.9%) had at least one surveillance negative blood culture collected following the index date of first positive blood culture. For breakdown by group, 97.6% (80/82) in the IV cohort had a negative blood culture and 75.8% (200/264) in the transition cohort had a negative blood culture ($P < 0.0001$).

4. Discussion

In this single-centre, retrospective cohort study of 346 patients with Gram-negative bacteraemia from a urinary source, no difference in treatment failure was observed when patients were compared based on the route (oral versus IV) of their definitive antibiotic therapy. Differences were demonstrated between cohorts when comparisons were made for rates of IV line-associated complications and hospital discharge/LoS. In the transition cohort, IV line-associated complications were rarer and patients were more likely to discharge sooner.

Based on these findings, it seems reasonable for clinicians to consider definitive therapy with a highly bioavailable and susceptible oral antibiotic when managing Gram-negative bacteraemia from a urinary source in patient populations similar to those included in this study. Critically ill patients, including those with septic shock, patients requiring an extended duration of therapy (beyond 21 days) and patients with polymicrobial infection, were excluded and should not be considered candidates for oral definitive therapy in the absence of additional data. Also, patients lacking source control and those with potential for non-compliance are beyond the context of this study. The differences observed for IV line-associated complications and hospital discharge/LoS demonstrate a potential benefit of transitioning to oral definitive therapy in appropriate patients, but this requires further study.

The results of this study are similar to those observed in a single-centre, retrospective cohort study with comparable methodology but smaller sample size [6]. In that study, the primary outcome, a composite of treatment failure, occurred in 3.8% of patients in the IV cohort versus 8.2% in the transition cohort ($P = 0.19$). Although there was no difference in failure between cohorts, the failure rates reported were somewhat higher than those observed in the current study. This is likely multifactorial,

Table 1
Characteristics of patients included in the intravenous (IV) and IV-to-oral transition study cohorts.

Characteristic	IV cohort (*N* = 82)	Oral transition cohort (*N* = 264)	*P*-value[a]
Age (years) [median (IQR)]	71 (59–79)	73 (62–82)	0.25
Male sex [*n* (%)]	44 (54)	106 (40)	0.03
Race[b] [*n* (%)]			0.45
White	78 (95)	242 (92)	
Other	4 (5)	19 (7)	
Immunocompromised[c] [*n* (%)]	34 (41)	56 (21)	<0.001
Urinary procedure and/or indwelling device[d] [*n* (%)]	41 (50)	81 (31)	0.001
Charlson comorbidity index[e] [median (IQR)]	5 (3–8)	5 (3–8)	0.86
Microbiology [*n* (%)]			0.049
Escherichia coli	46 (56)	183 (69)	
Klebsiella spp.	11 (13)	38 (14)	
Pseudomonas aeruginosa	12 (15)	17 (6)	
Enterobacter spp.	6 (7)	14 (5)	
Proteus mirabilis	4 (5)	5 (2)	
Citrobacter spp.	2 (2)	2 (1)	
Serratia spp.	0	3 (1)	
Morganella spp.	0	2 (1)	
Providencia spp.	1 (1)	0	
Time to receipt of culture-susceptible antibiotic[f] (days) [median (IQR)]	0 (0–1)	0 (0–0)	0.0004
Definitive antibiotic [*n* (%)]			
Ceftriaxone	35 (43)	–	
Ertapenem	21 (26)	–	
Cefepime	14 (17)	–	
Meropenem	3 (4)	–	
Piperacillin/tazobactam	2 (2)	–	
Aztreonam	2 (2)	–	
Ciprofloxacin	2 (2)	126 (48)	
Levofloxacin	3 (4)	103 (39)	
Trimethoprim/sulfamethoxazole	0	21 (8)	
Amoxicillin/clavulanic acid	–	6 (2)	
Cefpodoxime	–	3 (1)	
Cefdinir	–	2 (0.8)	
Cefalexin	–	2 (0.8)	
Ampicillin	0	1 (0.4)	

IQR, interquartile range.
[a] Group comparisons were made using the Wilcoxon rank-sum test and Pearson's χ^2 test for continuous and discrete variables, respectively.
[b] Three patients in the transition to oral cohort were missing details regarding race.
[c] Defined as a diagnosis of human immunodeficiency virus (HIV), active malignancy or receipt of chronic immunosuppressant therapy (prednisone 20 mg/day or equivalent, anti-rejection therapy, tumour necrosis factor-alpha inhibitors or chemotherapy) at the time of study inclusion.
[d] Defined as a urinary procedure occurring within 30 days prior to positive blood culture, an indwelling urinary device at the time of positive blood culture, or a urinary catheter inserted within 72 h of positive blood culture.
[e] Severity and age-weighted Charlson comorbidity index computed based on date of first positive blood culture (range 0–39).
[f] Calculated by subtracting the start date of culture-susceptible antibiotics from the date of first positive blood culture.

Table 2
Comparison between the intravenous (IV) and IV-to-oral transition study cohorts for rates of treatment failure and IV line-associated complications, and risk of discharge.

	IV cohort (*N* = 82)	Oral transition cohort (*N* = 264)	Oral vs. IV HR (95% CI)	*P*-value[a]
Treatment failure[b] [*n* (%)]	2 (2.4)	4 (1.5)	0.62 (0.11–3.39)	0.58
Infection-related death [*n* (%)]	0	0		
Positive microbiology [*n* (%)]	2 (2.4)	4 (1.5)		
IV line-associated complications[b] [*n* (%)]	5 (6.1)	1 (0.4)	0.08 (0.01–0.74)	0.03
New infection [*n* (%)]	0	0		
Thrombosis [*n* (%)]	2 (2.4)	0		
Device dysfunction [*n* (%)]	0	0		
Other[c] [*n* (%)]	3 (3.7)	1 (0.4)		
Hospital discharge			4.0 (3.2–5.1)	<0.001

HR, hazard ratio; CI, confidence interval.
[a] Group comparisons were made using univariate Cox regression models.
[b] Rates of treatment failure and IV line-associated complications were assessed in the period from the date of first negative blood culture (or the first date of culture-susceptible antibiotics if no repeat culture) through 21 days.
[c] In the IV cohort, 1 patient required an emergency department visit for IV line removal, 1 patient's line was unnecessarily left in for 5 days following antibiotic completion and 1 patient experienced redness/irritation at line insertion site; and in the transition to oral cohort, 1 patient experienced left hand/upper extremity oedema where the line was inserted.

but a potential reason may be inclusion of more severely ill patients. In the current study, patients with ICU stay >48 h were excluded, whereas Rieger et al. included patients regardless of their ICU LoS [6]. Also, Rieger et al. assessed patients for treatment failure for a longer duration (within 30 days of discharge) [6]. Two other retrospective studies compared oral definitive therapy options in patients with Gram-negative bacteraemia originating from a variety of sources. Mercuro et al. reported clinical success rates of 86.9% in patients who received β-lactam step-down therapy and 87.1% in patients who received fluoroquinolone step-

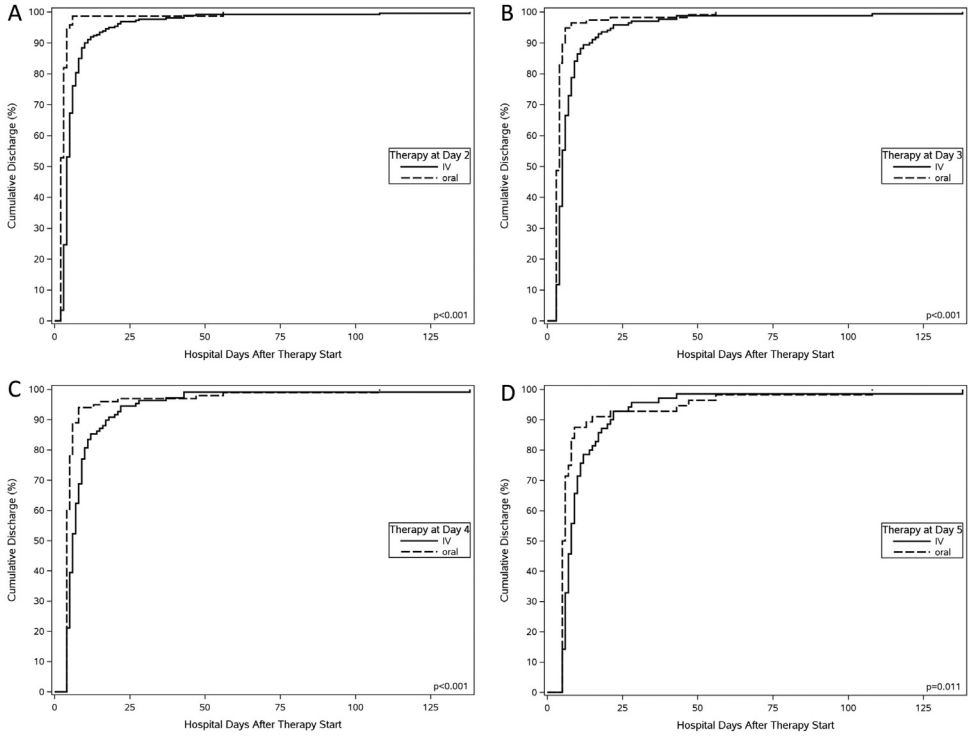

Fig. 2. Kaplan–Meier plots representing landmark curves on (A) Day 2, (B) Day 3, (C) Day 4 and (D) Day 5 of hospitalisation after therapy start for the intravenous (IV) and IV-to-oral transition study cohorts. Each plot depicts hospital discharge rates going forward from the respective hospitalisation day. Group comparisons were made using the log-rank test, and *P*-values are shown in the lower right corner of each plot.

down therapy (*P*-value not significant for non-inferiority) [5]. Upon comparing early (≤3 days) and late (>3 days) step-down therapy from IV therapy, clinical success rates remained similar [5]. Kutob et al. reported treatment failure rates of 2% in patients who received high bioavailability antibiotics (levofloxacin), 12% in patients who received moderate bioavailability antibiotics (ciprofloxacin, SXT) and 14% in patients who received low bioavailability antibiotics (β-lactams) ($P = 0.02$) [4]. Similar to the current study, the majority of patients received a fluoroquinolone or SXT. The overall rate of treatment failure (7.5%) was slightly higher than in the current study and may be due to use of a longer time frame to assess treatment failure (within 90 days from the onset of BSI) and inclusion of infections from all sources [4]. These three studies, in addition to ours, demonstrate that definitive management of Gram-negative BSI with an oral antibiotic may be a viable option, taking into account agent bioavailability and appropriate patient factors. Although Mercuro et al. found comparable success with oral β-lactams [5], we cannot support nor refute this given their very low frequency of use in the current study. Fluoroquinolones were likely relied upon for definitive oral therapy most commonly in all of the studies because of their excellent bioavailability (70–99%) and their ability to achieve high concentrations to exert their bactericidal effect [9].

The data presented in this study have significant implications on clinical practice and future management of this population. The low incidence of clinical failure supports the notion that Gram-negative BSIs from a urinary source in clinically stable patients are highly responsive to therapy, even when an oral fluoroquinolone is used for definitive management. In fact, this study and the aforementioned study by Rieger et al. [6] demonstrate that clinicians more commonly selected oral definitive therapy for these infections. With publication of these results and lack of management guidelines, more clinicians may gain confidence with transitioning to an oral fluoroquinolone in patients who are similar to those included in this study and do not have a known contraindication. It is also worth noting the brevity of IV therapy utilised in the transition cohort. Despite receiving only a median of 3 days of IV therapy before transition, this group responded extremely well and had very low rates of clinical failure, as highlighted above.

Although this study was designed to prevent and minimise confounding risks, several limitations do exist. The retrospective cohort design of this study introduces inherent risks, including the inability to randomise patients to different cohorts, and requires the investigators to rely on historical documentation. As a result, achievement of source control could not be determined for every subject. Also, as previously discussed, the cohorts in this study had some differing baseline characteristics, including the proportion of patients with immunocompromised status and urinary device or procedure. Each of these can impact a patient's response to therapy and their ability to clear infection [10,11]. Owing to the low therapeutic failure rate, a multivariate analysis could not be performed to allow adjustment for potential confounders. Sample size was limited and a matched analysis was not performed. In addition, a factor that may contribute to antibiotic failure is appropriateness of dose, which was not retrospectively assessed in this study. However, in our institution all antibiotic orders are evaluated by a clinical pharmacist at the time of initial dispensing to ensure appropriate dosing. Moreover, patients who were given antibiotics beyond 21 days may have experienced treatment failures that were not reported owing to their exclusion from the study. Lastly, antibiotic adverse effects were not collected. Although fluoroquinolones may be the optimal choice for oral definitive therapy in patients with Gram-negative bacteraemia from a UTI based on current data, they are not benign agents. Clinicians should monitor for known side effects, such as QTc prolongation, antibiotic-associated diarrhoea and *Clostridium difficile* infection, and tendon pain/rupture [12,13].

5. Conclusion

This retrospective analysis did not find a significant difference in the rate of clinical failure between patients treated exclusively with IV therapy compared with an oral transition strategy for Gram-negative BSI secondary to UTI. Consideration may be given to transitioning patients to a highly bioavailable oral antibiotic if they are clinically stable and have cleared blood cultures.

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Competing interests

None declared.

Ethical approval

This study was approved by the Institutional Review Board of Mayo Clinic (Rochester, MN) [16-006233].

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