Clinical Microbiology and Infection 30 (2024) 492–498

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Switch to oral antibiotics in Gram-negative bacteraemia: a randomized, open-label, clinical trial

Ali S. Omrani [1, 2, 3, *], Sulieman H. Abujarir [1, 2, †], Fatma Ben Abid [1, 2, 4, †], Shahd H. Shaar [1, †], Mesut Yilmaz [5], Adila Shaukat [1, 6], Mussad S. Alsamawi [1, 7], Mohamed S. Elgara [8], Mohamed Islam Alghazzawi [8], Khaled M. Shunnar [8], Ahmed Zaqout [1, 2], Yasser M. Aldeeb [1, 7], Wadha Alfouzan [9, 10], Muna A. Almaslamani [1, 2], SOAB Study Group[††]

[1)] *Communicable Diseases Center, Hamad Medical Corporation, Doha, Qatar*
[2)] *Division of Infectious Diseases, Department of Medicine, Hamad Medical Corporation, Doha, Qatar*
[3)] *Qatar University College of Medicine, Doha, Qatar*
[4)] *Weill Cornell Medicine-Qatar, Doha, Qatar*
[5)] *Department of Infectious Diseases and Microbiology, Istanbul Medipol University, Istanbul, Turkiye*
[6)] *Division of Infectious Diseases, Department of Medicine, Al Wakra Hospital, Hamad Medical Corporation, Al Wakra, Qatar*
[7)] *Division of Infectious Diseases, Department of Medicine, Al Khor Hospital, Hamad Medical Corporation, Al Khor, Qatar*
[8)] *Division of Internal Medicine, Department of Medicine, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar*
[9)] *Department of Microbiology, Farwania Hospital, Kuwait City, Kuwait*
[10)] *Faculty of Medicine, Kuwait University, Kuwait City, Kuwait*

ARTICLE INFO

Article history:
Received 9 August 2023
Received in revised form
11 October 2023
Accepted 12 October 2023
Available online 18 October 2023

Editor: L. Leibovici

Keywords:
Bacteraemia
Enterobacterales
Gram negative
Oral therapy
Step down
Switch

ABSTRACT

Objectives: To evaluate the safety and efficacy of switching from intravenous (IV) to oral antimicrobial therapy in patients with Enterobacterales bacteraemia, after completion of 3–5 days of microbiologically active IV therapy.

Methods: A multicentre, open-label, randomized trial of adults with monomicrobial Enterobacterales bacteraemia caused by a strain susceptible to ≥1 oral beta-lactam, quinolone, or trimethoprim/sulfamethoxazole. Inclusion criteria included completion of 3–5 days of microbiologically active IV therapy, being afebrile and haemodynamically stable for ≥48 hours, and absence of an uncontrolled source of infection. Pregnancy, endocarditis, and neurological infections were exclusion criteria. Randomization, stratified by urinary source of bacteraemia, was to continue IV (IV Group) or to switch to oral therapy (Oral Group). Agents and duration of therapy were determined by the treating physicians. The primary endpoint was treatment failure, defined as death, need for additional antimicrobial therapy, microbiological relapse, or infection-related re-admission within 90 days. Non-inferiority threshold was set at 10% in the 95% CI for the difference in the proportion with treatment failure between the Oral and IV Groups in the modified intention-to-treat population. The protocol was registered at ClinicalTrials.gov (NCT04146922).

Results: In the modified intention-to-treat population, treatment failure occurred in 21 of 82 (25.6%) in the IV Group, and 18 of 83 (21.7%) in the Oral Group (risk difference −3.7%, 95% CI −16.6% to 9.2%). The proportions of subjects with any adverse events (AE), serious AE, or AE leading to treatment discontinuation were comparable.

Discussion: In patients with Enterobacterales bacteraemia, oral switch, after initial IV antimicrobial therapy, clinical stability, and source control, is non-inferior to continuing IV therapy. **Ali S. Omrani, Clin Microbiol Infect 2024;30:492**

* Corresponding author. Ali S. Omrani, Communicable Diseases Center, Hamad Medical Corporation, Doha, Qatar.
E-mail address: aomrani@hamad.qa (A.S. Omrani).
† These authors contributed equally to this work: Sulieman H. Abujarir, Fatma Ben Abid, Shahd H. Shaar.
†† The members of SOAB Study Group are listed at Appendix B section.

https://doi.org/10.1016/j.cmi.2023.10.014
1198-743X/

Introduction

Enterobacterales blood stream infections are relatively common in hospitalized patients and are associated with considerable morbidity and mortality, especially when caused by multi-resistant strains [1,2]. Intravenous (IV) antimicrobial therapy has traditionally been the standard of care for patients with Gram-negative bacteraemia [3]. Oral antimicrobial therapy is associated with several potential benefits, including the prevention of vascular line-associated complications, facilitating early mobilization, discharge and return to baseline activities of daily living, and reducing health care costs [4,5].

Results from observational studies suggest that stepdown to oral antibiotics, after an initial period of IV therapy, maybe reasonable in selected patients with Gram-negative bacteraemia [6–9]. A switch from IV to oral antibiotics may be safe and effective in patients who are clinically stable and have one or more microbiologically active oral treatment options. However, the available data are derived from non-randomized studies and are thus subject to unmeasured confounding bias, even where analytical methods to reduce bias are implemented [10]. Furthermore, the outcomes in most of those studies were assessed after no more than 30 days of follow-up, whereas endpoint assessment at 90 days has been recommended in definitive antimicrobial therapy studies for Gram-negative blood stream infections [11]. The primary aim of this randomized clinical trial was to evaluate the 90-day safety and efficacy of switching from IV to oral antibiotic therapy in patients with Enterobacterales bacteraemia.

Methods

Study design and eligibility criteria

This was a pragmatic, open-label, multicentre, non-inferiority, randomized clinical trial. Patients aged 18 years or more who had monomicrobial blood stream infection caused by *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Serratia marcescens*, *Citrobacter* species, or *Proteus* species susceptible to one or more of an oral β-lactam, quinolone or trimethoprim/sulfamethoxazole were eligible for inclusion if they had completed 3–5 days of active IV antimicrobial therapy, were able to take oral medication, had been afebrile and haemodynamically stable for at least 48 hours, and had achieved adequate source control, if required. Exclusion criteria were allergy to the available active oral antimicrobial agents, pregnancy, infective endocarditis, infection of the central nervous system, terminal underlying illness with expected survival of less than 14 days, absolute neutrophil count of less than 1.0×10^9/L, and haematopoietic or solid organ transplantation within the preceding 90 days.

The study was conducted in full conformance with the principles of the Declaration of Helsinki and was approved by the research ethics committees in each of the participating centres. An independent Data Safety and Monitoring Board, comprised of two independent infectious disease physicians and an independent statistician, provided oversight. The protocol was registered at clinicaltrials.gov (NCT04146922).

Study population, stratification, and randomization

Patients were screened for enrolment in 11 sites in four countries (Bahrain, Kuwait, Qatar, and Türkiye). After obtaining written informed consent, eligible subjects were randomized to continue IV therapy (IV Group) or to switch to oral therapy (Oral Group). Randomization was by permuted blocks of 4–8 and was stratified by urinary source of bacteraemia. Castor EDC (Amsterdam, the Netherlands) was used for the randomization and for electronic data entry.

The intention-to-treat (ITT) population included all subjects who were randomized, whereas the modified ITT (mITT) population was limited to those who received at least one dose of the assigned treatment, and had documented outcomes at the end of follow-up.

Outcomes and procedures

The primary endpoint was treatment failure, defined as a composite of (a) death of any cause, (b) need for additional antimicrobial therapy with one or more microbiologically active agents, (c) microbiological relapse, and (d) infection-related re-admission; all within 90 days of initiation of microbiologically active antimicrobial therapy (definitions are provided in the data supplement file). Secondary endpoints included the individual components of the composite, hospital length of stay, and desirability of outcome ranking (DOOR) at 14 days.

The trial was intended to simulate routine clinical practice. The protocol did not require the collection of any specific clinical samples. The choice of antimicrobial agents, before and after randomization, the overall duration of therapy, the clinical assessments, and the laboratory investigations were all determined by the treating physicians, with or without consulting a specialist in infectious diseases. The decisions were guided by the causative pathogens' susceptibility testing reports and the subjects' clinical characteristics. However, the use of oral β-lactams in subjects with bacteraemia caused by extended spectrum β-lactamase-producing Enterobacterales was not permitted [12]. Furthermore, switch to oral agents after a minimum of 14 days of active IV therapy was permitted in participants who were randomized to the IV Group and had underlying infections that conventionally require prolonged antimicrobial therapy (e.g. bone and joint infections).

Sample size estimation

The assumptions for sample size estimation were indirectly derived from one randomized controlled trial and four cohort studies involving patients with Enterobacterales bacteraemia [7,8,13–15]. Using an estimated primary outcome rate of 16%, it was estimated that the inclusion of 438 evaluable subjects in the primary endpoint analysis would result in 80% power to demonstrate non-inferiority of oral switch within a 10% margin of a 95% CI, with a two-sided Type I error rate of 5%.

Statistical analysis

Descriptive results for quantitative variables are presented as mean and standard deviation or median with interquartile range (IQR), depending of data distribution. Numbers (percentages) are reported for qualitative variables. For the primary outcome, the group difference was compared by expressing the percentage of patients with treatment failure in the Oral Group minus the percentage in the IV Group. A corresponding two-sided 95% CI for the percentage difference, adjusted using a generalized linear model for urinary source of bacteraemia, was constructed. Switch to oral therapy would be considered non-inferior to continuing IV therapy if the upper bound of the CI for the difference in the mITT population was <10%. The 10% non-inferiority threshold was selected based on recent randomized clinical trials in patients with Gram-negative bacteraemia, and the US Food and Drug Administration's recommendations for clinical trials in complicated urinary tract infection [15,16]. A pre-planned interim analysis was to be performed once the first 50% of the target sample have completed

90 days of follow-up, with early discontinuation rules for futility or demonstrated benefit.

Hospital length of stay is presented as median (IQR), and the group difference for length of stay is presented as a ratio, along with corresponding 95% CI. For the DOOR analysis at 14 days, outcomes were ranked from the most to the least desirable as being home and not on any antimicrobial therapy, home on oral antibiotics, home on IV antibiotics, in hospital but not on active antimicrobial therapy, and in hospital and on active therapy. The likelihood of achieving a higher ranked outcome in the Oral Group, relative to the IV Group, is expressed as OR with 95% CI, adjusted for urinary source of bacteraemia. For the primary outcome in the ITT population, patients with missing outcome data were assumed to have a treatment failure. When only observed data were analysed, missing data were assumed to be missing at random. All data analyses were performed using Stata Statistical Software, Version 15.1 (StataCorp, College Station, Texas).

Results

Screening and enrolment

Between 20 October 2019 and 31 March 2020, a total of 69 subjects were enrolled (median 12 subjects per month). Thereafter, the COVID-19 pandemic resulted in severe disruption of clinical research and service delivery, resource allocation, and personnel deployment in all the study sites. Hence, during the period between 1 April 2020 and 27 May 2022, only an additional 105 subjects were enrolled (median 4 subjects per month) (Fig. S1). Given the severe and persistent impact on recruitment, and in consultation with the study's Data Safety and Monitoring Board, the Study Steering Committee decided to close the trial for further enrolment. Thus, the total number of subjects in the IV Group and the Oral Group were 85 and 89 in the ITT population, and 82 and 83 in the mITT population, respectively (Fig. 1).

Demographic and clinical characteristics of the enrolled subjects

Approximately half (89, 51%) of the enrolled subjects were females, and the mean age (±standard deviation) was 56.6 years (±16.7). Diabetes (99, 57%) and chronic kidney disease (28, 16%) were the most frequent underlying co-morbidities (Table 1). Median (IQR) Pitt Bacteraemia Score was 1 (0–1). The urinary tract (105, 60%) was the most common source of bacteraemia, and *E. coli* (116, 67%) and *Klebsiella* species (42, 24%) were the most frequent causative pathogens. Extended spectrum β-lactamase production was documented in 28 (16% of the tested isolates), and carbapenem resistance in 2 (3% of the tested isolates) (Tables S2 and S3). Post-randomization, oral cephalosporins, and β-lactam/β-lactamase inhibitor combinations were the most frequent agents used in the Oral Group, whereas parenteral cephalosporins and carbapenems predominated in the IV Group. The overall median duration of active antimicrobial therapy was 12 days (IQR 10–15) (Tables 2, S4 and S5).

Outcomes

In the mITT population, treatment failure was documented in 21 (25.6%) subjects in the IV Group and 18 (21.7%) in the Oral Group, with an absolute risk difference of −3.7% (95% CI −16.6% to 9.2%). Similarly, the upper bound of the 95% CI around the absolute risk difference for treatment failure in the ITT population was below 10% (Table 3). There was no statistically significant differences between the two groups in the incidence of the individual components of the composite, though need for additional active antimicrobial therapy and microbiological relapse were more

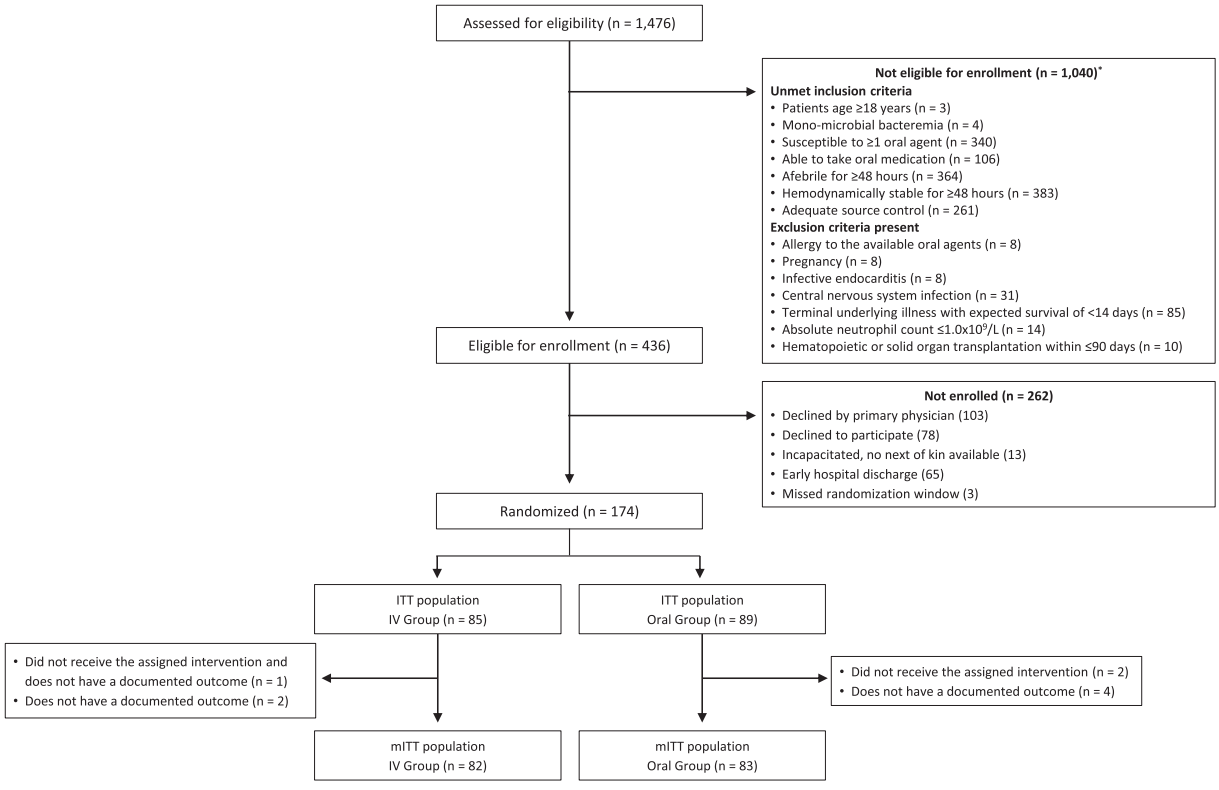

Fig. 1. Patient recruitment, randomization, and flow through the study. *Did not meet >1 inclusion criterion ($n = 390$), has >1 exclusion criterion ($n = 28$), both ≥1 inclusion, and ≥1 exclusion criterion ($n = 124$).

Table 1
Baseline characteristics at the time of Enterobacterales bacteraemia

Variable	IV Group (n = 85)	Oral Group (n = 89)
Female sex	38 (45%)	51 (57%)
Age (y)[a]	55.5 (±17.9)	57.6 (±15.5)
Hospital location at the time of bacteraemia		
Emergency department	38 (45%)	42 (47%)
Hospital ward	40 (47%)	39 (44%)
Intensive care unit	5 (6%)	6 (7%)
Outpatient	2 (2%)	2 (2%)
Functional capacity before the index bacteraemia		
Independent	67 (80%)	74 (84%)
Needs assistance with activities of daily living	4 (5%)	8 (9%)
Dependent for activities of daily living	13 (15%)	6 (7%)
Underlying co-morbidities		
Diabetes	46 (54%)	53 (60%)
Chronic liver disease	6 (7%)	7 (8%)
Chronic kidney disease	11 (13%)	17 (19%)
Cardiovascular disease	10 (12%)	10 (11%)
Cerebrovascular disease	9 (11%)	3 (3%)
Dementia	3 (4%)	2 (2%)
Active malignant disease	8 (9%)	8 (9%)
Chronic lung disease	1 (1%)	3 (3%)
Connective tissue disease	1 (1%)	2 (2%)
HIV infection	1 (1%)	0 (0%)
Charlson co-morbidity score[b]	3 (1–6)	3 (1–5)
Immune suppressive therapy		
None	82 (96%)	84 (94%)
Prednisolone	3 (4%)	2 (2%)
Adalimumab	0 (0%)	1 (1%)
Infliximab	0 (0%)	1 (1%)
Mycofenolate	0 (0%)	1 (1%)
Weight (kg)[a]	74.5 (±19.2)	75.6 (±17.4)
Temperature (°C)[a]	38.3 (±1.0)	38.1 (±1.1)
Heart rate (per min)[a]	102 (±22)	105 (±23)
Systolic blood pressure (mmHg)[a]	110 (±18)	109 (±19)
Mechanical ventilation	1 (1%)	2 (2%)
Vasopressors	2 (2%)	3 (3%)
Peripheral white cell count ($\times 10^9$/L)[a]	12.8 (±6.2)	13.3 (±7.2)
Haemoglobin (g/dL)[a]	11.3 (±2.4)	11.3 (±1.9)
Platelets ($\times 10^9$/L)[b]	200 (148–284)	207 (153–282)
Serum creatinine (μmol/L)[b]	89 (72–132)	91 (66–154)
Urea (mmol/L)[b]	6.1 (4.3–10.1)	6.7 (4.2–11.3)
Potassium (mmol/L)[a]	4.0 (±0.6)	4.1 (±0.7)
Sodium (mmol/L)[a]	134 (±5)	135 (±4)
Alanine transaminase (IU/L)[b]	19 (12–55)	21 (13–43)
Aspartate transaminase (IU/L)[b]	26 (17–59)	25 (18–41)
Alkaline phosphatase (IU/L)[b]	105 (75–151)	114 (86–152)
Albumin (g/L)[b]	30.3 (±7.4)	30.0 (±6.3)
Total bilirubin (μmol/L)[b]	14 (8–22)	14 (7–24)

[a] Mean ± standard deviation.
[b] Median (interquartile range).

Table 2
Infection and antimicrobial therapy variables

Variable	IV Group (n = 85)	Oral Group (n = 89)
Pitt bacteraemia score[a]	1 (0–1)	1 (0–1)
Source of bacteraemia		
Urinary tract	51 (60%)	54 (61%)
Intra-abdominal	14 (16%)	8 (9%)
Biliary	4 (5%)	8 (9%)
Primary bacteraemia	8 (9%)	7 (8%)
Respiratory tract	2 (2%)	8 (9%)
Skin and soft tissue	2 (2%)	0 (0%)
Vascular line	1 (1%)	2 (2%)
Other	3 (4%)	2 (2%)
Enterobacterales species		
E. coli	55 (65%)	61 (69%)
Klebsiella species	22 (26%)	20 (22%)
Enterobacter species	6 (7%)	6 (7%)
Citrobacter species	1 (1%)	0 (0%)
Proteus species	0 (0%)	1 (1%)
Serratia marcescens	1 (1%)	1 (1%)
ESBL-producing organism[b]	17/84 (20%)	11/88 (13%)
Device in place at the time of bacteraemia		
None	67 (80%)[c]	66 (75%)[c]
Urinary device	13 (15%)	12 (14%)
Central venous access	2 (2%)	5 (6%)
Biliary stent or drain	1 (1%)	5 (6%)
Tracheostomy	1 (1%)	0 (0%)
Source control required[d]	18 (21%)	28 (31%)
Days of pre-randomisation active IV antimicrobial therapy[a]	4 (3–5)	4 (3–5)
Pre-randomization antimicrobial therapy[d]		
β-lactam/β-lactamase inhibitor combination	19 (22%)	27 (30%)
Carbapenem	40 (47%)	27 (30%)
Cephalosporin	26 (31%)	34 (38%)
Fluoroquinolone	0 (0%)	1 (1%)
Trimethoprim/sulfamethoxazole	0 (0%)	0 (0%)
Post-randomization antimicrobial therapy[d]		
β-lactam/β-lactamase inhibitor combination	15 (18%)	27 (30%)
Carbapenem	23 (27%)	0 (0%)
Cephalosporin	44 (52%)	31 (35%)
Fluoroquinolone	2 (8%)	17 (19%)
Trimethoprim/sulfamethoxazole	1 (1%)	14 (16%)
Total duration of antimicrobial therapy (d)[a]	11 (8–14)	14 (11–16)

ESBL, extended spectrum β-lactamase; IV, intravenous.
[a] Median (interquartile range).
[b] Expressed as the number of the ESBL-producing isolates over the total number of isolates tested.
[c] One missing value.
[d] Tables S3–S5.

frequent in the IV Group, and infection-related re-admission in the Oral Group (Tables 3 and S6).

In the mITT population, the median hospital length of stay was significantly shorter in the Oral Group (6 days, IQR 5–8) compared with the IV Group (9 days, IQR 6–14); ratio 0.74 (95% CI 0.58–0.94, p 0.01). Only one subject, in the IV Group, had documented *Clostridioides difficile* infection. DOOR analysis did not indicate a significantly higher likelihood of achieving a higher ranked outcome at 14 days in the Oral Group compared with the IV Group (OR 0.93, 95% CI 0.53–1.70; p 0.86) (Fig. 2).

Adverse events

The incidence of adverse events, including those that were serious or led to treatment discontinuation, was not significantly different between the two study groups (Tables 4 and S7).

Discussion

Our results demonstrate that switching to oral antimicrobial therapy in patients with Enterobacterales bacteraemia, subject to source control and clinical stability, is non-inferior to continuing IV antibiotic therapy. All-cause, 90-day mortality was very low in both study groups. Moreover, oral switch was very well-tolerated and was associated with a significantly shorter hospital stay.

As widely experienced, the impact of the COVID-19 pandemic on clinical research resulted in the study's closure before reaching its target sample size [17]. Nevertheless, the enrolled sample was adequate to demonstrate non-inferiority of switching to oral therapy, compared with continuing IV treatment. One likely explanation for this is that the observed primary outcome rate of 24% is considerably higher than the original estimate of 16%. Furthermore, had recruitment continued, the pre-planned interim analysis at 50% of the target sample size would have probably resulted in early study termination for demonstrated benefit.

Table 3
Primary and secondary outcomes

Outcome	Population	IV Group	Oral Group	Difference (95% CI)[a]
Treatment failure within 90 d	ITT[b]	24 (28.2%)	22 (24.7%)	−3.7% (−16.6% to 9.3%)
	mITT[c]	21 (25.6%)	18 (21.7%)	−3.7% (−16.6% to 9.2%)
90-d all-cause mortality	ITT[b]	6 (7.1%)	7 (7.9%)	0.8% (−7.0% to 8.6%)
	mITT[c]	3 (3.7%)[d]	3 (3.6%)[e]	−0.04% (−5.8% to 5.7%)
Additional antimicrobial therapy	ITT[b]	13 (15.3%)	8 (9.0%)	−6.8% (−16.1% to 2.6%)
	mITT[c]	10 (12.2%)	4 (4.8%)	−7.1% (−15.5% to 1.3%)
Microbiological relapse	ITT[b]	13 (15.3%)	10 (11.2%)	−4.1% (−14.1% to 5.9%)
	mITT[c]	10 (12.2%)	6 (7.2%)	−4.8% (−14.0% to 4.3%)
Infection-related re-admission	ITT[b]	12 (14.1%)	19 (21.3%)	7.2% (−4.0% to 18.3%)
	mITT[c]	9 (11.0%)	15 (18.1%)	7.5% (−3.1% to 18.1%)

ITT, intention-to-treat; IV, intravenous; mITT, modified intention-to-treat.
[a] Group differences expressed as the Oral Group minus the IV Group, adjusted for urinary source of bacteraemia.
[b] ITT IV Group ($n = 85$), Oral Group ($n = 89$).
[c] mITT IV Group ($n = 82$), Oral Group ($n = 83$).
[d] Gastrointestinal bleeding ($n = 1$), COVID-19 ($n = 1$), and cancer ($n = 1$).
[e] End-stage liver disease ($n = 1$), and COVID-19 ($n = 2$).

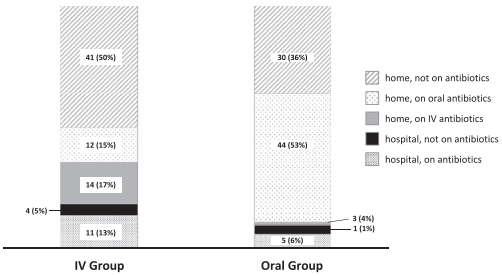

Fig. 2. Desirability of outcome ranking analysis at day 14 (mITT population). OR for a higher-ranking outcome with switch to oral antimicrobial therapy is 0.93 (95% CI 0.53–1.70; p = 0.86). mITT, modified intention-to-treat.

Table 4
Adverse event summaries

Category	IV Group ($n = 85$)	Oral Group ($n = 89$)	p[a]
Any adverse events	36 (42.4%)	32 (36.0%)	0.44
Grade 3–5 adverse events	18 (21.2%)	21 (23.6%)	0.72
Serious adverse events	16 (18.8%)	19 (21.3%)	0.71
Adverse events leading to treatment discontinuation	2 (2.4%)[b]	1 (1.1%)[c]	0.61

[a] Fisher's exact test.
[b] Elevated liver enzymes ($n = 1$), injection site reaction ($n = 1$).
[c] Vomiting ($n = 1$).

The pragmatic study design allowed closer resemblance of routine clinical practice and may hence enhance the generalizability of its findings. Although the emphasis was on switching to oral antimicrobial therapy as a broad strategy, *in vitro* susceptibility testing, selection of therapeutic agents, and dosing regimens were not standardized. Some observational studies suggested that in patients with Gram-negative bacteraemia, switching to agents with relatively higher oral bioavailability, such as fluoroquinolone, may be superior to β-lactams [18]. In this study, the majority of patients in the Oral Group were transitioned to oral β-lactam/β-lactam inhibitor combinations or cephalosporins, and this did not seem to result in excess failures. This, and related important questions, would be best addressed in dedicated randomized clinical trials that compare outcomes based on specific oral switch protocols, including standardized susceptibility testing, agent selection, and dosing regimens, and pharmacokinetic monitoring [19,20].

Given the evidence that 7 days of effective therapy may be adequate in selected patients with Gram-negative bacteraemia, the subjects in this study were randomised after receiving no more than 5 days of active IV antimicrobial therapy [15]. On the other hand, receipt of at least 3 days of active IV antimicrobial therapy was required. It is not presently clear if earlier switch to oral agents, or even upfront oral therapy, for Enterobacterales bacteraemia is as effective as IV treatment [21]. Interestingly, DOOR analysis did not indicate a significantly higher likelihood of achieving a higher ranked outcome at 14 days in the Oral Group compared with the IV Group. This appears to be largely because patients who were switched to oral therapy were more likely to be discharged from hospital earlier, but received significantly longer courses of antimicrobial treatment. This may be a reflection of a lower threshold to prescribe longer courses of oral therapy and lower confidence in its effectiveness. Stewardship efforts to maximize potential benefits of IV to oral switch should, simultaneously, minimize unnecessary prolongation of oral antimicrobial therapy.

More than 70% of the patients who were screened for enrolment in this study were not eligible, suggesting that switch to oral therapy may not be feasible in a majority of patients with Enterobacterales bacteraemia. Approximately 23% of those who were screened were excluded because of a lack of an active oral antimicrobial agent for the blood culture isolate. Fosfomycin trometamol, which retains activity against some multidrug resistant Enterobacterales, was recently shown to be a reasonable oral switch option for patients with bacteraemic urinary tract infections [22]. Oral options for the treatment of multidrug resistant Enterobacterales may expand further with the potential future availability of oral carbapenems (e.g. tebipenem) and newer oral β-lactam/β-lactamase inhibitors (e.g. ceftibuten/avibactam) [23,24]. To enhance their clinical utility, clinical development programmes for such agents should ideally incorporate their assessment as potential treatment options for patients with Gram-negative bacteraemia.

Other groups which were excluded in this study were those with infective endocarditis or central neurological infections, as well as neutropoenic patients. Whereas current evidence suggests that transition to oral antibiotics is a safe and effective option for selected patients with infective endocarditis caused by Gram-positive bacteria, the evidence is extremely limited for those involving Enterobacterales [25]. For neurological infections, ongoing randomized trials are investigating whether oral stepdown therapy is feasible, although it is likely that only a minority of such infections would be caused by Enterobacterales [26]. In haematology patients with neutropoenic fever, even in the absence of documented bloodstream infection, current evidence suggests that early switch to oral antimicrobial therapy is not non-inferior to

continuing IV treatment [27]. For the foreseeable future, such patients will probably continue to be excluded from clinical pathways that promote IV to oral switch in Gram-negative bacteraemia.

In addition to the above limitations, the open-label nature of the study and the extreme impact of COVID-19 on clinical capacity and service delivery may have influenced some of the treating physicians' clinical decision making, including earlier switch for perceived clinical failure and earlier hospital discharge.

Conclusion

In patients with Enterobacterales bacteraemia, oral switch after initial IV antimicrobial therapy, clinical stability, and source control, is non-inferior to continuing IV therapy.

Author contributions

Conceptualization: ASO. Methodology: ASO. Data curation: ASO, SHA, FBA, SHS, MY, AS, MSA, MSE, MIA, KMS, AZ, YMA, WA, MAA, FA, MN, NA, SB, RC, CK, AAY, ETT, BES, IIB, BC, MMA, HA, MSE, and EM. Formal analysis: ASO and SHS. Funding acquisition: ASO. Project administration: ASO, SHA, FBA, SHS, and MAA. Writing—original draft preparation: ASO. Writing—review, editing and approval of the submitted version: all authors.

Transparency declaration

Part of the data was presented at the 33rd European Congress of Clinical Microbiology and Infectious Diseases, Copenhagen, Denmark, 15–18 April 2023. ASO received speaker honoraria from Gilead, Pfizer, and MSD. WA received speaker honoraria from Pfizer, MSD, and bioMérieux, and a research grant from Pfizer unrelated to this work. The other authors have declared no potential conflict of interest.

The study was funded by the Medical Research Center, Hamad Medical Corporation, Doha, Qatar (MRC-01-19-254).

Acknowledgements

We thank the Data and Safety Monitoring Board members for their support: Dr Patrick Harris (University of Queensland, Brisbane, Australia), Professor Jesús Rodriguez-Baño (Hospital Universitario Virgen Macarena, Seville, Spain), and Aaron Dane (Danestat Consulting, Macclesfield, UK). We also thank Paul Basset (Statsconsultancy, Amersham, UK) for the statistical analyses, and Neha Gopinath, Sruthi Desmond, and Asha Alex for their administrative support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.10.014.

Appendix B

SOAB Study Group

Manaf Alqahtani, Faisal Alshaikh (Bahrain Defence Force Hospital, Bahrain); Mohammad Nazish, Noura Almerdasi, Simin Bangri (Farwania Hospital, Kuwait City, Kuwait); Rumeysa Cakmak (Istanbul Medipol University, Istanbul, Türkiye); Celali Kurt, Arzu Altuncekic Yildirim (Ordu University, Ordu, Türkiye); Elif Tukenmez-Tigen, Buket Erturk Sengel (Marmara University School of Medicine, Istanbul, Türkiye); Ilker Inanc Balkan, Bilge Çağlar (Istanbul University Carrahpasa Medical School, Istanbul, Türkiye); Mohamed M. Abufaied, Mohsen S. Eledrisi (Hamad General Hospital, Doha, Qatar); Hatem Abusriwil (Hazm Mebaireek General Hospital, Doha, Qatar); Emad Elmaghboul (Microbiology, Hamad Medical Corporation, Doha, Qatar).

References

[1] McNamara JF, Righi E, Wright H, Hartel GF, Harris PNA, Paterson DL. Long-term morbidity and mortality following bloodstream infection: a systematic literature review. J Infect 2018;77:1–8. https://doi.org/10.1016/j.jinf.2018.03.005.
[2] Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis 2019;19:56–66. https://doi.org/10.1016/s1473-3099(18)30605-4.
[3] Broom J, Broom A, Adams K, Plage S. What prevents the intravenous to oral antibiotic switch? A qualitative study of hospital doctors' accounts of what influences their clinical practice. J Antimicrob Chemother 2016;71:2295–9. https://doi.org/10.1093/jac/dkw129.
[4] Lau BD, Pinto BL, Thiemann DR, Lehmann CU. Budget impact analysis of co nversion from intravenous to oral medication when clinically eligible for oral intake. Clin Ther 2011;33:1792–6. https://doi.org/10.1016/j.clinthera.2011.09.030.
[5] Keller SC, Dzintars K, Gorski LA, Williams D, Cosgrove SE. Antimicrobial agents and catheter complications in outpatient parenteral antimicrobial therapy. Pharmacotherapy 2018;38:476–81. https://doi.org/10.1002/phar.2099.
[6] Tamma PD, Conley AT, Cosgrove SE, Harris AD, Lautenbach E, Amoah J, et al. Asso ciation of 30-day mortality with oral step-down vs continued intravenous therap y in patients hospitalized with Enterobacteriaceae bacteremia. JAMA Intern Med 2019;179:316–23. https://doi.org/10.1001/jamainternmed.2018.6226.
[7] Kutob LF, Justo JA, Bookstaver PB, Kohn J, Albrecht H, Al-Hasan MN. Effectiveness of oral antibiotics for definitive therapy of Gram-negative bloodstream infections. Int J Antimicrob Agents 2016;48:498–503. https://doi.org/10.1016/j.ijantimicag.2016.07.013.
[8] Mercuro NJ, Stogsdill P, Wungwattana M. Retrospective analysis comparing oral stepdown therapy for enterobacteriaceae bloodstream infections: fluoroquinolones versus β-lactams. Int J Antimicrob Agents 2018;51:687–92. https://doi.org/10.1016/j.ijantimicag.2017.12.007.
[9] Sutton JD, Stevens VW, Chang NN, Khader K, Timbrook TT, Spivak ES. Oral β-lacta m antibiotics vs fluoroquinolones or trimethoprim-sulfamethoxazole for definitive treatment of Enterobacterales bacteremia from a urine source. JAMA Netw Open 2020;3:e2020166. https://doi.org/10.1001/jamanetworkopen.2020.20166.
[10] Barrowman MA, Peek N, Lambie M, Martin GP, Sperrin M. How unmeasured confounding in a competing risks setting can affect treatment effect estimates in observational studies. BMC Med Res Methodol 2019;19:166. https://doi.org/10.1186/s12874-019-0808-7.
[11] Harris PNA, McNamara JF, Lye DC, Davis JS, Bernard L, Cheng AC, et al. Proposed primary endpoints for use in clinical trials that compare treatment options for bloodstream infection in adults: a consensus definition. Clin Microbiol Infect 2017;23:533–41. https://doi.org/10.1016/j.cmi.2016.10.023.
[12] Hawkey PM, Warren RE, Livermore DM, McNulty CAM, Enoch DA, Otter JA, et al. Treatment of infections caused by multidrug-resistant gram-negative bacteria: report of the British society for antimicrobial chemotherapy/healthcare infection society/British infection association joint working party. J Antimicrob Chemother 2018;73:iii2–78. https://doi.org/10.1093/jac/dky027.
[13] Giannella M, Pascale R, Toschi A, Ferraro G, Graziano E, Furii F, et al. Treatment duration for Escherichia coli bloodstream infection and outcomes: retrospective single-centre study. Clin Microbiol Infect 2018;24:1077–83. https://doi.org/10.1016/j.cmi.2018.01.013.
[14] Nelson AN, Justo JA, Bookstaver PB, Kohn J, Albrecht H, Al-Hasan MN. Optimal duration of antimicrobial therapy for uncomplicated Gram-negative bloodstream infections. Infection 2017;45:613–20. https://doi.org/10.1007/s15010-017-1020-5.
[15] Yahav D, Franceschini E, Koppel F, Turjeman A, Babich T, Bitterman R, et al. Seven versus 14 days of antibiotic therapy for uncomplicated Gram-negative bacteremia: a noninferiority randomized controlled trial. Clin Infect Dis 2019;69:1091–8. https://doi.org/10.1093/cid/ciy1054.
[16] U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Complicated urinary tract infections: developing drugs for treatment. Guidance for Industry; 2018. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070981.pdf. [Accessed 5 August 2023].
[17] Bratan T, Aichinger H, Brkic N, Rueter J, Apfelbacher C, Boyer L, et al. Impact of the COVID-19 pandemic on ongoing health research: an ad hoc survey among investigators in Germany. BMJ Open 2021;11:e049086. https://doi.org/10.1136/bmjopen-2021-049086.
[18] Punjabi C, Tien V, Meng L, Deresinski S, Holubar M. Oral fluoroquinolone or trimethoprim-sulfamethoxazole vs. ß-lactams as step-down therapy for Enterobacteriaceae bacteremia: systematic review and meta-analysis. Open Forum Infect Dis 2019;6:ofz364. https://doi.org/10.1093/ofid/ofz364.
[19] Tong SYC, Yahav D, Daneman N. Which trial do we need? Highly bioavailable oral beta-lactams versus quinolones or trimethoprim-sulfamethoxazole for

gram-negative bacteraemia. Clin Microbiol Infect 2023;29:1110–3. https://doi.org/10.1016/j.cmi.2023.04.011.
[20] Landersdorfer CB, Gwee A, Nation RL. Clinical pharmacological considerations in an early intravenous to oral antibiotic switch: are barriers real or simply perceived? Clin Microbiol Infect 2023;29:1120–5. https://doi.org/10.1016/j.cmi.2023.04.009.
[21] Tamma PD, Cosgrove SE. Which trial do we need? Early oral antibiotic therapy for the treatment of gram-negative bloodstream infections. Clin Microbiol Infect 2023;29:670–2. https://doi.org/10.1016/j.cmi.2023.02.012.
[22] Sojo-Dorado J, López-Hernández I, Hernández-Torres A, Retamar-Gentil P, Merino de Lucas E, Escolà-Vergé L, et al. Effectiveness of fosfomycin trometamol as oral step-down therapy for bacteraemic urinary tract infections due to MDR *Escherichia coli*: a post hoc analysis of the FOREST randomized trial. J Antimicrob Chemother 2023;78:1658–66. https://doi.org/10.1093/jac/dkad147.
[23] Eckburg PB, Muir L, Critchley IA, Walpole S, Kwak H, Phelan AM, et al. Oral tebipenem pivoxil hydrobromide in complicated urinary tract infection. N Engl J Med 2022;386:1327–38. https://doi.org/10.1056/NEJMoa2105462.
[24] Karlowsky JA, Hackel MA, Stone GG, Sahm DF. In vitro activity of ceftibuten-avibactam against β-lactamase-positive Enterobacterales from the ATLAS global surveillance program. Antimicrob Agents Chemother 2023;67:e0134622. https://doi.org/10.1128/aac.01346-22.
[25] McDonald EG, Aggrey G, Tarık Aslan A, Casias M, Cortes-Penfield N, Dong MQ, et al. Guidelines for Diagnosis and management of infective endocarditis in adults: a WikiGuidelines group consensus statement. JAMA Netw Open 2023;6:e2326366. https://doi.org/10.1001/jamanetworkopen.2023.26366.
[26] Bodilsen J, Brouwer MC, van de Beek D, Tattevin P, Tong S, Naucler P, et al. Partial oral antibiotic treatment for bacterial brain abscess: an open-label randomized non-inferiority trial (ORAL). Trials 2021;22:796. https://doi.org/10.1186/s13063-021-05783-8.
[27] Coyle V, Forde C, McAuley DF, Wilson RH, Clarke M, Plummer R, et al. Early switch to oral antibiotic therapy in patients with low-risk neutropenic sepsis (EASI-SWITCH): a randomized non-inferiority trial. Clin Microbiol Infect 2023. https://doi.org/10.1016/j.cmi.2023.07.021. S1198-743X(23)00349-X.