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Effectiveness of oral step-down therapy and early oral switch for bloodstream infections caused by Enterobacterales: A post hoc emulation trial of the SIMPLIFY trial

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ABSTRACT

Objectives: We investigated the effectiveness of early oral switch for treating Enterobacterales bloodstream infection (BSI) by performing a post hoc emulation trial of the SIMPLIFY trial.
Methods: We conducted a post hoc analysis of a randomized controlled trial. We specified the target trial characteristics selecting patients who achieved clinical stability on day 5. We categorized patients into those who switched on day 5 and those who continued intravenously. The primary outcome was clinical cure at the test of cure. We set a propensity score for being switched on day 5 to reduce confounding. We ran simple, not-propensity-adjusted, and propensity-adjusted logistic regression models to ascertain the association of switch on day 5 with clinical cure.
Results: Among 303 patients who achieved clinical stability on day 5, 110 (36.3%) were switched orally on day 5, and 193 (63.7%) were kept intravenously. We detected no difference in clinical cure between those switched on day 5 and those continued intravenously (risk ratios 1.04, 95% confidence intervals [CI] 0.98-1.10). Propensity-adjusted analysis did not show an association between day 5 switch and clinical cure (OR 2.10, 95% CI 0.96-7.41).
Conclusion: Oral step-down therapy on day 5 was not associated with worse clinical cure for Enterobacterales BSI.

Introduction

Bloodstream infections (BSI) caused by Gram-negative bacteria are common in both healthcare and community settings [1]. In Europe, nearly 1200,000 community-onset BSI episodes occur annually [2], with hospitalization required in up to 88% of the cases [3]. To ensure adequate plasma drug concentrations and broad-spectrum coverage, these infections have traditionally been managed with intravenous (IV) antimicrobials for the full treatment duration. Recently, there has been growing interest in the role and safety of oral step-down therapy for Enterobacterales BSI [4], with several studies, including a small randomized controlled trial (RCT), showing encouraging results [5–10]. Potential benefits of oral step-down therapy include shorter hospital stays, reduced use of venous catheters and associated complications, lower healthcare costs, and improved patient comfort [11,12]. However, its implantation remains inconsistent [4,9].

This post hoc analysis of an RCT aimed to assess the effectiveness and safety of early oral switch timing in the treatment of Enterobacterales BSI.

Methods

Study design and setting

We conducted a post hoc analysis of the SIMPLIFY trial, an investigator-driven, open-label, multicentric, pragmatic RCT. Our goal was to perform a target emulation trial comparing early oral switch on day 5 vs continued IV therapy in patients with Enterobacterales BSI. Table 1 presents the key features of the ideal trial and the emulation analysis, while the full ideal trial protocol is available in the Supplementary Material (Trial Protocol in Supplementary Material). This study adheres to STROBE reporting guidelines (STROBE checklist in Supplementary Material).

Data source

Data were derived from the SIMPLIFY trial, which enrolled patients with Enterobacterales BSI treated empirically with an antipseudomonal beta-lactam. Patients were randomized to either continue the antipseudomonal beta-lactam or de-escalate to alternative antibiotics based on a predefined protocol. The SIMPLIFY trial's details, including eligibility criteria and treatment assignment, have been published previously [13]. Per the study protocol, patients who achieved clinical stability and could tolerate oral treatment were eligible for an oral switch starting from day 5. The study received ethical approval from the Hospital Universitario Virgen Macarena Ethics Committee.

Eligibility criteria

We included patients from the SIMPLIFY trial who achieved clinical stability by day 5. Clinical stability was defined as clinical improvement, being afebrile and with hemodynamically stable for at least 24 hours, with adequate source control and no secondary active foci. Patients who did not achieve stability by day 5 were excluded.

Treatment strategy and assignment

The index date was set to day 5 after blood culture collection, as this was the earliest point at which treatment group assignment was known per the SIMPLIFY protocol. Patients were classified into two groups: those who switched to oral therapy (SOT) on day 5 and those who either switched later or remained on IV therapy for the full treatment duration (control group). A subgroup analysis compared outcomes between patients who switched on day 5 to either oral fluoroquinolones/cotrimoxazole or oral beta-lactams.

Follow-up and outcomes

Patients were followed until test of cure (TOC), conducted 3-5 days after treatment completion, with additional follow-up extending to 60 days. The primary outcome was clinical cure at TOC, defined as symptoms resolution without treatment modification. We analyzed this outcome in the trial's modified intention-to-treat population (mITT), considering patients lost to follow-up at TOC as treatment failures. Secondary outcomes included clinical cure at day 60 in the clinically evaluable population, microbiological cure (defined as sterile follow-up blood cultures) in the microbiologi-

Table 1
Features of the ideal target trial and the emulation trial.

Feature	Ideal target trial	Emulation trial
Inclusion criteria	– Age ≥18 years – Monomicrobial bacteremia due to Enterobacterales needing at least 5 days of IV therapy – Receipt of active monotherapy with IV beta-lactam or fluoroquinolone, both empirical (started <24 h after blood cultures were taken) and targeted – Clinical stability on day 5 of therapy – Source control realized within day 5 if required – Able to take oral drugs – Negative pregnancy test was required for women of childbearing age	As ideal target trial
Exclusion criteria	– Life expectancy less than 30 days – Pregnancy/breastfeeding – Isolation of carbapenemase-producing Enterobacterales – Neutropenia less than 500 cells per μL at randomization – Planned duration of treatment of more than 28 days	As ideal target trial
Treatment strategies	a) Oral switch at day 5 with one of the allowed oral antibiotic options b) Continue intravenous therapy with oral switch after day 5	As ideal target trial
Treatment assignment	Randomization in a 1:1 allocation ratio to a treatment strategy on day 5 from therapy commencement	Exposure assigned according to the treatment administration as performed in the SIMPLIFY trial
Follow-up	Starts when randomization is performed and ends at day 30	As ideal target trial
Outcome	Clinical cure at test of cure (3-5 days after therapy completion)	As ideal target trial
Casual contrast	Modified intention-to-treat analysis	Modified intention-to-treat population from the SIMPLIFY trial

cally evaluable population, BSI recurrence by day 60, all-cause mortality at day 60 in the mITT population.

Statistical analysis

We described continuous variables with median and interquartile ranges and categorical variables with frequencies and percentages. Basal features of SOT and control group patients were compared. We used the Wilcoxon rank-sum for continuous variables and Fisher's exact test for categorical variables. A *P*-value <0.05 was considered statistically significant. Crude risk differences (RD) and risk ratios (RR) with 95% confidence intervals (CI) between SOT patients and the control group were calculated. If missing data were present for the outcomes, we considered them as event occurrence.

Because patients were not randomized for SOT, we set a propensity score (PS) for being switched on day 5 including all available, potentially relevant exposures before day 5 using a generalized boosted model due to the large variety of response variables and the absence of formal distributional assumptions. The covariates to include in the PS were chosen by investigator consensus. We verified the PS performance by visually inspecting the balance of variables and verifying the standardized mean differences (SMD) in the pseudo-populations created after applying the inverse probability of treatment weighting (IPTW). Subsequently, we conducted bivariate analyses of all variables with an SMD >0.10 in comparing the two switch time groups to predict clinical cure at TOC. We developed non-PS and PS-adjusted logistic regression models to evaluate the association between early oral switch on day 5 and the clinical cure at TOC. To have reliable standard errors and CIs for the PS-adjusted model, we performed 1000 bootstrap resamples of the data, recalculating the PS and refitting the logistic regression model for each sample. From each fitted model, we then extracted the regression coefficients and examined the distribution of these to calculate the 95% CIs for each regression variable.

Sensitivity analysis was performed by comparing patients SOT on days 5 or 6 vs all other patients. We also performed a sensitivity analysis considering the oral switch as a time-dependent variable in non-PS and PS-adjusted Cox regression models.

We conducted the statistical analyses with R software v4.2.2 and RStudio v2023.06.0+421 https://www.R-project.org/ [accessed on 8 March 2024]).

Results

Participants and descriptive analysis

Of the 331 patients included in the SIMPLIFY mITT population, 28 were excluded due to lack of clinical stability by day 5, leaving 303 patients for analysis. Among them, 110 (36.3%) were SOT on day 5, while 193 (63.7%) were continued IV therapy beyond day 5 (control group) (Figure 1). All patients requiring source control had it performed before day 5. The number of patients in the control group who switched to oral per day is reported in Supplementary Material (Table S1). Among the control group, 122 patients (63.2%) were switched after day 7 or were never switched. The clinically evaluable and microbiologically evaluable populations included 99 and 85 patients in the SOT on day 5 group, and 191 and 167 patients in the control group, respectively.

Table 2 compares patient characteristics between the two groups. They were similar in age, underlying conditions, exposure to invasive procedures, acquisition type, infection severity, and etiology. However, patients in the day 5 switch group were more frequently fully dependent for basic activities and had a higher prevalence of urinary tract or unknown-source infections. They also more commonly received oral beta-lactams, while cotrimoxazole and fluoroquinolones were more frequently used in the control group.

Outcomes analysis

In the mITT population, clinical cure at the TOC visit was achieved in 95.4% (105/110) of patients switched on day 5 and 91.7% (177/193) in the control group (RR: 1.04; 95% CI: 0.98-1.10). Among those who did not reach clinical cure, four patients in the control group died, while no deaths occurred in the early switch group. In the clinically evaluable population, the rates were 97.0% and 92.6%, respectively (RR: 1.04; 95% CI: 0.99-1.10). No significant differences were observed for clinical cure at day 60, mortality, or microbiological cure (Table 3). However, recurrence was less frequent in SOT group (10.9% vs 24.3%; RR 0.45, 95% CI 0.24-0.80).

A PS for switching on day 5 was developed using a generalized boosted model. The variables included are shown in Supplementary Material, Table S2. The PS model showed a balanced distribution of baseline variables (Figure S1, Table S3). PS-adjusted bi-

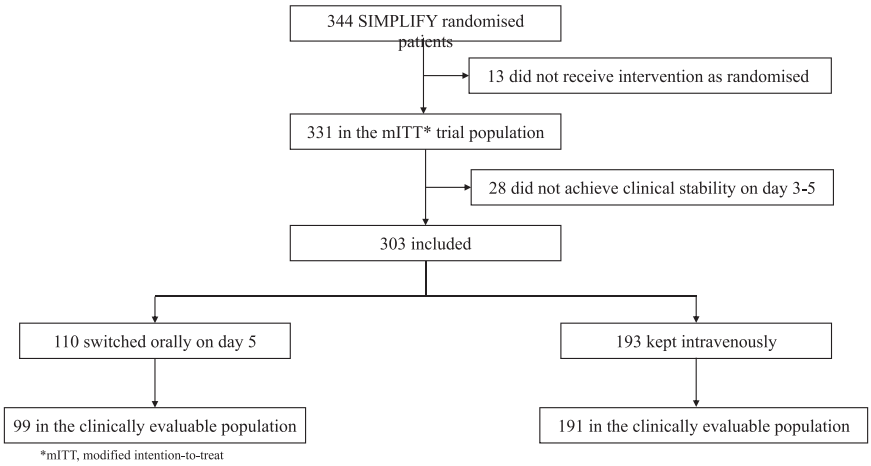

Figure 1. Study diagram.

variate analyses of all variables resulted in an SMD > 0.10 when comparing the two groups to predict clinical cure at TOC are reported in Table S4. Since none of the variables altered the direction of the association between the early switch and clinical cure, we performed both non-IPTW and IPTW-adjusted logistic regression models. The non-PS-adjusted model yielded an OR for clinical cure of 1.90 (95% CI, 0.72-5.94), while the PS-adjusted one yielded an OR of 2.10 (95% CI, 0.96-7.41).

Eight patients among those who were switched on day 5 experienced adverse events, while there were 19 adverse events in the IV group.

In a sensitivity analysis, we compared patients SOT on days 5 and 6 with those who switched after day 6 or never switched. The first had higher clinical cure rate at TOC compared with those who continued intravenously (143/149 [96%] vs 139/154 [90%] (Table S5). The non-IPTW-adjusted model yielded an OR of 2.57 (95% CI, 1.01-7.39), and the IPTW-adjusted one yielded an OR of 2.85 (95% CI, 1.33-8.01).

We analyzed the variable oral switch as time-dependent. In this analysis, we did not find an association of oral switch with clinical cure in the non-PS-adjusted model (HR, 1.40 [95% CI 0.98-1.99]). Conversely, we found an association in the PS-adjusted model (HR, 1.40 [95% CI 1.03-1.89]).

Oral switch on day 5 with beta-lactams vs cotrimoxazole or fluoroquinolones

Among patients SOT on day 5, we compared those receiving beta-lactams to those receiving cotrimoxazole or fluoroquinolones. *Escherichia coli* as BSI etiology was more frequent among those receiving oral beta-lactams (44/57 [77.0%] vs 34/53 [64.0%]). Regarding outcomes, we found similar clinical outcomes. Clinical cure at TOC was reached by 54/57 (95.0%) and 51/53 (96.0%) with beta-lactams and oral cotrimoxazole or fluoroquinolones, respectively (RR 0.98; 95% CI 0.91-1.07); clinical cure data at day 60 were 56/57 (98.0%) vs 50/53 (94.0%], RR 1.04 [95% CI 0.97-1.12]), recurrence at day 60 (2/57 [3.5%] vs 2/53 [3.7%], RR 0.93 [95% CI 0.14-6.37]), microbiological cure at TOC (51/57 [89.5%] vs 48/53 [90.6%], RR 0.99 [95% CI 0.87-1.12]), and death at day 60 (1/57 [1.8%] vs 2/53 [3.8%], RR 0.46 [95% CI 0.04-4.98).

Discussion

In this post hoc analysis of the SIMPLIFY trial, which included patients with Enterobacterales bacteremia requiring at least 5 days of IV treatment at recruitment, we investigated whether early switch to oral therapy was associated with worse clinical cure. To emulate a randomized trial, we included only patients who had achieved a clinical response by day 5. In the adjusted analysis, we found no evidence that switching to oral therapy at day 5 was harmful. A previous target trial emulation on uncomplicated Gram-negative BSI reported similar results, strengthening the evidence for this approach in clinical practice [14]. Additionally, a recent small RCT found oral switch noninferior to continued IV therapy in Enterobacterales BSI when performed after 3-5 days of IV treatment [10]. In an observational study comparing oral step-down therapy with beta-lactams vs fluoroquinolones or cotrimoxazole in Gram-negative BSI from urinary source (where 30-day mortality rates were 3% and 2.6%, respectively), the median switch time was between 4 and 5 days [15], meaning that 50% of the patients were switched after 5 days. Despite focusing on urinary-source BSI, these results are comparable to ours, with a mortality rate of 2.8% in the oral switch group at day 5. Similarly, an RCT on cholangitis-associated BSI found no difference in 30-day microbiological eradication between patients switched on day 6 vs day 10 [6]. Although the study had a small sample size, the microbiological eradication of 93.3% in the early switch group was similar to the 96% microbiological cure observed in our group switched at day 5. A key inclusion criterion in our study was the requirement for at least 5 days of IV therapy. While our findings support switching to oral therapy no later than day five in clinically stable patients, an earlier switch may be equally safe for those improving sooner.

There is ongoing debate regarding the efficacy of beta-lactams vs fluoroquinolones or cotrimoxazole for oral step-down therapy. Some observational studies, particularly those using high-dose beta-lactams, found no significant differences [15–17], while others suggested inferior outcomes with beta-lactams [18,19]. Although our study lacked the power for definitive conclusions, we observed similar 60-day recurrence rates between beta-lactams and other oral options (3.5% vs 3.7%) [20]. Randomized trials are needed to clarify these differences.

Our study has several limitations. First, patients were not randomized to oral switch at day 5, so residual confounding cannot be ruled out. Second, trial screening processes, particularly clinician discretion, may limit generalizability [21]. However, the pragmatic trial design and switch criteria likely reflect real-world practice. Third, low event rates for recurrence and microbiological failure reduced statistical power, preventing firm conclusions on these outcomes. Additionally, these low rates raise the question of how many patients need to be treated to prevent clinical harm with both strategies. This issue may be particularly relevant when planning future RCTs on this topic. Fourth, given RCT evidence support-

Table 2
Comparison between patients switched on day 5 vs those either kept intravenously or switched later.

	Oral switch at day 5, $N = 110$	Control group, $N = 193$	*P*-value
Age, median years (IQR)	72 (64-79)	73 (65-80)	0.68
Female sex	37 (34.0)	87 (45.0)	0.053
Charlson index, median (IQR)	3 (1-4)	2 (1-5)	0.94
Underlying conditions			
Congestive heart failure	13 (12.0)	24 (12.0)	>0.99
Chronic pulmonary disease	19 (17.0)	25 (13.0)	0.31
Solid-organ cancer	33 (30.0)	60 (31.0)	0.90
Hematological cancer	1 (0.9)	4 (2.1)	0.66
Diabetes mellitus	40 (36.0)	71 (37.0)	>0.99
Chronic kidney disease	27 (25.0)	42 (22.0)	0.57
Obstructive uropathy	13 (12.0)	17 (8.8)	0.43
Chronic liver disease	12 (11.0)	21 (11.0)	>0.99
Obstructive biliary tract disease	18 (16.0)	44 (23.0)	0.24
Immunosuppressive drug use	14 (13.0)	29 (15.0)	0.61
Dependent for basic activities	4 (3.6)	24 (12.0)	0.012
Invasive procedures			
Nephrostomy	4 (3.6)	6 (3.1)	>0.99
Biliary stent	4 (3.6)	16 (8.3)	0.15
Ureteral stent	2 (1.8)	7 (3.6)	0.50
Central venous catheter	5 (4.5)	19 (9.8)	0.12
Nosocomial acquisition	22 (20.0)	40 (21.0)	0.88
Severe sepsis/septic shock	27 (25.0)	46 (24.0)	0.89
Source of bacteremia			
Urinary tract	51 (46.0)	65 (34.0)	0.028
Biliary tract	35 (32.0)	83 (43.0)	0.054
Intra-abdominal infection, other than biliary tract	6 (5.5)	21 (11.0)	0.14
Unknown	10 (9.1)	5 (2.6)	0.020
Others	8 (7.2)	19 (9.8)	0.53
Nonurinary source	59 (54.0)	128 (66.0)	0.37
Etiology of bacteremia			
Escherichia coli	78 (71.0)	123 (64.0)	0.25
Klebsiella spp.	16 (14.5)	44 (22.8)	0.11
Others	16 (14.5)	26 (13.2)	0.93
Pitt score, median (IQR)	0 (0-1)	0 (0-1)	0.66
Total duration of antibiotic therapy, median days (IQR)	10 (9-13)	11 (9-14)	<0.001
Intravenous therapy duration, median days (IQR)	5 (5-5)	8 (7-11)	<0.001
Oral therapy duration, median days (IQR)	4 (3-7)	2 (0-4)	<0.001
Source control in first 72 h[a]	77/80 (96.2)	113/122 (92.6)	0.54
Oral drug used			0.048
Ciprofloxacin	48 (44.0)	60 (61.0)	
TMP/SMX	5 (4.5)	3 (3.0)	
Cefuroxime	24 (22.0)	17 (17.0)	
Cefixime	6 (5.5)	6 (6.1)	
Amoxicillin/clavulanate	12 (11.0)	7 (7.1)	
Amoxicillin	15 (14.0)	4 (4.0)	
Ertapenem[b]	0 (0.0)	2 (2.0)	
Not switched to oral drugs	0 (0.0)	94/193 (48.7)	
Oral antibiotic class			0.036
β-lactams	57 (52.0)	36 (36.0)	
TMP/SMX or fluoroquinolones	53 (48.0)	63 (64.0)	

IQR, interquartile range; TMP/SMX, trimethoprim/sulfamethoxazole.
[a] Only patients in whom source control was needed are included in this variable.
[b] Ertapenem was considered an oral drug according to trial protocol.

Table 3
Outcome of patients who were switched to oral therapy at day 5 and control group.

Outcomes	Oral switch at day 5	Control group	RD (95% CI)	RR (95% CI)
Modified intention-to-treat population	$N = 110$	$N = 193$		
Clinical cure at TOC	105 (95.4)	177 (91.7)	0.04 (−0.02, 0.09)	1.04 (0.98, 1.10)
Clinical cure at day 60	106 (96.3)	164 (84.9)	0.11 (0.05, 0.17)	1.13 (1.06, 1.21)
Death at day 60	3 (2.7)	10 (5.2)	0.02 (−0.02, 0.07)	1.02 (0.98, 1.07)
Recurrence until day 60	12 (10.9)	47 (24.3)	−0.13 (−0.21, −0.05)	0.45 (0.24, 0.80)
Clinically evaluable population	$N = 99$	$N = 191$		
Clinical cure at TOC	96 (97.0)	177 (92.6)	0.04 (−0.01, 0.09)	1.04 (0.99, 1.10)
Microbiologically evaluable population	$N = 85$	$N = 167$		
Microbiological cure at TOC	82 (96.5)	152 (91.0)	0.05 (−0.01, 0.11)	1.06 (0.99, 1.13)

RD, risk difference; RR, relative risk; TOC, test of cure.

ing 7-day regimens for Gram-negative BSI, switching before day 5 may be feasible for many patients [22–24]. Fourthly, this post hoc analysis did not reach the estimated sample size of 112 patients per group, limiting statistical power. However, we believe these data may contribute for future meta-analysis on this topic. Finally, although we found no evidence that a switch on day 5 either protected against or posed a risk for clinical failure, the broad CI highlight the limited precision of our estimates. Indeed, the CI suggested a potential positive association between early oral switch and clinical cure, possibly indicating residual confounding.

Our study also has several strengths. Firstly, it leverages high-quality data from a previous RCT population. Secondly, it includes a larger number of patients who switched to oral antibiotics on day 5 compared to previous studies. Thirdly, we employed a rigorous methodology within the emulation trial framework to minimize potential bias. Although the SIMPLIFY trial was not an observational study, we designed this post hoc analysis as a target trial emulation to account for the loss of randomization benefits and to improve the applicability of our finding to real-world observational data.

In conclusion, our study provides evidence supporting the safety of oral step-down therapy in patients with Enterobacterales BSI after 5 days of IV treatment, provided their clinical condition allows it. Ideally, future research should focus on RCT with larger sample sizes and tailor oral switch timings to patients' clinical status rather than to rigid time points. These studies could help establish best practices for safely transitioning patients to oral therapy.

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Availability of data and materials

Luis Eduardo López-Cortés and Jesús Rodríguez-Baño had full access to the data in the study, verified the data in the study, and were responsible for the decision to submit for publication. Individual, anonymized data would be shared after a signed agreement with Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla if requested with the objective of performing a meta-analysis with individual patients' data. Requests should be submitted to the corresponding author. Interested researchers should obtain the approval of the Ethic Committee CEIM Provincial de Sevilla. A database in SPSS file with the requested data and a dictionary of terms would be provided.

Author contributions

Study design and funds proposal: JR-B, LEL-C, PR-G. Critical review of study design: all other authors. Study coordination: LEL-C, JR-B, CR-F, JB-F. Monitoring coordination: CR-F, EM-M. Microbiological studies: MD-V; all other authors: recruitment of patients, follow-up, and collection of patients' data. Analyses of data: ER, JRB, LEL-C. Drafting of the manuscript: ER, LEL-C, JR-B. Critical review of manuscript: all other authors.

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Declarations of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.107917.

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