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Original article

Seven-versus 14-day course of antibiotics for the treatment of bloodstream infections by Enterobacterales: a randomized, controlled trial

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ABSTRACT

Objective: To prove that 7-day courses of antibiotics for bloodstream infections caused by members of the Enterobacterales (eBSIs) allow a reduction in patients' exposure to antibiotics while achieving clinical outcomes similar to those of 14-day schemes.
Methods: A randomized trial was performed. Adult patients developing eBSI with appropriate source control were assigned to 7 or 14 days of treatment, and followed 28 days after treatment cessation; treatments could be resumed whenever necessary. The primary endpoint was days of treatment at the end of follow-up. Clinical outcomes included clinical cure, relapse of eBSI and relapse of fever. A superiority margin of 3 days was set for the primary endpoint, and a non-inferiority margin of 10% was set for clinical outcomes. Efficacy and safety were assessed together with a DOOR/RADAR (desirability of outcome ranking and response adjusted for duration of antibiotic risk) analysis.
Results: 248 patients were assigned to 7 ($n = 119$) or 14 ($n = 129$) days of treatment. In the intention-to-treat analysis, median days of treatment at the end of follow-up were 7 and 14 days (difference 7, 95%CI 7 −7). The non-inferiority margin was also met for clinical outcomes, except for relapse of fever (−0.2%, 95%CI −10.4 to 10.1). The DOOR/RADAR showed that 7-day schemes had a 77.7% probability of achieving better results than 14-day treatments.
Conclusions: 7-day schemes allowed a reduction in antibiotic exposure of patients with eBSI while achieving outcomes similar to those of 14-day schemes. The possibility of relapsing fever in a limited

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number of patients, without relevance to final outcomes, may not be excluded, but was overcome by the benefits of shortening treatments. **José Molina, Clin Microbiol Infect 2022;28:550**

Introduction

The duration of antimicrobial treatment for bloodstream infections caused by members of the Enterobacterales (eBSIs) has traditionally been supported by experts' opinions. Different scientific societies propose treating catheter-related eBSI for a variable duration of between 7 and 14 days [1,2], and no recommendations exist for other sources. The current scenario of rapidly spreading bacterial resistance at a global level mandates initiatives to stop this threat [3], and shortening the duration of antibiotic treatments is probably one of the most effective measures to avoid the emergence of resistance [4]. Producing good-quality evidence to support the effectiveness of shorter courses of antibiotics should be a priority, especially for common clinical situations. Hitherto, two non-inferiority trials have been published showing similar outcomes in patients receiving 7 versus 14 days of antibiotic treatment for bacteraemia caused by Gram-negative bacilli [5,6]. However, the question remains open for specific subgroups of patients—such as immunocompromised patients or males with urinary tract infections—for whom short courses may not be as effective as longer ones [7,8]. Thus, additional evidence would be still useful to allow balancing more accurately the theoretical benefits of shortening antibiotic treatments (i.e. reduced risk of adverse reactions or superinfections) versus the potential for impaired effectiveness in some patients.

The aim of the present trial was to prove that a 7-day course of antibiotics will allow a reduction in patients' exposure to antibiotics while achieving clinical outcomes similar to those of the traditional 14-day schemes for treating patients with eBSI.

Materials and methods

Design

This was an open-label, multicentre, randomized, controlled, phase IV trial. Five Spanish hospitals participated in the trial between September 2014 and September 2016.

Participants

Adults over the age of 18 years with a diagnosis of eBSI were recruited. Hospitalized patients and outpatients were eligible. Exclusion criteria were: (a) pregnancy, (b) eBSI with a non-controlled source and no expectation of being controlled in the subsequent 24 h, (c) patients undergoing chemotherapy with neutropenia <500 cells/mm^3 expected for more than 7 days, (d) eBSI secondary to infections requiring prolonged antibiotic treatment (e.g. osteomyelitis, meningitis, prostatitis, etc.), (e) concomitant infection requiring antibiotic treatment at the time of the diagnosis of the eBSI, (f) eBSI caused by a carbapenemase-producing member of the Enterobacterales, (g) polymicrobial bacteraemia, and h) expectation of survival <48 h. In the initial study protocol, patients diagnosed after randomization of a previously unnoticed exclusion criterion were excluded from the analysis; to avoid potential biases, these patients were included *post hoc* in the intention-to-treat (ITT) analysis.

Intervention and follow-up

Patients were randomized to receive either 7 days or 14 days of any fully active antibiotic treatment—oral or parenteral—against the microorganism isolated, and according to local guidelines. Follow-up blood cultures were obtained after 48 to 72 hours of treatment. To stop the antibiotic treatment, patients were required have a negative follow-up blood culture, and to have remained apyretic and without symptoms of infection for at least 72 h. If these requirements were not met on the day of the scheduled stop, the treatment was continued and the patient re-evaluated each 48–72 hours until all criteria were fulfilled. Patients were followed until 28 days after stopping the antibiotic treatment; for all patients, in-person visits were performed on days +7 and + 14 after the initiation of the treatment, and additional telephone interviews were performed on days +14 and + 28 after the end of antibiotic treatment (Fig. 1). Treatment could be resumed or prolonged whenever considered necessary by the physician in charge. Decisions on the antibiotic agent, oral step-down, hospital discharge, and the management of eventual complications were also decided by the physician in charge without restrictions.

Microbiological assays were performed following the usual routine of microbiology laboratories from the respective participating centres (Supplementary Material File 1).

Outcomes

The primary endpoint was the total number of days of antibiotic treatment prescribed to the patient for any reason, from the day of the first positive blood sample collection until the end of the follow-up. Clinical outcome was assessed through relapse of the eBSI, relapse of fever and clinical cure (defined as resolution of all signs and symptoms of infection) at the end of follow-up. Additional secondary endpoints included crude mortality, superinfections (defined as infections different from the initial episode occurring during the follow-up), and adverse events at the end of the follow-up. A superiority design was defined for the primary endpoint, and a non-inferiority design for clinical outcomes.

Survival was recorded for all randomized patients for safety reasons, including those lost to follow-up; in the latter cases this information was obtained from regional healthcare-system databases.

A full list of definitions for the main clinical variables can be found in the Supplementary Material File 1.

Sample size

Sample size was calculated for the primary endpoint and for clinical outcome endpoints, according to the only meta-analysis available at the moment of designing the trial including bacteraemic infections from different sources (pneumonia, pyelonephritis, peritonitis, etc.) [9]. This study showed a rate of clinical failure of 13.5% for short treatments versus 4.1% for prolonged treatments, without significant heterogeneity among all syndromes analysed. The definition of clinical failure varied among studies in the meta-analysis and included survival, relapses and

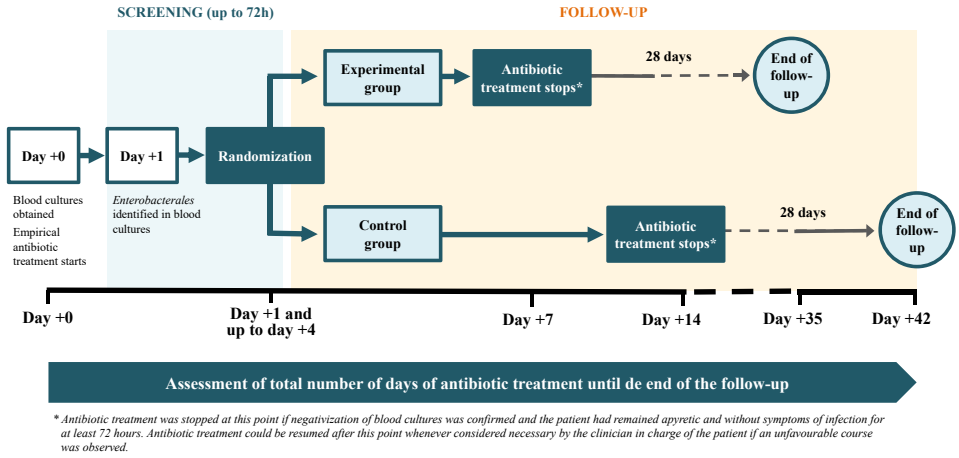

Fig. 1. Randomization and follow-up process.

resolution of symptoms. Assuming a mean of 14 days (SD 7.53) of antibiotic use for the prolonged-treatment arm and 10% of patients lost to follow-up, 40 patients would provide an 80% power at two-sided α 0.05 to detect a difference of at least 3 days of treatment between the two arms. To test the non-inferiority for variables of clinical outcome, 119 patients in each group would be necessary with a 10% non-inferiority margin, 1-sided α 0.025, and the same power and losses, increasing target sample size to 238 patients. A pre-scheduled interim analysis was set when half the sample was recruited.

Randomization

Simple randomization was performed in a 1:1 ratio, stratified by sites through a predesigned randomization list. Randomization was performed up to 72 h after the identification of Enterobacterales in the blood samples (typically, up to 3–4 days after blood cultures were taken). The process was centralized in the coordinating centre, and performed online through an automatic system integrated in the electronic case report form (eCRF). The randomization list was computer-generated (Epidat 4.0 software). Only after the eCRF was fulfilled with inclusion and exclusion criteria did the system provide the group allocation. The information technology department responsible for the eCRF and the clinical trials unit were the only custodians of the randomization list.

Blinding

An open-label design was chosen for pragmatic reasons.

Statistical methods

We tested the superiority of the short regimen by calculating the difference between group medians (95%CI) using the Hodges–Lehmann estimator. Regarding non-inferiority endpoints, one-sided 97.5%CI for the difference between treatments in the proportion of patients were computed with the Newcombe–Wilson score method. Outcomes were compared between groups with the χ^2 test, Fisher's exact test or Mann-Whitney U-test as appropriate.

As a sensitivity analysis, a DOOR/RADAR (desirability of outcome ranking and response adjusted for duration of antibiotic risk) analysis was performed post hoc; this innovative methodology was published after the design of this trial [10]. In the case of our trial, this analysis seemed useful to balance the expected benefits of shortening antibiotic treatments (i.e. reducing adverse effects due to prolonged antibiotic exposure) with the potential risk of impaired effectiveness. To do so, we designed an ordinal scale with five outcome categories: (a) cure without incidences, (b) cure with relapsing fever, (c) cure with a severe adverse event, (d) not cured, and (e) death. The comparison between arms is established in terms of the probability of having a better DOOR score for the experimental group compared with the controls, so that if the short-treatment strategy was better than the prolonged treatments, this probability would be >50%.

Analysis of missing data was performed through multiple imputations (five imputed datasets) [11]. Analyses were performed with SPSS version 19.0.

Ethical aspects

The trial was approved by the regional Ethical Committee for Clinical Research and the Spanish Agency of Medicines and Medical Devices (EudraCT: 2013-002148-95), and was conducted following the principles of the Helsinki Declaration and national regulations (RD 223/2004). All patients signed an informed consent before their recruitment. The trial methodology was registered before its initiation in *clinicaltrials.gov* (NCT02400268). All items from the WHO Trial Registration Data Set are included in the registry.

Results

Baseline characteristics

Among 248 randomized patients, 231 (93.1%) were assessed for the primary and secondary outcomes, with 17 patients lost to follow-up (nine in the short-treatment arm and eight in the prolonged-treatment arm) (Fig. 2, Supplementary Material Files 3 and 4). Baseline characteristics were in general well balanced between groups, except for respiratory source and chronic kidney disease, which were more frequent in the control group (Table 1).

Outcomes

The median length of antibiotic treatment at the end of the follow-up was 7 (7–14) in the experimental group and 14 (14–16) in the control arm (difference 7, 95%CI 7–7) in the ITT population. No significant differences were observed regarding the other endpoints at the end of follow-up, including mortality, relapse of eBSI, relapse of fever, superinfections, or drug-related adverse events.

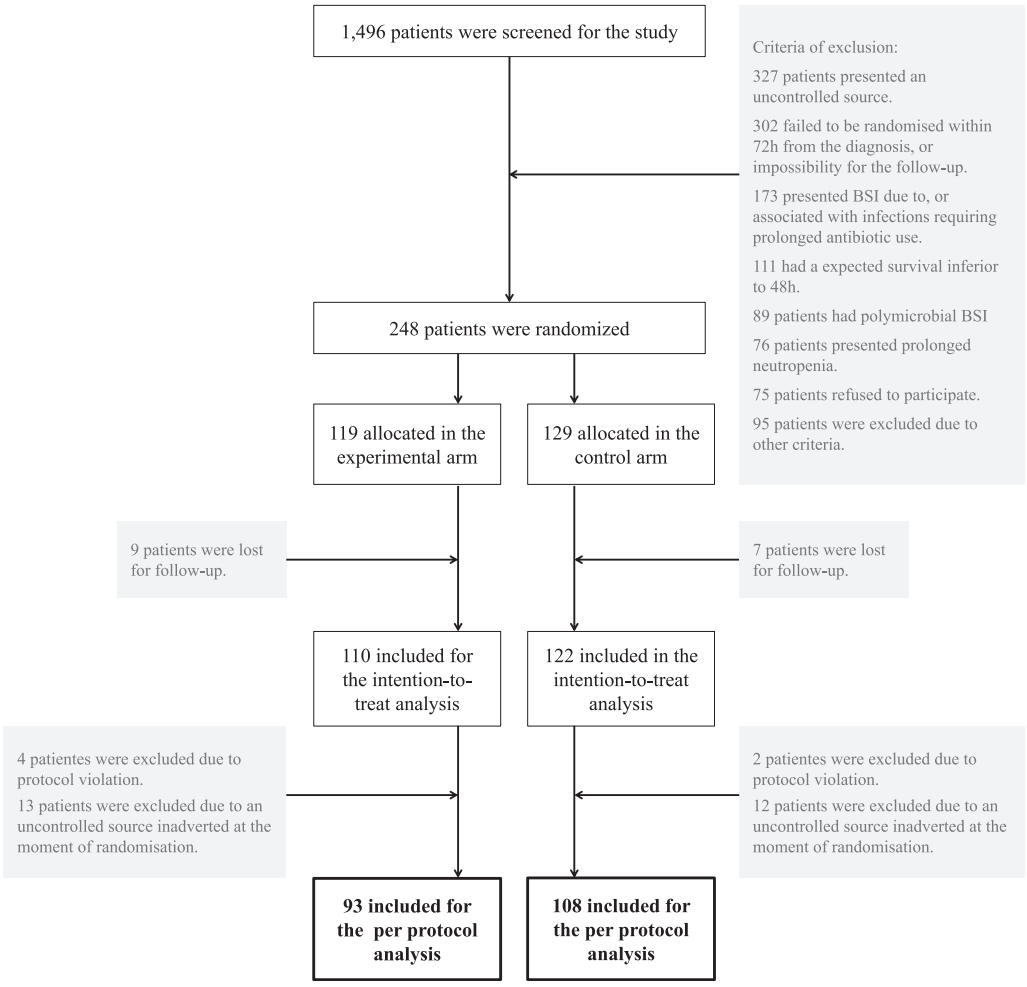

Fig. 2. Flowchart for randomization and patient allocation.

The non-inferiority margin was met for all clinical outcomes except for relapse of fever, which was more frequent in the experimental group (difference in absolute risk −0.2% (97.5%CI −∞ to 10.1) (Table 2, Fig. 3). No significant differences were observed between groups for the causes of relapsing fever (Supplementary Material File 6). The multiple imputation analysis of missing data produced similar results (Table 2).

The DOOR/RADAR analysis showed that patients receiving 7-day courses had 77.7% higher probabilities of achieving better results compared to those receiving 14-day courses, considering altogether clinical cure, adverse events, mortality and antibiotic exposure (Table 3, Supplementary Material File 8).

Safety

No statistically significant differences were detected in different safety variables, including severe adverse events or drug-related reactions (Table 2, Supplementary Material File 7).

Discussion

The results of this trial suggest that 7-day courses of antibiotics may be the preferential strategy for treating bacteraemic infections caused by Enterobacteriaceae, whenever an adequate control of the source is provided.

In order to ensure the safety of the intervention, some secondary endpoints were settled. Compared to 14-day treatments, non-inferiority was shown for clinical cure and relapse of eBSI. The predefined non-inferiority margin was barely unmet for the relapse of fever. It should be noted that not proving non-inferiority is not the same as proving inferiority. However, real-life practice tells us that there may be individual patients for whom 7 days of treatment might be insufficient, whilst no differences in final outcomes were proved in our trial. The need to retreat a limited number of cases should be balanced with the effects of systematically giving prolonged antibiotic treatments to all patients, since the ecological costs of doing so may be unaffordable in the current era of antibiotic crisis [12,13]. The risk of superinfections or other drug-related adverse events should also be balanced when choosing the duration of treatment. Although the trial was not designed to assess this aspect, a trend towards an increased risk of treatment-related adverse events was observed among patients with 14-day treatments, as already suggested by previous studies [14,15].

The aforementioned reasons justified the addition of the DOOR/RADAR analysis. This novel analysis is helpful for randomized trials to define the optimal therapeutic strategy, since considering exclusively the primary endpoint may not allow researchers to accurately balance a proven benefit (i.e. reducing treatment duration) with other potential harms (i.e. impaired effectiveness or side effects) [10,16]. In this case, this analysis pointed towards the 7-day

Table 1
Baseline characteristics of included patients

	Experimental ($n = 119$)	Control ($n = 129$)
Sex female	58/118 (49.2%)	59/129 (45.7%)
Age (median, Q1–Q3)	65 (53–77.5) ($n = 116$)	68 (53–77) ($n = 126$)
Recruiting centre		
HUVR	58/119 (48.7%)	60/129 (46.5)
HUVV	33/119 (27.7%)	35/129 (27.1%)
HURS	13/119 (10.9%)	15/129 (11.6%)
HUVM	13/119 (10.9%)	12/129 (9.3%)
HRM	2/119 (1.7%)	7/129 (5.4%)
Patient care		
Outpatient	25/116 (21.6%)	36/125 (28.8%)
Inpatient	91/116 (78.4%)	90/125 (71.2%)
Charlson index ≥3[a]	54/119 (45.4%)	56/129 (43.4%)
Comorbidities		
Diabetes	45/118 (38.1%)	38/129 (29.5%)
Chronic kidney disease	18/118 (15.3%)	32/129 (24.8%)
Haemodialysis	4/118 (3.4%)	8/129 (6.2%)
Collagenopathies	6/118 (5.1%)	4/129 (3.1%)
Hepatopathy	10/118 (8.5%)	13/129 (10.1%)
Malignancies	32/118 (27.1%)	32/129 (24.8%)
Dementia	3/118 (2.5%)	5/129 (3.9%)
Solid organ transplantation	5/118 (4.2%)	6/129 (4.7%)
Microorganism		
Escherichia coli	76/118 (66.4%)	79/129 (61.2%)
Klebsiella pneumoniae	21/118 (17.6%)	18/129 (14%)
Enterobacter spp.	11/118 (9.2%)	15/129 (11.6%)
Citrobacter spp.	4/118 (3.4%)	3/129 (2.3%)
Serratia marcescens	3/118 (2.5%)	4/129 (3.1%)
Klebsiella oxytoca	2/118 (1.7%)	5/129 (3.9%)
Other	6/118 (5%)	4/129 (3.1%)
Mechanisms of resistance		
ESBL	16/118 (13.6%)	12/129 (9.3%)
AmpC	4/118 (3.4%)	9/129 (7.1%)
BSI acquisition		
Community	49/118 (41.5%)	54/129 (41.9%)
Healthcare-related	33/118 (28.0%)	30/129 (23.3%)
Hospital	36/118 (30.5%)	45/129 (34.9%)
Source of BSI		
Urinary	70/118 (59.3%)	66/129 (51.2%)
Intraabdominal	16/118 (13.6%)	18/129 (14%)
Vascular	14/118 (11.9%)	16/129 (12.4%)
Respiratory	3/118 (2.5%)	12/129 (9.3%)
Unknown	10/118 (8.5%)	11/129 (8.5%)
Other	5/118 (4.2%)	6/129 (4.7%)
Source requiring drainage	30/116 (25.9%)	26/121 (21.5%)
Inadequate empirical treatment	28/117 (23.9%)	25/128 (19.5%)
Presentation sepsis/septic shock	16/108 (13.4%)	17/115 (13.2%)
Other relevant risk factors		
Immunosuppressant drugs	17/118 (14.4%)	14/129 (10.9%)
Previous ICU stay (30 days)	13/118 (11.0%)	8/129 (6.2%)
Previous surgery (30 days)	13/118 (11.0%)	10/129 (7.8%)
Permanent indwelling urinary catheter	15/118 (12.7%)	15/129 (11.6%)
Previous urinary obstruction	7/118 (5.9%)	14/129 (10.9%)
Previous biliary obstruction	8/118 (6.8%)	8/129 (6.2%)

Q1–Q3, quartile 1 to quartile 3; BSI, bloodstream infection; ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; HUVR, Virgen del Rocío University Hospital; HUVV, Virgen del Valme University Hospital; HRS, Reina Sofía University Hospital; HUVM, Virgen Macarena University Hospital; HRM:, Regional Hospital of Malaga.

[a] The stratification of the Charlson index was set post hoc to identify the standardized definition of patients with high or very high comorbidity [17].

treatment as the strategy of choice, showing that patients receiving short treatments had a 77.7% probability of achieving better results, considering together clinical cure, adverse effects and antibiotic exposure.

Before our study, there have been two randomized trials addressing the optimal duration of the treatment of eBSI [5,6]. Consistently with our results, the former non-inferiority trials did not find differences in outcomes of patients treated during 7 days compared to those receiving 14 days of treatment. Our trial adds an insight into the magnitude of the beneficial effect of shortening antibiotic treatment in this scenario through the DOOR/RADAR analysis, which could encourage the adoption of this strategy in routine clinical practice.

Finally, our sample included a considerable rate of immunosuppressed patients (over 10%), cephalosporin-resistant eBSI (over 15%), and infections with a severe clinical presentation (over 13%), reinforcing the reproducibility of its results in real-life situations. The new data provided by this trial, added to those previously published [5,6], may enable proper meta-analyses which could confirm this hypothesis for these subsets of patients.

A number of limitations of this study should be addressed. The intervention of the trial was closely related to the primary endpoint,

Table 2
Primary and secondary endpoints, measured at the end of the follow-up (28 days after antibiotic treatment interruption)

	7 days (n = 119)	14 days (n = 129)	Between-group absolute risk difference (1-sided CI 97.5%)
Days of treatment (median, Q1–Q3)			
ITT population[a]	7 (7–14) (n = 110)	14 (14–16) (n = 124)	7 (7–7)
PP population[b]	7 (7–10.5) (n = 93)	14 (14–15) (n = 108)	7 (7–7)
MI analysis	8 (7–16.4)	14 (14–17)	7 (6–7)
Death[a]			
ITT population	3/119 (2.5%)	9/129 (7.0%)	−4.5% (−∞ to 1.2)
PP population	1/93 (1.1%)	6/108 (5.6%)	−4.5% (−∞ to 1.1)
Relapse of the BSI			
ITT population	7/108 (6.5%)	6/121 (5.0%)	1.5% (−∞ to 8.4)
PP population	5/93 (5.4%)	5/107 (4.7%)	0.7% (−∞to 7.8)
MI analysis	9/119 (7.6%)	7/129 (5.4%)	2.1% (−∞ to 8.9)
Relapse of fever[b]			
ITT population	21/110 (19.1%)	23/119 (19.3%)	−0.2% (−∞ to 10.1)
PP population	17/93 (18.3%)	19/106 (17.9%)	0.4% (−∞ to 11.3)
MI analysis	25/119 (21.0%)	26/129 (20.2%)	0.9% (−∞ to 11.0)
Absence of clinical cure			
ITT population	8/110 (7.3%)	12/122 (9.8%)	−2.6% (−∞ to 5.1)
PP population	1/93 (1.1%)	7/108 (6.5%)	−5.4% (−∞ to 0.4)
MI analysis	13/119 (10.9%)	15/129 (11.6%)	−0.7% (−∞ to 7.5)
Superinfections			
ITT population	16/110 (14.5%)	23/121 (19.0%)	−4.5% (−∞ to 5.4)
PP population	11/93 (11.8%)	20/107 (18.7%)	−6.9% (−∞ to 3.4)
MI analysis	19/119 (16.0%)	26/129 (20.2%)	−4.2% (−∞ to 5.5)
Safety			
Adverse events[c]	51/119 (42.9%)	53/129 (41.1%)	1.8% (−∞ to 13.9)
Severe adverse events	15/119 (12.6%)	27/129 (20.9%)	−8.3% (−∞ to 1.1)
Readmissions or prolongation of hospitalization	15/119 (12.6%)	27/129 (20.9%)	−8.3% (−∞ to 1.1)
Drug-related adverse reaction[d]	7/119 (5.9%)	12/129 (9.3%)	−3.4% (−∞ to 3.5)
Acute kidney injury	3/119 (2.5%)	1/129 (0.8%)	1.7% (−∞ to 6.4)
Diarrhoea	2/119 (1.7%)	3/129 (2.3%)	−0.6% (−∞ to 3.9)
Rash	1/119 (0.8%)	4/129 (3.1%)	−2.3% (−∞ to 2.0)

Q1–Q3, interquartile range; PP, per protocol; ITT, intention to treat; MI, multiple imputation; BSI, bloodstream infection.
[a] Survival was recorded for all randomized patients. In the case of patients lost to follow-up, these data were obtained by access to healthcare databases.
[b] Causes for relapsing fever are detailed in Supplementary Material File 6.
[c] Adverse events were defined as any adverse health incidence in a patient or subject of a clinical trial treated with a drug, even if it does not necessarily have a causal relationship with such treatment.
[d] Adverse reactions with a definite, probable, or possible relationship with the study drug were considered for the analysis. All safety analyses were performed in the intention to treat cohort.

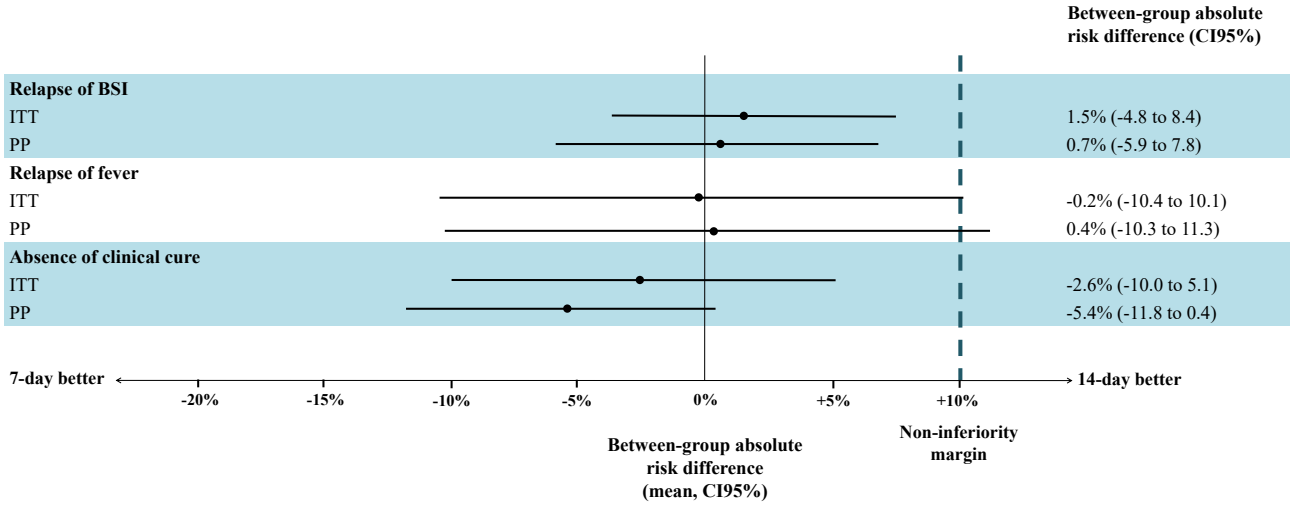

Fig. 3. Non-inferiority analysis for clinical outcome measures.

and was the basis for explaining the differences in antibiotic exposure between groups. Setting this endpoint responded to the aim of the trial—to reduce unnecessary duration of antibiotic use—and was consistent with the methodology of the few preceding trials with similar purposes [12]. It must be noted that the endpoint included any antibiotic treatment received from randomization and until the end of the follow-up, and thus it depended on the clinical course of the infection. The need for frequent retreatments would

Table 3
Distribution of patients per desirability of outcome ranking (DOOR) in the per protocol cohort

	7 days ($n = 93$) n (%)	14 days ($n = 108$) n (%)
Cure without incidences	69 (74.2)	77 (71.3)
Cure with relapsing fever	10 (10.8)	6 (5.6)
Cure with a severe adverse event	12 (12.9)	16 (14.8)
Not cured	1 (1.1)	3 (2.8)
Death	1 (1.1)	6 (5.6)
Probability of a better DOOR/RADAR score in the experimental arm[a]	**77.7% (95%CI 76.8–78.5)**	

[a] Detailed score calculations are provided in Supplementary Material File 8.

have attenuated the differences between the trial arms if the 7-day strategy were ineffective. On the contrary, a median reduction in treatment duration of 50% was achieved in the experimental arm, proving the efficiency of the intervention.

The power of our sample is limited to prove the non-inferiority for less-frequent clinical outcomes, such as mortality, which was low, probably due to the syndrome tackled by the trial. The prevalence of events assessing recurrent illness (relapses, relapsing fever, or absence of clinical cure) were comparable to the clinical failure rate reported in the meta-analysis of Havey et al. [9], and thus, we believe our sample is properly empowered to evaluate this key point when assessing shortened treatments.

Our study included several differences in the follow-up compared to previous trials. First, randomization was carried out early after the diagnosis of the eBSI, in order to avoid a potential risk of bias through the selection of patients with the best responses to treatment. This may have enabled the recruitment of patients with initially unnoticed uncontrolled sources; considering this, we believe that the favourable outcomes achieved, even in the ITT analyses, provides robustness to the conclusions. Second, follow-up was set at 28 days starting from treatment cessation. Since relapses are unlikely to occur during antibiotic treatment, follow-up was set equally for both groups after its discontinuation. To avoid any interference because of the differences in the follow-up, adverse effects were assessed in absolute terms but also considered by days of follow-up (Supplementary Material File 7), without significant differences.

In conclusion, this trial points to a 7-day course of antibiotics as the preferential treatment for eBSI, as long as the source is properly controlled. The potential impact of implementing this recommendation in clinical practice would be significant in the fight against bacterial resistance. A possible need for retreating a limited number of patients after short courses without clinical impact on the final outcomes cannot be discarded by this trial, but seemed to be overcome by the benefits of shortening antibiotic treatments.

Author contributions

JMC and JM conceived and designed the study. CRF and BS supervised and coordinated the accomplishment of legal procedures required for the trial as well as its monitoring. JM, JPS, MH, ELJ, CN, EL, RAM, AIAG, AC, BGG, JEC, IMG and AVM recruited and performed the clinical follow-up of patients. CR and CI recorded data in the trial database. EM performed the statistical analysis. JM, JMC, JP, JMR, JEC, JT and JRB collaborated in the achievement of the public funds and provided the team with the human resources required for the development of the study. All authors contributed in the discussion of the results and approved the final version of this manuscript. Other members of the SHORTEN trial team made substantial contributions to the study; they include: Blanca Solano, Verónica González-Galán, Esteban Hinojosa, Francisco López-Bernal, Marta Suñer, José Ángel Noval, Álvaro Giráldez, Antonio Navarro, María Jesús Rodríguez-Hernández, Yolanda Borrego, Paloma Gil, José Antonio Lepe, Isabel Morales, Pilar Retamar, Marina de Cueto, Juan José Castón and Elisa Vidal.

Transparency declaration

LELC declares consulting fees from Novartis and MSD, honoraria for lectures from Correvio, ViiV and Gilead, and participation on the advisory board for Angelini. AC declares honoraria for lectures from Pfizer and Shionogu. The remaining authors declare no conflicts of interests. The SHORTEN trial is a non-commercial, investigator-driven clinical trial supported by a grant from the Regional Ministry of Health of Andalusia (PI-0161/2013) and by Plan Nacional de I+D+i and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía y Competitividad, Spanish Network for Research in Infectious Diseases (REIPI, RD12/0015/0001, RD12/0015/0002, RD12/0015/0010), co-financed by the European Development Regional Fund "A way to achieve Europe" ERDF and by Plan Nacional de I+D+i and Instituto de Salud Carlos III, Subdirección General de Evaluación y Fomento de la Investigación, Ministerio de Economía y Competitividad, Spanish Clinical Research Network (SCReN, PT13/0002/0010). The trial obtained competitive public funds from the Regional Ministry of Health of Andalusia (PI-0161/2013). These organizations did not participate in the analysis of the study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.09.001.

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