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Randomised, open-label, non-inferiority clinical trial on the efficacy and safety of a 7-day vs 14-day course of antibiotic treatment for uncomplicated enterococcal bacteraemia: the INTENSE trial protocol

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ABSTRACT

Introduction *Enterococcus* spp is responsible for 8%–15% of total bacteraemias with an associated global mortality around 23%–30%. Regarding the clinical management of enterococcal bacteraemia, the evidence on the duration of antibiotic treatment is scarce and the studies do not discriminate between complicated and uncomplicated bacteraemia.

Methods The INTENSE study is a multicentre, open-label, randomised, pragmatic, phase-IV clinical trial to demonstrate the non-inferiority of a 7-day vs 14-day course for the treatment of uncomplicated enterococcal bacteraemia and incorporating the early switching to oral antibiotics when feasible. The primary efficacy endpoint is the clinical cure at day 30±2 after the end of the treatment. Secondary endpoints will include the rate of relapse or infective endocarditis, length of stay, duration of intravenous therapy, *Clostridioides difficile* infection and the evaluation of the safety of both treatment arms through the recording and analysis of adverse events. For a 6% non-inferiority margin and considering a 5% withdrawal rate, 284 patients will be included.

Analysis The difference in proportions with one-sided 95% CIs will be calculated for the clinical cure rate using the control group as reference. For secondary categorical endpoints, a similar analysis will be performed and Mann-Whitney U-test will be used to compare median values of quantitative variables. A superiority analysis applying the response adjusted for days of antibiotic risk will be performed if there were incidents in recruitment; will allow obtaining results with 194 patients recruited.

Ethics and dissemination The study has obtained the authorisation from the Spanish Regulatory Authority, the approval of the ethics committee and the agreement of the directors of each centre. Data will be published in peer-reviewed journals.

Trial registration number NCT05394298.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ As a pragmatic trial, it will be conducted under real-life conditions, and the results can be immediately applied in routine practice settings.
⇒ This is a multicentre study, which entails a shorter recruitment time, a more representative sample of patients and better generalisation of the results.
⇒ The development of a definition for uncomplicated bacteraemia applied to enterococcal aetiology could contribute to protocolisation of clinical management.
⇒ As an open-label trial, a remote automatic randomisation system will be used, and a blinded external evaluation will be implemented to reduce bias.
⇒ The small sample size expected for the bacteraemia caused by *Enterococcus faecium* could make it difficult to obtain specific conclusions in the analysis by subgroups.

INTRODUCTION

Enterococcus spp are the fourth cause of bacteraemia, being responsible for 8%–15% of all episodes.[1–5] The incidence of *Enterococcus faecalis* bacteraemia has increased in recent years, mainly due to the ageing of the population and greater contact with the healthcare environment.[2–4 6] Despite this, the number of published studies is lower than for *Staphylococcus aureus* or *Enterobacterales*. In fact, most of the relevant studies on enterococcal bacteraemia were published in the 1980s and 1990s, focusing on patients with infective endocarditis.[7 8] The crude mortality rate of enterococcal bacteraemia is high (23%–30%), above that reported for *Escherichia coli*, *S. aureus* and *Streptococcus* species, partly because *Enterococcus* spp frequently affect elderly patients with significant comorbidities.[7–9]

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Regarding the clinical management of enterococcal bacteraemia, the evidence is scarce[10–12] and only one recent study retrospectively analysed patients with uncomplicated vancomycin-resistant enterococcal bacteraemia by excluding those with evidence of deep infection and requiring prolonged antibiotic therapy.[13] To the best of our knowledge, the latest international clinical guideline providing recommendations focused on catheter-associated bacteraemia and recommended a treatment duration between 7 and 14 days.[14] The Spanish guideline, published in 2018, also includes this recommendation, but the authors highlight that a shorter duration could be feasible if there are no complications.[15] Bartoletti *et al* recently published a bundle of measures for clinical management, but no indicators related to duration of therapy were included.[16] More recently, Rosselli Del Turco *et al* proposed durations of antibiotic treatment between 1 and 6 weeks depending on the main source of infection and result of echocardiography and other additional diagnostic procedures.[17]

On the other hand, according to data from a recent survey of 385 infectious disease (ID) experts from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), a large variation was found when asking for the management of *E. faecalis* bacteraemia. The majority of requested participants answered in favour of switching from intravenous to oral regimens, the median duration of treatment was 10 days, with a mode value of 14 days and 39% of participants used combination therapy.[18]

In summary, the evidence on the duration of treatment for enterococcal bacteraemia is still under construction, it is not yet clear which patients would benefit from a shorter duration of antibiotic treatment or an early switch to sequential oral treatment.

Based on the preliminary results of a prospective observational multicentre cohort study,[19 20] we hypothesised that patients at low risk of complications and recurrence would only need 7 days of treatment. In order to identify which patients would potentially benefit from a short course of treatment, we propose the definition of 'uncomplicated enterococcal bacteraemia', which includes episodes with low-risk sources, including urinary tract, biliary tract, catheter related, abdominal infection (when focus has been controlled in the first 72 hours) and primary bacteraemia (if all diagnostic efforts have been made to identify the focus); without endovascular complications (endocarditis or thrombophlebitis) or low risk of developing them, and those without septic metastases.

The objective of this study is to demonstrate the non-inferiority of a 7-day antibiotic treatment regimen compared with a 14-day regimen for the treatment of uncomplicated enterococcal bacteraemia in terms of efficacy, using the antibiotics recommended for this entity and incorporating the early switching to oral antibiotics when feasible.

Study hypothesis and objectives

The study is based on three hypotheses: (1) a 7-day treatment regimen for uncomplicated enterococcal bacteraemia (including oral sequential therapy if feasible) is not inferior to 14-day treatment regimen in terms of efficacy and safety, and would be superior in terms of length of hospital stay and antibiotic exposure; (2) A significant proportion of patients will be treated by early switching to oral antibiotics, and the outcome of these patients will be similar to those treated intravenously and (3) Microbiological characteristics of *E. faecium* and *E. faecalis* strains that cause relapses and complicated bacteraemia can be identified.

Study objectives

The primary objective of the study will be to demonstrate the non-inferiority of a 7-day antibiotic treatment regimen over a 14-day regimen for the treatment of uncomplicated enterococcal bacteraemia, in terms of efficacy. Secondary objectives will include: (1) to compare the length of hospital stay in both treatment groups; (2) to describe the outcome in patients in whom early switch to oral antibiotics was provided; (3) to assess the frequency of *C. difficile* infection; (4) to determine which microbiological factors of *Enterococcus* spp may influence the clinical evolution and the risk of relapse; (5) to evaluate the safety of the two treatments and (6) to establish and test the definition of 'uncomplicated enterococcal bacteraemia'.

Study design, setting and study period

The INTENSE study is a multicentre, open-label, randomised, pragmatic, phase-IV clinical trial to prove the non-inferiority of a 7-day course of treatment vs 14-day course of treatment for the treatment of uncomplicated enterococcal bacteraemia. We used the PRECIS-2 tool to evaluate the level of pragmatism of our design[21] and followed the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) recommendations for interventional trials.[22] The trial will be conducted at 22 public and academic hospitals in Spain. A 24-month recruitment period is planned. Patients will be detected from the daily review of blood culture results by microbiologists and IDs physicians participating in the study at each centre. In those patients with isolation of *E. faecalis* or *E. faecium*, treatment will be recommended following evidence-based guidelines. On days 5–6 from the collection of the first positive blood cultures, patients will be assessed for inclusion in the study. Inclusion and exclusion criteria are detailed in box 1. In summary, patients with monomicrobial *Enterococcus* spp bacteraemia with a negative control blood culture on days 2–3, no metastatic complications and no permanent endovascular device will be candidates for inclusion. In case of abscessed foci, these should be drained within 72 hours. All patients meeting at least one of the exclusion criteria will be recorded as screening failure to determine the target population.

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Box 1 Inclusion and exclusion criteria

Inclusion criteria

1. Hospitalised adult patients (≥18 years) with monomicrobial *Enterococcus faecalis* or *Enterococcus faecium* bacteraemia.
2. Negative control blood culture conducted between days 2 and 3 from the first positive blood culture.
3. Disappearance of fever (>37.8°C) within the first 72 hours.
4. Signed informed consent (online supplemental file).

Exclusion criteria

1. Patients with limited life expectancy in whom only conservative clinical management had been decided.
2. Haemodynamic instability on days 5–6.
3. Patients who have an endovascular device, prosthetic heart valve.
4. Focus of bacteraemia not adequately controlled defined as non-drained abscess, bile duct infection associated with plastic stents not removed or not replaced within the first 72 hours of bacteraemia, other infections related to non-removed stents, prostatitis, infective endocarditis or infections requiring prolonged treatment such as joint and bone infections.
5. Presence of metastatic foci of infection distant from the presumed primary source.
6. Existence of a secondary focus, different from the initial focus.
7. Severe neutropenia (<500 cells/mm^3) at the time of diagnosis of bacteraemia.
8. Pregnancy and breast feeding.

Sample size calculation

The sample size was estimated for non-inferiority endpoint using Ene V.3.0 software. Because there are no previous randomised trials on the treatment duration for enterococcal bacteraemia, we used data from the PROBAC cohort for our estimations.[19 20] In this cohort, the rate of death or relapse in patients with 7 vs 14 days of treatment was 13.2% and 17.7%, respectively. For a significance level of 5% and 80% power to reject the null hypothesis for one-sided proportions, and assuming the outcome proportions in the control and experimental groups, for a non-inferiority margin of 6%, it will be necessary to include 134 patients per group in a 1:1 ratio, with a total of 268 patients. A withdrawal rate of 5% is expected; therefore, 284 patients (142 in each group) will be needed. For the choice of the absolute non-inferiority margin, we considered the 10% used in previous trials on the duration of treatment for BSI due to gram negative bacteria[23 24]; however, in the absence of previous trials in bacteraemia due to *Enterococcus* spp, we opted for a more demanding margin because the risk of relapse may be higher with these micro-organisms.

Trial intervention and control

Experimental group (short-course arm): A short-course regimen of 7 days with an appropriate antibiotic treatment (in vitro active antibiotic received within 24 hours prior to blood culture sampling), and provided resolution of bacteraemia has been achieved (a negative control blood culture on days 2–3 from the sampling of the first blood culture).

Control group (long-course arm): A long-course regimen of 14 days with an appropriate antibiotic treatment, and provided resolution of bacteraemia has been achieved.

Oral treatment: In order to facilitate the discharge of patients in both arms and reduce the risk of complications, the change to oral therapy is allowed at any time from inclusion in the study, in patients with haemodynamic stability who tolerate oral treatment, at the discretion of the responsible physician.

Following treatments will be accepted as appropriate antibiotic treatment[14 17]:

1. Ampicillin 2 g/6 or 8 hours intravenously for ampicillin-susceptible isolates.
2. Vancomycin 15 mg/kg/day intravenously (with determination of trough plasma levels on days 2–3 of treatment, if available, and consistent dosage adjustment to achieve the therapeutic target based on AUC/MIC), linezolid 600 mg/12 hours intravenously or daptomycin 8–10 mg/kg/day intravenously in case of ampicillin-resistant strains and/or patients with allergy to beta-lactam antibiotics.
3. In patients with intra-abdominal or soft tissue infections in which a polymicrobial infection is suspected, treatment with amoxicillin/clavulanic acid 1 g/8 hours intravenously, piperacillin/tazobactam (ampicillin-susceptible isolate) 4 g/8 hours intravenously or the combination of vancomycin, linezolid or daptomycin (see dose above) with antibiotics active against gram-negative and anaerobic bacteria, will be considered as appropriate.
4. For switching to oral treatment, the following drugs could be used: amoxicillin 1 g/8 hours or amoxicillin/clavulanic acid 875/125 mg/8 hours if polymicrobial infection is suspected and linezolid 600 mg/12 hours.

Dosing can be adjusted in patients with renal insufficiency according to the labels of each antibiotic. Considering that all drugs are approved for enterococcal bacteraemia in Spain, the drugs will be provided by each participating hospital by regular procedures of their Pharmacy Hospitals departments.

Randomisation

Recruited patients will be randomised by rating 1:1, allowing the assignment to intervention or control arm. Assignment to each treatment arm will be performed using the automated randomisation system integrated into the electronic case report form (eCRF). The randomizeR package of V.2.0.0 was used for generating the randomisation list with the R V.4.1.1 (10 August 2021) and will be kept in the CTU for easy access in case of a technical failure of the eCRF. Stratified randomisation based on *Enterococcus* species will be performed to ensure the inclusion of a similar number of cases caused by each species in both treatment arms.

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Table 1 Schedule of visits and assessments

Assessment	Day 0	Days 2–3	Visit 0 (Days 5–6)	End of Treatment visit (Days 7 or 14±2)*	Test of Cure visit (Day 30±2)	Follow-up visit (Day 90±2)*
Inclusion/exclusion criteria			X			
Pregnancy test			X			
Informed consent			X			
Randomisation			X			
Clinical history/anamnesis			X	X*	X	X*
Physical examination	X	X	X	X*	X	X*
SOFA score			X	X*	X	X*
Haematology/biochemistry	X		X	X*	X	X†
Blood culture		X			X	
Concomitant medication			X	X		X
Antibiotic traceability			X	X		X
Adverse events			X	X	X	X

*The visit can be done by telephone if the patient is not hospitalised. In this case, physical examination or laboratory tests are not needed.
†Unnecessary if the patient is not admitted
SOFA, Sequential Organ Failure Assessment.

Follow-up scheme

Patients included in this study will be follow-up until 90 days (±2) after the completion of the appropriate antibiotic treatment (follow-up visit). The follow-up visits are organised in four scheduled visits. The screening visit (visit 0) is performed on days 5–6, the end of treatment visit should be performed on day 7 or day 14 depending on the arm randomised and the test of cure (TOC) visit is performed on day 30±2. The visiting schedule is specified in table 1.

Outcome measures

The primary efficacy endpoint is clinical cure at day 30±2 after the end of the treatment (TOC visit); it will be assessed in the intention-to-treat population, which includes all randomised patients. This endpoint is composite by (A) survival in TOC; (B) no need to prolong treatment beyond the pre-established duration, or to restart antibiotic therapy with coverage against *Enterococci* for any reason within 30 days after completion of antibiotic treatment and (C) absence of diagnosis of infective endocarditis or relapse of enterococcal bacteraemia in TOC (new isolation in blood culture of *Enterococcus* spp with the same species and phenotype of the first isolate after 30 days of completion of adequate antibiotic therapy).

We decided to use a composite primary endpoint to include a relevant and hard endpoint such as survival, but since mortality may not be due to infection, we also include clinical success as an endpoint, as recommended in a consensus document for trials in bacteraemia.[25] To control for potential investigator bias, the result will be checked by collection of objective clinical data at visit 0 and TOC, including temperature, blood pressure, respiratory and heart rates, Glasgow score and examination of specific signs; and calculation of the SOFA score at visit 0 and TOC.

Secondary endpoints will include the rate of relapse of bacteraemia or infective endocarditis diagnosis, length of stay, duration of intravenous therapy, *C. difficile* infection and the evaluation of the safety of both treatment arms. Those variables will be evaluated at visit 0 and TOC visit in clinically evaluable population.

Statistical analysis

The difference in proportions with one-sided 95% CIs will be calculated for the clinical cure rate at TOC using the control group as reference. For secondary categorical endpoints (*C. difficile* infection, other secondary infections and adverse events), a similar analysis will be performed. Also, median length hospital stay, duration of intravenous therapy and changes in SOFA score in TOC compared with Visit 0, will be compared by Mann-Whitney U-test between both study arms. Subgroups analysis will be performed on those patients who did or did not receive sequential oral treatment, those with bacteraemia due to *E. faecalis* or *E. faecium*, by source of bacteraemia, and by age and Charlson index. Multivariate analysis using logistic regression will be performed to control for residual imbalances between study arms; this analysis will include the different antibiotics used and the sequential to oral treatment as a qualitative variable as well as the duration of oral treatment.

In addition, we will perform a superiority analysis applying the response adjusted for days of antibiotic risk (RADAR) methodology. This method overcomes the limitation of evaluating different endpoints separately.[26 27] For its calculation, patients are first classified on the basis of four mutually exclusive hierarchical levels corresponding to the patient's clinical outcome: (A)

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survival at day 30 after completion of treatment without incident, (B) survival with a serious adverse event (SAE), (C) diagnosis of relapse or infective endocarditis and (D) death. All patients are classified according to their category, where patients with a better clinical outcome (or those with lower admission days in case of a tie) have a more favourable classification. We classified patients with enterococcal bacteraemia in the PROBAC cohort into these four hierarchical levels and calculated a sample size comparing the means of both arms. For a power of 80% to detect differences in the contrast of the null hypothesis (H0: mean difference equals the non-inferiority limit) using a one-sided Student's t-test for two independent samples, taking into account that the significance level is 5%, and assuming that the non-inferiority limit is 0.30, the mean rank value of the control group is 1.50, the mean of the experimental group is 1.42 and the SD of both groups is 1.03, it will be necessary to include 92 patients in the control arm and 92 patients in the experimental arm, with a total of 184 patients. Considering that the expected drop-out rate is 5%, it would be necessary to recruit a total of 194 patients. Then, if there were incidents in recruitment, the RADAR-adjusted analyses will allow obtaining results with a need for only 194 patients recruited.

Interim analysis

An interim analysis will be performed when 50% of the sample (n=71 patients per arms) is included and monitored. This analysis will be carried out, to ensure that there are no safety or efficacy aspects that require the suspension of the trial, and to avoid possible biases related to the open nature of the study. The evaluation of the results will be carried out by an independent committee (three experts not participating as researchers in this study), blinded to treatment assignment. Prior to the start of the trial, the composition of the committee and its organisation will be sent to the ethic committee for its approval. Prior to the setting-up of the study, a guide with the information and time frames for the data safety monitoring board will be approved and signed by all the members of the committee.

Microbiological procedures

Blood cultures, bacterial identification and antibiotic susceptibility testing will be performed in local laboratories using standard microbiological procedures. The isolates will be sent to the Department of Microbiology of the H.U. Virgen Macarena, where a study of antibiotic susceptibility, clonality, determination of resistance genes and virulence of the first isolate from all patients included will be carried out. In those cases, presenting relapse, the consecutive isolate will be also analysed and compared with the first isolate. Bacterial identification will be confirmed by MALDI-TOF mass spectrometry (MALDI Biotyper, Bruker Daltonics), and antimicrobial susceptibility testing will be carried out by broth microdilution in Mueller-Hinton for ampicillin, penicillin, vancomycin, daptomycin and linezolid; agar dilution in Mueller-Hinton agar supplemented with glucose-6-phosphate for fosfomycin, while screening for high-level resistance to aminoglycosides will be performed using Brain Heart Infusion (BHI) agar supplemented with 500 mg/L gentamicin and BHI agar supplemented with 1000 mg/L streptomycin. In isolates with low susceptibility or resistance to glycopeptides, the presence of non-susceptible subpopulations will be determined by culture on BHI agar supplemented with 6 mg/L vancomycin. The interpretation will be done by following EUCAST clinical breakpoints, except for daptomycin and fosfomycin, for which the Clinical & Laboratory Standards Institute (CLSI)

recommendations will be used. Genotyping of the isolates will be carried out by Pulsed Field Gel Electrophoresis (PFGE), multi locus sequence typing (MLST) and single-nucleotide polymorphism analysis. Phylogenetic analysis will be performed with the CSI Phylogeny V.1.4 bioinformatics tool (https://cge.cbs.dtu.dk/services/CSIPhylogeny-1.4). Genomes will be sequenced using the Illumina MiSeq system, de novo assemblies and gene annotations will be performed using the CLC Genomics Workbench V.9.5.2 (Qiagen) system and RAST server (http://rast.nmpdr.org/), respectively. Analysis of antimicrobial resistance genes and virulence genes will be performed on isolates from patients with recurrent bacteraemia. For this purpose, the complete genome sequences will be analysed in ResFinder V.3.2 and Virulence Finder V.4.1 tools (https://cge.cbs.dtu.dk/services).

Safety and adverse event reporting

Safety of all the drugs included in the study will be followed from the signing of the informed consent until the final follow-up visit, 30±2 days after the end of the treatment (TOC) through the collection of all AEs occurred (any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment). In those subjects who experience diarrhoea (three or more stools per day of decreased consistency) during the study, the detection of *C. difficile* toxin in faeces will be requested. The investigator will evaluate and record the AE in detail, including the start and end date, the description of the event, severity, evolution, outcome and his/her suspicion of the relationship of the AE with the trial treatments and the measures adopted. All the AEs will be recorded in the clinical history and will be collected in the eCRF and any SA will be notified in less than 24 hours to the Department of Pharmacovigilance (FV-UICEC-HUVR), which is responsible for receiving, registering and resolving queries and for identifying any suspected unexpected serious adverse reactions (SUSAR). SUSAR must be notified to the regulatory authorities, ethics committees and investigators within a period of 15 calendar days.

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Study organisation

The study coordinating group is formed by the clinical team which includes specialists in IDs and microbiology at the coordinating site (Hospital Universitario Virgen Macarena), and the Clinical Research and Clinical Trials Unit (Hospital Universitario Virgen del Rocío), the personal of which are expert in legal, ethics pharmacovigilance and monitoring of clinical trials. Data collection will be performed by trained collaborators at each participating centre into an electronic and restricted-access eCRF. The study will be monitored through local visits, telephone calls and periodic revision of the eCRFs to verify the rate of patient inclusion, compliance with the protocol procedures, completeness and accuracy of the data and verification of the original documents. The coordinating group will have access to the final trial data set.

Data collection, management and monitoring

The personal data of the participating subjects will be processed confidentially pursuant to the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of the processing of personal data (General Data Protection Regulations) and the provisions of the Organic Law 3/2018, of 5 December, on Personal Data Protection and digital rights guarantee. All the information regarding the procedures, treatments options, treatment allocation, number of visits and procedures, adverse events known for the drugs used for the study and information related to the voluntary participation and possibility of withdrawal the study without any negative consequence is written in an approved patient information sheet approved by the EC. The anonymity of the subjects will be maintained at all times. Any material related to the trial, such as study samples will be anonymous and identifiable only by the patient's alphanumeric study code and only the researcher and collaborators will be able to relate said data with the patient and with his clinical history. Therefore, the identity of the patient will not be revealed except in case of medical emergency or legal requirement (health authorities or EC). The data from this study will be used only for the specific purposes of the study.

Ethics and dissemination

The study will be developed in accordance with the principles of the Declaration of Helsinki and according to current legal regulations (Spanish Royal Decree 1090/2015, EU Regulation CE536/2014). The study has obtained the authorisation of the Spanish Regulatory Agency (AEMPS, Agencia Española del Medicamento y Productos Sanitarios) and the approval by CEIm provincial de Sevilla (Comité Ético de Investigación con Medicamentos-EC). Protocol amendments will be subject to review and approval by the CEIm, and will be communicated to relevant parties by the study coordinating group. An approved informed consent form will be requested by the attending physician and must be signed before any study procedures are performed. Patients may withdraw from the study at any time without prejudice, as is documented and explained at the time of providing consent. The communication of results and publications will comply with the provisions of current legal regulations for clinical trials with medicinal products. The results will be published in peer-reviewed journals and the authorship criteria of the International Committee of Medical Journal Editors will be followed.

Patient and public involvement statement

Patients or the public are not involved in the design, or conduct, or reporting, or dissemination plans of this clinical trial.

DISCUSSION

The INTENSE trial is a phase IV, pragmatic, open clinical trial to demonstrate the non-inferiority of short antibiotic treatment in terms of efficacy with respect to the long treatment in uncomplicated enterococcal bacteraemia. The clinical management of *Enterococcus* spp bloodstream infection is under discussion and a few papers have been published recently in this regard. Clinical practice guidelines recommend duration of 7–14 days of treatment, without specifying the scenario when selecting one or another. This is why the duration used in clinical practice is heterogeneous and depends on many factors that are taken into account when choosing one duration or the other, including the age of the patient, presence of intravascular, urinary or biliary devices, structural pathology of the urinary or biliary tract, presence of septic thrombophlebitis, etc. In the presence of all these characteristics, it is to be expected the presence of a complicated bacteraemia requiring a longer antibiotic treatment.

Previous studies focused on the management of *S. aureus* and *Candida* spp bacteraemia have demonstrated the effectiveness of using bundles composed by different indicators to increase the homogenisation of clinical management. By improving the adherence to these bundles a better short-term and medium-term prognosis has been demonstrated.[28 29] Recently, in a single-centre study, patients with enterococcal bacteraemia who received consultation with ID specialists were more likely to undergo repeat cultures to ensure clearance, echocardiography, surgical intervention and have better appropriate antibiotic duration, defined as 14 days for uncomplicated bacteraemia. These patients had significantly lower 30-day mortality than the comparator group.[30] In a quasi-experimental study, the introduction of a bundle for the management of enterococcal bloodstream infection which includes ID consultation, echocardiography, follow-up blood cultures and early targeted antibiotic treatment, was associated with improved 30-day and 1-year survival.[16] However, in none of these bundles a short course of antibiotics was evaluated, so the efficacy and safety of the duration remains to be determined.

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The development of a definition of uncomplicated bacteraemia applied to enterococcal aetiology could contribute to protocolising clinical management and would allow the selection of low-risk patients in whom the duration of 14 days treatment would be reduced by 50%. This reduction in the duration of antibiotic treatment not only leads to a significantly lower exposure to antibiotic pressure but is also associated with a lower risk of developing antibiotic-associated adverse events, including *C. difficile* infection,[31] mucosal or invasive candidiasis,[32] superinfections caused by multidrug resistant organisms, and toxicity or drug interactions.[33]

On the other hand, regarding to sequential oral therapy, in the survey of experts in IDs carried out by ESCMID society, 21% (80/388) of the respondents have never applied sequential oral treatment and 29% (111/388) have only applied it in very specific situations.[18] This contrasts with recently available data supporting the use of oral therapy as a continuation of intravenous treatment in many infections, including endocarditis.[34] While this information is probably sufficient to validate the switch to oral treatment once the infection is controlled, we believe it is necessary to provide more specific information to make the switch to oral treatment.

In this proposal, we include the most recent management aspects of treatment of enterococcal bacteraemia used in actual practice, including sequential oral therapy with amoxicillin, amoxicillin/clavulanic acid or linezolid, and incorporating this aspect into the analysis. Previous versions of the study protocol included ciprofloxacin as a sequential oral therapy option, but it was removed because it is only an accepted treatment option in uncomplicated urinary tract infection (UTI),[35] as recommended by reviewers of the manuscript. No patient recruited so far has received ciprofloxacin as an oral step-down option. This change was approved by the Spanish regulatory agency (AEMPS) on 24 February 2023 and the local ethics committee on 16 March 2023.

The incorporation of oral treatment poses specific challenges for study analysis, but we consider it mandatory for a pragmatic study. Likewise, the limited experience in the literature on early sequential oral treatment for this aetiology implies that prolonged treatment must be administered intravenously. Therefore, the reduction in the duration of treatment, and especially the early change to sequential oral treatment, would reduce hospital length of stay and discard the venous catheter as soon as it is no longer essential for patient management, thus reducing the risk of hospital acquired infections and other adverse outcomes.[36]

In this clinical trial, all patients with enterococcal bacteraemia are potential candidates until inclusion and exclusion criteria can be verified on day 5, which could potentially improve follow-up and consequently the clinical management of this aetiology, irrespective of whether they are included in the clinical trial or not. This pragmatic trial will be conducted under real-life conditions, a natural environment for clinical research that could involve the immediate integration of results into routine clinical practice.[37]

Study status

- Funding for the study was approved on 1 December 2021 and available for study expenses on 1 January 2022.
- Authorisation from the Spanish Regulatory Authority was obtained on 21 February 2022, code No EudraCT 2021-003891-15.
- Approval for the Ethics Committee for the 22 sites included was obtained on 10 December 2021.
- Protocol and patient information sheet, V.1.0, approved on 31 January 2021.
- First patient inclusion occurred on 15 July 2022.
- Current protocol and patient information sheet, V.3.0, approved on 24 February 2023.

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