

BMJ Open Efficacy of cloxacillin versus cefazolin for methicillin-susceptible *Staphylococcus aureus* bacteraemia (CloCeBa): study protocol for a randomised, controlled, non-inferiority trial

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ABSTRACT

Introduction Methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia is a common and severe disease responsible for approximately 65 000 deaths every year in Europe. Intravenous antistaphylococcal penicillins (ASP) such as cloxacillin are the current recommended antibiotics. However, increasing reports of toxicity and recurrent stock-outs of ASP prompted healthcare providers to seek for alternative antibiotic treatment. Based on retrospective studies, cefazolin, a first-generation cephalosporin, is recommended in patients at risk of severe ASP-associated toxicity. We hypothesised that cefazolin has a non-inferior efficacy in comparison to cloxacillin, with a better safety profile for the treatment of MSSA bacteraemia.

Methods and analysis The CloCeBa trial is an open-label, randomised, controlled, non-inferiority trial conducted in academic centres throughout France. Eligible patients are adults with MSSA bacteraemia without intravascular device or suspicion of central nervous system infection. Patients will be randomised (1:1) to receive either cloxacillin or cefazolin by the intravenous route, for the first 14 days of therapy. The evaluation criteria is a composite criteria of negative blood cultures at day 5, survival, absence of relapse and clinical success at day 90 after randomisation. Secondary evaluation criteria include both efficacy and safety assessments. Three ancillary studies are planned to describe the epidemiology of β -lactamase encoding genes, the ecological impact and pharmacokinetic/pharmacodynamic parameters of cefazolin and cloxacillin. Including 300 patients will provide 80% power to demonstrate the non-inferiority of cefazolin over cloxacillin, assuming 85% success rate with cloxacillin and taking into account loss-to-follow-up, with a 0.12 non-inferiority margin and a one-sided type I error of 0.025.

Ethics and dissemination This protocol received authorisation from the ethics committee Sud-Est I on 13

Strengths and limitations of this study

- First randomised controlled trial to compare the safety and efficacy of cefazolin and cloxacillin for treatment of methicillin-susceptible *Staphylococcus aureus* bacteraemia.
- Pragmatic trial designed to interfere as little as possible with usual care.
- Investigation of the potential impact of different types of *S. aureus* β -lactamases on the patients' outcome and analysis of the ecological impact of both antibiotics.
- No stratification on the site of infection but on vascular access-associated bacteraemia.
- Exclusion of patients with central nervous system infections.

November 2017 (2017-87-PP) and French National Agency for Medicines and Health Products (170661A-43). Results will be disseminated to the scientific community through congresses and publication in peer-reviewed journals.
Trial registration number NCT03248063 and 2017-003967-36.

BACKGROUND

Rationale

Staphylococcus aureus bacteraemia (MSSA) is the second cause of community-acquired or hospital-acquired bloodstream infections. About 200 000 cases occur every year in Europe and the overall mortality is estimated around 30%.^{1,2} Most of *S. aureus* are susceptible to antistaphylococcal penicillins (ASP) such as cloxacillin, with a prevalence of

resistance around 20% in France.³ ASP such as cloxacillin or oxacillin are recommended as first-line agents. No alternative has yet proven a similar efficacy.

This leader position of methicillin has been shaken during the past decade: first, the safety of ASP has been questioned, as both hypersensitivity reactions and renal impairment have been reported in >10% of patients.^{4 5} Premature discontinuation of ASP attributed to adverse events that occurred in >20% of patients treated with high doses of oxacillin (12 g/day) for complicated MSSA bacteraemia.⁶ This might be linked to ageing and to the growing number of cumulative comorbid conditions, including chronic kidney disease with decreased glomerular filtration rate. Second, stock-outs of antimicrobials are increasing. In 2011, the production of the main generic for injectable oxacillin, the first-line ASP for severe staphylococcal infections in France, was stopped. More recently, a prolonged stock-out of the alternative, cloxacillin, due to manufacturing issues, further complicated the situation.

For these reasons, alternatives to ASP are needed. Cefazolin, a semi-synthetic first-generation cephalosporin administered by parenteral route, could be a good candidate for several reasons: a similar efficacy, based on several large observational studies⁷⁻¹¹; a favourable safety profile^{4 6 12-14} and a convenient administration schedule. These data led the American Heart Association, the Infectious Disease Society of America and the European Society of Cardiology to consider cefazolin as the first alternative line agent for treatment of MSSA-associated infective endocarditis.^{15 16} However, these recommendations are based on observational studies, and a face-to-face comparison of both antibiotics is jeopardised by the heterogeneity of studies design and populations. No randomised clinical trial has been performed so far.

Objective and hypothesis

The objective of this trial is to compare the therapeutic efficacy and the safety of cloxacillin and cefazolin for the treatment of MSSA bacteraemia in adult patients. Our hypothesis is that cefazolin is not inferior to cloxacillin and has a more favourable safety profile than cloxacillin.

METHODS AND DESIGN

General information

This is an open-label, randomised, controlled, phase IV, parallel-groups non-inferiority trial comparing the efficacy of cloxacillin versus cefazolin for the treatment of MSSA bacteraemia in adults. This trial will involve patients from academic hospitals throughout France. Study sites can be obtained from the Sponsor's representative.

The trial has been registered at the Clinical Trials Registry as NCT03248063 and on the European Clinical Trials Database as 2017-003967-36. Any substantial amendment made to the protocol by the coordinating investigator will be sent to the sponsor for approval. After approval is given, the sponsor will obtain, prior to

implementing the amendment, approval from the ethics committee and health authorities.

A scientific committee has been constituted for this trial. Its roles are to define the objectives of the research, to propose changes of the protocol during research and to determine the methodology and the publication plan. The scientific committee will meet every 12 months. A steering committee dedicated to the conduct of the research and to the coordination of participating centres will meet on a pluriannual basis.

After completion of the trial, publication of the results is intended in a peer-reviewed scientific journal. Granting full access to the protocol or participant-level dataset is not intended.

Participants

For the duration of the study, the sponsor will take out an insurance policy covering the sponsor's own third-party liability as well as the third-party liability of all the investigators involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the study participant and their beneficiaries.

Inclusion criteria

Prior to enrolment in the trial, patients must fulfil all the following criteria:

1. Age above 18 years;
2. Positive blood culture for Gram-positive cocci and a time-to-positivity ≤ 20 hours;
3. At least one set of blood culture positive to MSSA identified by GeneXpert PCR (Xpert MRSA-SA BC, Cepheid, Sunnyvale, California, USA).

Non-inclusion criteria

Patients with any of the following criteria will not be eligible for the trial:

1. Previous type 1 or grade 3-4 hypersensitivity reaction to β -lactams;
2. Known pregnancy or breastfeeding women;
3. Empirical antimicrobial therapy for >48 hours;
4. Chronic renal failure defined by a creatinine clearance estimated < 30 mL/min/1.73 m²;
5. Presence of an intravascular implant (vascular or valvular prosthesis or cardiovascular implantable electronic device);
6. Strong clinical suspicion for infective endocarditis associated with central neurological signs;
7. Brain abscess;
8. Current other antibiotic therapy which cannot be ceased or substituted by study treatment;
9. Mixed blood culture with more than one pathogen (excluding contaminants: *Corynebacterium* sp, *Propionibacterium* sp, coagulase-negative staphylococci, *Micrococcus luteus*, *Rothia* spp);
10. Absence of written informed consent from the patient or a legal representative (if appropriate);
11. Limitation of care with expected life duration below 90 days;

12. Patient under guardianship or trusteeship;
13. No affiliation to social security (beneficiary or assignee);
14. Subject already involved in another clinical trial except trials evaluating imaging techniques.

Randomisation

Patients will be randomly assigned in a 1:1 ratio into one of the two treatment groups. The randomisation list will be computer-generated, stratified by centre and vascular access-associated bacteraemia, with blocks of various sizes. The randomisation list will be implemented in the electronic Case Report Form (eCRF) to ensure appropriate allocation concealment.

Experimental design

Study treatments

Patients included in the experimental group will receive intravenous treatment by cefazolin, 25–50 mg/kg every 8 hours (without exceeding the maximum daily dose of

6 g/day), administered as a 60 min infusion. Doses will be adapted in patients with renal failure (glomerular filtration rate between 30 and 50 mL/min).

Patients included in the control group will receive intravenous treatment by cloxacillin, 25–50 mg/kg every 6 hours (without exceeding the maximum daily dose of 12 g/day), administered as a 60 min infusion. Doses will be adapted in patients with renal failure (glomerular filtration rate between 30 and 60 mL/min) associated with hepatic dysfunction.

The compliance with the allocated treatment will be evaluated at every follow-up visit in a specific case report form by the investigator in charge of the patient. On the day of hospital discharge, a diary will be delivered to the patient to evaluate the compliance with the treatment.

Participant timeline

Schedule for enrolment, interventions and assessments are summarised in [table 1](#) and [figure 1](#). Total

Table 1 Schedule of enrolment, interventions and assessment in the CloCeBa trial

	Day 0 (inclusion)	Day 1	Day 3	Day 5	Day 7	EoST (±1)	EoAT (±3)	Day 90 (±7)
Visit	V1				V2		V3	V4
GenExpert PCR	X							
Inclusion/non-inclusion criteria	X							
Informed consent	X							
Randomisation	X							
Sociodemographic data	X							
Medical history	X							
Concomitant medications	X				X		X	X
Vital signs	X	X			X		X	X
Physical examination	X	X			X		X	X
Urinary β-hCG for women in childbearing age	X							
Blood cell and platelet count	X	X	X		X	X	X	X
Plasma creatinine and urea	X	X	X		X	X	X	X
Liver function tests (AST, ALT, prothrombin ratio)	X	X	X		X	X	X	X
C reactive protein	X							
Blood culture*		X	X	X				X
Record of cardiac ultrasonography result					X			
Rectal swab†		X			X		X	X
Pharmacokinetic analysis‡			X					
Adverse events	X	X	X	X	X	X	X	X
Coproculture with <i>Clostridium difficile</i> tests in case of diarrhoea	X	X	X	X	X	X	X	X

*All blood culture performed between day 0 and day 7 will be collected. All included patients will have a set of blood cultures on days 1, 3, 5 and 90.

†In a subgroup of 150 patients (75 in each treatment groups) included in Bichat, Beaujon and Henri Mondor hospitals.

‡In a subgroup of 50 patients (25 in each treatment group) included in Bichat and Beaujon hospitals.

ALT, alanine transaminase; AST, aspartate transaminase; β-hCG, β-human chorionic gonadotropin; EoAT, end of antibiotic treatment; EoST, end of study treatment.

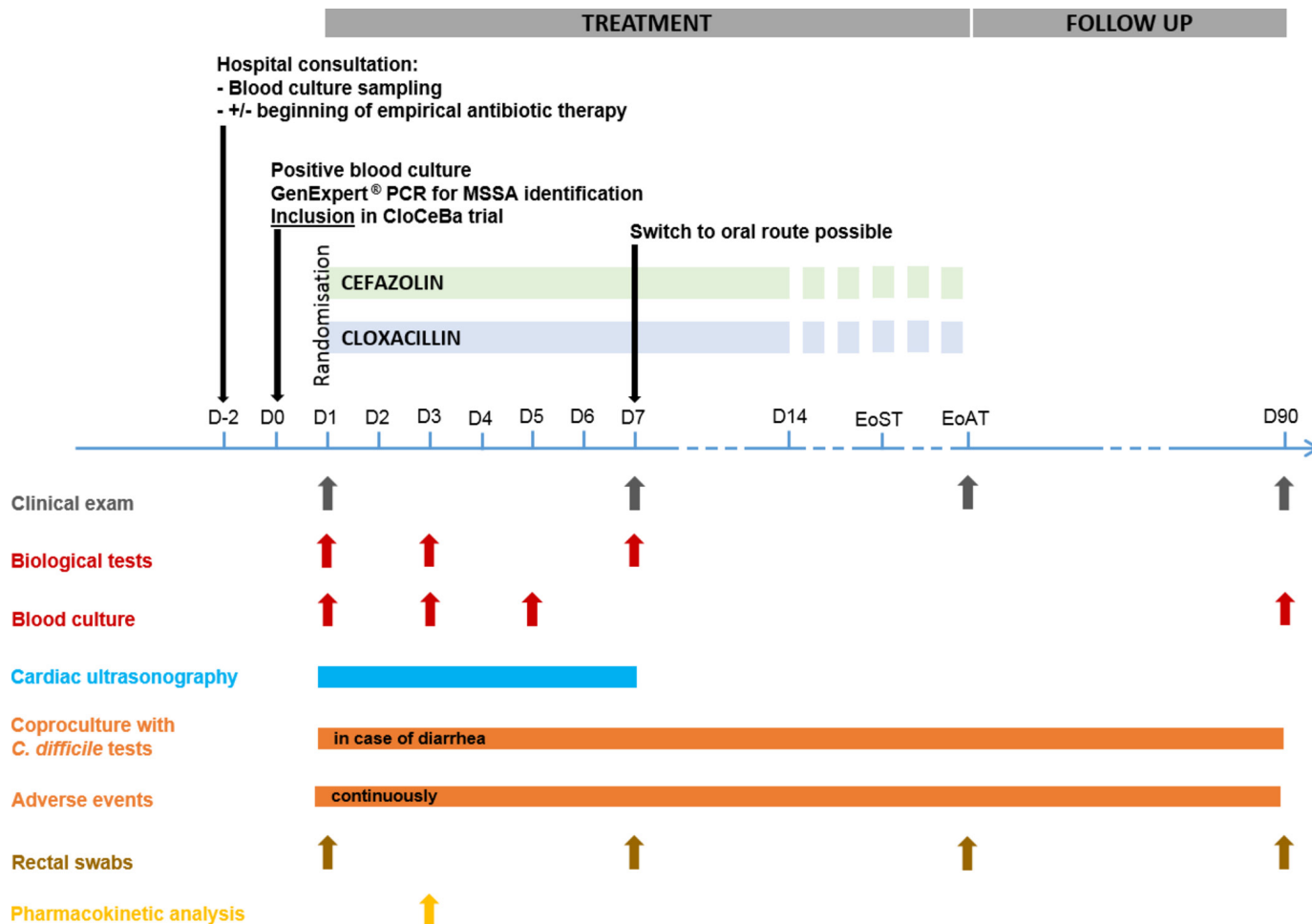


Figure 1 Schematic representation of the experimental design of the CloCeBa clinical trial. Eligible patients with confirmed methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia will be randomised to receive either cloxacillin or cefazolin by intravenous route and followed up until day 90. Antibiotic treatment will be administered for at least 14 days. Investigators will be allowed to switch for oral route after 7 days of antibiotic treatment. Clinical and bacteriological efficacy as well as clinical and biological adverse events will be monitored until the end of the follow-up. All patients will undergo cardiac transthoracic ultrasonography to search for infective endocarditis within 7 days after randomisation.

inclusion period is expected to be 4 years. In order to ease patients' inclusion, pairs of investigators have been constituted, including an infectious disease specialist and a bacteriologist.

Patients with a positive blood culture for Gram-positive cocci and a time-to-positivity ≤ 20 hours will be assessed for eligibility. The cut-off of 20 hours for the time-to-positivity was chosen according to data from the VIRulence STaphylocoque (VIRSTA) study,¹⁷ in which about 90% of *Staphylococcus aureus* bacteremia (SAB) were positive in < 20 hours after blood sampling. Median and 75th percentile were 13 and 18 hours after blood sampling. Concordant data have already been reported.¹⁸ This will allow to reduce screening costs.

A rapid molecular test for detection of protein A, *mecA* and *mecSCC* genes will be performed on the blood culture by GeneXpert real-time PCR, according to the manufacturer's specifications (Xpert MRSA-SA BC).¹⁹

Patients with MSSA-positive blood culture will be randomised after full information and verification of inclusion criteria by the investigator in charge of the

patient. There will be no limitation on the nature of antibiotics that patients might receive prior to the randomisation. However, antibiotic treatment active against MSSA should have begun within 48 hours before the randomisation.

All included patients will undergo transthoracic echocardiography within 7 days following randomisation for diagnosing infective endocarditis. Other radiological examinations will be performed depending on the clinical suspicion for the origin of bacteraemia or for the presence of deep abscess.

According to the guidelines, patients with MSSA bacteraemia will be treated with intravenous antimicrobial therapy for at least 14 days.²⁰⁻²⁴ As currently recommended, investigators will be encouraged to use the intravenous route for the entire duration of treatment. However, in order to interfere as little as possible with usual practice in each centre, the antimicrobial therapy will be left to the choice of the physician in charge of the patient after a minimum of 7 days of intravenous treatment. The total treatment duration will be left to

the clinician in charge but will include at least 14 days of antistaphylococcal agent. Consensus guidelines will be provided in order to harmonise total treatment duration according to the final diagnosis. These guidelines have been developed using a methodology inspired by the Delphi method as part of the TEP-STAR clinical trial (NCT03419221, coordinating investigator V. Le Moing, scientific director X. Duval, sponsor CHU de Montpellier, Montpellier, France), which aims at evaluating the impact of systematic PET/CT on the management of patient with *S. aureus* bacteraemia. Antimicrobials for switch from the randomised antibiotic treatment will be left to the choice of the investigator in charge of the patient. Treatments other than antibiotics will be authorised during the trial according to usual care. Patients retention in the study will be achieved by regular contacts between the trial team and the participants.

Day 0 (D0) is the day of inclusion, and D1 is the day of beginning the antibiotic treatment assigned by randomisation.

Clinical evaluation for efficacy and safety will be performed at D0, D7, at end of all antibiotic treatment (EoAT), and D90 after the beginning of therapy. Blood cultures for efficacy evaluation will be performed at D1, D3, D5 and D90. Biological evaluation for safety will be performed at D0, D1, D3, D7, at end of study treatment (EoST), at EoAT and at D90.

Three ancillary studies will be performed. First, the epidemiology of *blaZ* β -lactamases will be studied in all strains of *S. aureus* isolated from the blood culture vials. Second, the impact on the intestinal microbiota will be performed on a subgroup of 150 patients recruited in three centres from Paris area (75 in each treatment group). For that purpose, rectal swabs will be collected just before the beginning of the randomised treatment and at D7, EoAT and D90. A biocollection of faecal samples will be constituted in patients included in this ancillary study for future analysis of the faecal microbiota. Third, a pharmacokinetic ancillary study will be performed on a subgroup of 50 patients (25 in each treatment group) recruited in two centres from Paris area. For pharmacokinetic calculations, plasma cefazolin and cloxacillin levels will be determined at D3, just before the seventh administration of cefazolin and the ninth administration of cloxacillin and 1, 1.5, 2 and 4 hours after the beginning of infusion.

Primary outcome measure

The primary end point is a composite efficacy criterion of the following: survival at D90, bacteriological success at D5, absence of relapse at D90 and clinical success at D90. Bacteriological success is defined as obtaining a negative set of blood culture without relapse. Relapse of the bacteraemia is defined by a new episode of *S. aureus* bacteraemia with a strain having an in vitro antibiotic susceptibility pattern similar to that isolated at inclusion. Clinical success is defined as the resolution of all signs and symptoms related to the infection.

Secondary outcomes measure

Secondary outcomes are classified as efficacy secondary end points or safety secondary end points.

Efficacy secondary end points

1. Mortality rate at D90.
2. Proportions of patients with a negative set of blood culture at D3, at D5 and at D90.
3. Proportion of patients with bacteriological success at D5 in whom a strain of *S. aureus* with identical in vitro antibiotic susceptibility pattern than the one isolated at inclusion is isolated from at least one blood culture during the follow-up.
4. Proportions of patients improving all signs and symptoms related to the infection at D7 and at D90.
5. Proportion of patients for whom the antibiotic duration from randomisation is in accordance with consensus guidelines.
6. Desirability of outcome ranking, computed using the following algorithm²⁵: (i) therapeutic success without adverse event, (ii) therapeutic success with ≥ 1 adverse event (except death), (iii) survival without therapeutic success without adverse event, (iv) survival without therapeutic success with ≥ 1 adverse event (except death), (v) death.

Safety secondary end points

1. Proportions of patients with any adverse event at D7, at EoST and at EoAT.
2. Proportions of patients with any grade 3 or 4 adverse event at D7, at EoST and at EoAT.
3. Proportion of patients with premature discontinuation of studied antibiotic therapy due to the occurrence of an adverse event.
4. Proportion of patients with *Clostridium difficile* infection.

End points for the three ancillary studies

1. For the epidemiology of *S. aureus blaZ* resistance genes, (i) distribution of type A, type B, type C and type D *blaZ* genes, (ii) distribution of cloxacillin and cefazolin minimum inhibitory concentrations (MIC).
2. For the impact on the intestinal microbiota, (i) proportion of patients with emergence of third-generation cephalosporin-resistant enterobacteria in faecal swabs at D7, at EoAT and at D90.
3. For the pharmacokinetic/pharmacodynamic study, (i) total body clearance and volume of distribution of cloxacillin and cefazolin, (ii) distribution of the area under the curve/MIC ratio, of the C_{\max} /MIC ratio, of the C_{res} /MIC ratio and of the proportion of time during which the antibiotic concentration is above the MIC.

Data collection

The trial is conducted in accordance with relevant regulations and standard operating procedures, including data protection. The data will be collected on an electronic case report form. We will undertake monitoring visits of collaborator sites to confirm the integrity of collected

data. Data will be the propriety of the sponsor. The persons responsible for the quality control of the data will take all necessary precautions to ensure the confidentiality of information related to the investigational medicinal products, the trial, trial participants and in particular the identity of the participants and the results obtained.

Safety and adverse events monitoring

All adverse events will be collected regardless of their grade of severity. The choice of continuing therapy will be at the discretion of the investigator. All adverse events will be collected and classified in grades from mild (grade 1) to life-threatening (grade 4) following the Common Terminology Criteria for Averse Events (V.4.0) of the National Institutes of Health and National Cancer Institute.²⁶ The worsening of the severity grade of an adverse event (including worsening after possible improvement) will be considered as a new adverse event.

In cases of biological abnormalities at inclusion (because of a chronic disease or acute MSSA infection) equivalent to grade X, only increasing severity under treatment to grade X+1 or higher will be considered as an adverse event. *C. difficile* infection will be defined according to the current guidelines.²⁷ Adverse events will be notified as soon as possible to the sponsor by the investigator in charge of the patient.

No Data Monitoring Committee has been constituted for this trial as studied drugs are both recommended for the treatment of MSSA bacteraemia.

Statistical considerations

Sample size calculation

Few data are available for computing the number of subjects required. With the assumption of 85% of treatment efficacy at day 90 after the end of therapy¹² with cloxacillin with a non-inferiority margin of 12% and balanced group size, the inclusion of 139 patients in each group will allow to evidence the non-inferiority of cefazolin over cloxacillin with 80% power and a one-sided alpha risk of 0.025. In order to take into account lost to follow-up patients, 300 patients will be included.

Choice of patients included in the analyses

The intention-to-treat population is composed by all randomised patients, maintaining each patient in the group assigned by randomisation whether they have or not followed the treatment assigned by randomisation. The modified intention-to-treat population is defined by all randomised patients who received at least one dose of treatment allocated by randomisation. The per-protocol population is defined by all patients treated by antimicrobial for at least 14 days, including intravenous cefazolin or cloxacillin for the first 7 days following inclusion, irrespective of the randomisation arm.

The principal criterion analysis will be performed on the per-protocol population. All other efficacy analyses will be performed on the intention-to-treat population.

Safety analyses will be performed on the modified intention-to-treat population.

Statistical analysis

The principal end point of the study is the proportion of patients with treatment success at D90 after beginning of therapy. A non-inferiority analysis of the proportion of patients with treatment success at D90 in the cefazolin group versus the cloxacillin group will be performed, assuming a non-inferiority margin of 0.12. For secondary end points, proportions will be compared according to treatment group by means of a X^2 test or a Fisher's exact test, as appropriate. Desirability of outcome ranking is a 5-level hierarchical criterion. The distributions of ranks will be compared between treatment groups using non-parametric Wilcoxon test. Non-inferiority analysis will be performed using a 2.5% type I error. All other statistical analyses will have a significance level of 5%. Multiple imputation methods will be used to deal with bias induced by missing data. Sensitivity analysis will be performed to test robustness of the results.

Patient and public involvement

Patients or public were not involved in the design of this trial. All participating patients will receive a notification of the research results by their investigating physician.

DISCUSSION

Current recommendations of the use of cefazolin are based on retrospective studies with a low level of evidence, while the morbidity and mortality of MSSA bacteraemia is high. This trial will provide new insights for its management and provide evidence-based data for recommendations.

The CloCeBa trial is pragmatic and is designed to interfere as few as possible with usual care and practice. Despite the current recommendations of a treatment duration of at least 14 days by the intravenous route, an oral switch is frequently initiated after 7 days of intravenous treatment in patients with mild disease. In addition, due to the frequency of adverse events occurring with ASP, cefazolin is increasingly used. However, the potential hydrolysis of cephalosporin by type A β -lactamase produced by some *S. aureus* strains exhibited in vitro inoculum effect, while animal studies produced conflicting results.⁷ This question will be investigated in this trial, as human data are lacking on this question. The efficacy of studied antibiotics will be balanced with their ecological impact on the emergence of third-generation cephalosporin-resistant enterobacteria in the intestinal microbiota. Indeed, the context of increasing antibiotic resistance raises concerns about the effect of antibiotics, especially on the faecal microbiota.^{28–30}

If cefazolin has a non-inferior efficacy and a better safety profile than cloxacillin, it could be preferred for patients with risk factors for penicillin-associated adverse events such as allergy or renal toxicity. In addition, as

stock-outs of antimicrobial treatments are increasingly common, especially for injectable ASP, an alternative with well-documented similar efficacy would be most welcome.

This trial has some limitations. First, this is an open-label trial. As both antibiotics are administered by the intravenous route but with different administration schedule (every 6 hours for cloxacillin and every 8 hours for cefazolin), it would have been quite difficult from a practical point of view to administer both the study treatment allocated by randomisation and the placebo. This would have led to six perfusions per day, to which eventual other intravenous therapy must be added. Second, there is no precise matching of study treatment according to the site of infection but matching is restricted to vascular access-associated bacteraemia. Precise matching was not possible, as the source of bacteraemia is most often unknown at the beginning of antibiotic treatment. Waiting for definite diagnosis of the source of bacteraemia for allocating study treatment would have led to several days of uncontrolled antibiotic before beginning of study treatment, when the first days of treatment are crucial for treatment efficacy. This would have biased the results and favoured the non-inferiority of cefazolin. Moreover, reducing the scope of the trial to a more selective recruitment strategy would have led to a prohibitively long inclusion period and to limited generalisability of the trial results. Here, we tried to shorten as much as possible the time interval between blood culture positivity and the allocation of study treatment, and to mimic the standard antibiotic therapy patients usually received in the context of MSSA bacteraemia. In addition, letting the antibiotic administered as intravenous to switch therapy to the choice of the investigator in charge of the patient might result in a heterogeneous study population. However, the randomisation process should ensure that antibiotic therapy administered before randomisation and after the switch to oral therapy is similar between the two treatment groups.

Despite its limitations, the CloCeBa trial will be the first randomised trial addressing the question of the efficacy and safety of cloxacillin versus cefazolin for the treatment of MSSA bacteraemia. It is likely to have important implications for patients.

ETHICS AND DISSEMINATION

Results will be disseminated to the scientific community through congresses and publication in peer-reviewed journals.

TRIAL STATUS

This trial has begun in June 2018. Inclusions are expected to finish in June 2022.

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Contributors CB, WV, FM, XD and F-XL conceived the study and obtained funding. VLM, TF, LM, PT, MW, FV, ML, PL, CQ and NG participated in the design of the trial. CB, FM and ME-F provided statistical expertise. CB and F-XL wrote the first draft of the manuscript. All authors read and approved the manuscript in its final version.

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Disclaimer The funder and the sponsor did not have any role in the study design.

Competing interests None declared.

Patient consent Not required.

Ethics approval This study was approved by the local ethics committee Sud-Est I (2017-87-PP) and French National Agency for Medicines and Health Products (170661A-43).

Provenance and peer review Not commissioned; externally peer reviewed.

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