

BMJ Open Opportunities for antibiotic optimisation and outcome improvement in patients with negative blood cultures: study protocol for a cluster-randomised crossover trial, the NO-BACT study

Silvia Jiménez-Jorge ¹, Zaira R Palacios-Baena ²,
Clara M Rosso-Fernández,^{1,3} José A Girón-Ortega,⁴ Jesús Rodríguez-Baño,²
Pilar Retamar²

To cite: Jiménez-Jorge S, Palacios-Baena ZR, Rosso-Fernández CM, *et al.* Opportunities for antibiotic optimisation and outcome improvement in patients with negative blood cultures: study protocol for a cluster-randomised crossover trial, the NO-BACT study. *BMJ Open* 2019;**9**:e030062. doi:10.1136/bmjopen-2019-030062

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2019-030062>).

Received 26 February 2019

Revised 14 October 2019

Accepted 25 November 2019



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Silvia Jiménez-Jorge;
silviajimenezjorge@gmail.com

ABSTRACT

Introduction Patients with negative blood cultures (BCx) represent 85%–90% of all patients with BCx taken during hospital admission. This population usually includes a heterogeneous group of patients admitted with infectious diseases or febrile syndromes that require a blood culture. There is very little evidence of the clinical characteristics and antibiotic treatment given to these patients.

Methods and analysis In a preliminary exploratory prospective cohort study of patients with BCx taken, the clinical/therapeutic characteristics and outcomes/antimicrobial stewardship opportunities of a population of patients with negative BCx will be analysed. In the second phase, using a cluster randomised crossover design, the implementation of an antimicrobial stewardship intervention targeting patients with negative BCx will be evaluated in terms of quality of antimicrobial use (duration and de-escalation), length of hospital stay and mortality.

Ethics and dissemination This study has been and registered with clinicaltrials.gov. The findings of our study may support the implementation in clinical practice of an antimicrobial stewardship intervention to optimise the use of antibiotics in patients with negative BCx. The results of this study will be published in peer-reviewed journals and disseminated at national and international conferences.

Trial registration number NCT03535324.

INTRODUCTION

Performing blood cultures (BCx) is usual practice in patients admitted to the emergency services with signs of severe infection and those admitted to hospital as inpatients; it is also recommended practice for most admitted patients with suspected infectious syndromes. There is evidence that the management of bacteraemia by infectious diseases specialists is associated with a better prognosis,¹ but very little about the management of patients who continue to show signs of infection despite a negative

Strengths and limitations of this study

- A cluster crossover design was selected to control for potential confounding factors and to ensure its feasibility given that this is an educational intervention in which potential contamination through prescriber exposure can be controlled.
- Since the nature of the intervention groups does not allow for blinding, a robust primary outcome was selected (days of treatment) and external assessment by a blinded committee was included.
- This is a multicentre study.
- The findings could make a significant contribution to improving antimicrobial prescribing in patients with negative blood cultures.
- Limitations of the study include: the risk of selection bias in cluster randomised trials; the nature of the Antimicrobial Stewardship Programs (ASP) intervention may consist basically of an unsolicited advice programme by an ASP expert; and the absence of blinded intervention.

blood culture result. The treatment and management of patients with negative BCx is not very common, and in the literature is confined to specific syndromes such as endocarditis.² In general, only 10%–15% of BCx are positive.³

At the same time, the population with negative BCx is very heterogeneous and there is at present very little information available about the epidemiological, clinical, therapeutic and prognostic characteristics of this population. In some infectious syndromes, such as pneumonia or pyelonephritis, the absence of bacteraemia has been associated with a better prognosis.^{4,5} In addition, prognostic tests for these patients have not been systematically established in

the available literature. The treatment strategies and evaluation of antibiotics in this population are often conflicting. Some studies that have compared the characteristics of patients with bacteraemia and those with negative BCx in specific infectious syndromes have observed a trend towards greater use of antibiotics in the negative BCx group.⁴ Most patients with negative BCx receive antibiotic treatment, which is maintained regardless of the result. In short, there is a lack of information about the indications for and adequacy of the use of antimicrobials in these patients.

Antimicrobial Stewardship Programs (ASP) are developed in clinical circumstances where an intervention in the treatment of patients is associated with improved patient prognosis and cost-effective management of the available resources. The conditions of the intervention may be established randomly or based on predefined selection criteria: a specific population, a specific antibiotic, a specific infectious syndrome or specific characteristics of the prescription (duration, sequential oral therapy, etc).⁶ Since this is a simple population to identify, possible areas of interest include knowledge of the incorrect use of antimicrobials in patients with negative BCx and the potential beneficial impact of the ASP on these patients. With respect to the type of intervention recommended

for development of an ASP, audits and feedback have proven to be the most effective for modifying prescribing habits.^{7 8} Audit-based programmes are associated with improvements in the quality of antimicrobial use and improved resource management, without negatively affecting patient safety. The objective of an audit is to evaluate and, where appropriate, modify different elements of the prescription. In the present study, an intervention is proposed on day 3 and days 5–7 after BCx extraction to evaluate the possibilities of de-escalation, sequential oral therapy or end of early treatment, based on the available evidence.

A systematic review and meta-analysis conducted by Davey *et al*⁸ highlighted that the lack of consistency between the multiple ASP interventions included meant that the quality of the evidence was inadequate. Most studies published to date included in that review used a quasi-experimental design, a before–after intervention and frequently lacked a non-intervention control arm. Controlled clinical trials with cluster-type assignment on the other hand are presented as a suitable design for assessing the impact of interventions on patient groups.⁹ Interventions with an educational component aimed at the group of prescribers are subject to interactions between subjects in the same physical or

Table 1 Schedule of enrolment and assessments: cohort study and cluster-randomised trial—NO-BACT, 2018–2020

Timepoint	Cohort study (October 2018–September 2019)					
	Day 0 (BCx extraction)	Day 2 (post-BCx)	Day 5–7 (post-BCx)	Day 30 (post-BCx)		
Enrolment	X					
Assessment of adequacy of antimicrobial treatment		X	X			
Evaluation of mortality and length of stay				X		
Timepoint	Cluster-randomised trial (October 2019–December 2020)					
	Visit 0 (2 days post-BCx)	Visit 1 (3 days post-BCx)	Visit 2 (4 days post-BCx)	Visit 3 (5–7 days post- BCx)	Visit 4 or end of antibiotic treatment	Visit 5 (30 days post-BCx)
Clinical evaluation*	X	X	X	X	X	X
Assessment of prescription adequacy†	X					
Blood analysis‡	X		X			
De-escalation or indication for stopping antibiotics		X				
Acceptance record of the intervention		X		X		
Assessment of de- escalation and oral sequential therapy			X	X		

*Vital signs/symptoms, capillary blood glucose (if available), diuresis (if available), collections drainage (if available), anamnesis and physical examination 'exploration of devices', description of focus and severity (quick Sequential Organ Failure Assessment score, description of severity of Systemic Inflammatory Response Syndrome).

†Peer evaluation of adherence to the reference guide, based on clinical syndrome and severity.

‡Hemogram, general biochemistry with procalcitonin and C-reactive protein, gasometry with lactate.

BCx, blood cultures.

Table 2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Cohort study	
Age ≥ 18 years with BCx extraction (two samples taken from peripheral veins).	Patients discharged from hospital within the first 48 hours following the BCx extraction.
	Patients with life expectancy of less than 30 days.
Cluster-randomised trial*	
Age ≥ 18 years being treated in the specific preselected departments and have had BCx that meet the following criteria:	Patients discharged from hospital within the first 48 hours following the BCx extraction.
1. Negative BCx.	
2. Receiving active antibiotic therapy within 48 hours of extraction.	
	Limitation of therapeutic effort indication.
	Patients with life expectancy of less than 30 days.
	Severe neutropenia at the time of randomisation (<500 cells/mm ³).
	Pregnancy or lactation.
	A positive BCx in the previous 7 days.

*Cluster: units assigned to intervention, clinical units treating patients with BCx extracted for diagnosis, in which optimisation of the educational intervention is deemed to be most beneficial, according to the results of the cohort study performed in phase I.
BCx, blood cultures.

functional area. Group clinical trials (clusters) make it possible to assign interventions to complete functional groups such as clinical units, specific wards or hospitals.

There are no controlled intervention studies in the recent literature on the optimisation of patients with negative BCx. Hence, the two main research objectives of the NO-BACT study are:

1. To investigate the clinical characteristics and therapeutic management of a cohort of patients with BCx extractions (negative and positive). In this exploratory phase, preliminary information will be gathered for a

predefined intervention aimed at the optimisation of antibiotic treatment.

2. To investigate the efficacy and safety of a programme to optimise antibiotic use aimed at patients with negative BCx using a cluster-randomised controlled trial (CRT).

METHODS AND ANALYSIS

Study design

This study has two separate phases, each with a different design.

Phase I is an exploratory prospective cohort study of patients who have had a BCx extraction; phase II is a two-group, CRT with randomised sequential crossover assignment to an ASP intervention.

Participants and study settings

This multicentre study will be conducted at three academic hospitals in Spain with extensive experience of ASPs: Hospital Universitario Virgen Macarena (Seville), Hospital Universitario Puerta del Mar (Cádiz) and Hospital Universitario Lozano-Blesa (Zaragoza). For the CRT, each hospital will participate with six clusters corresponding to six clinical units (functional clinical departments such as Intensive Care Unit (ICU), Urology, etc), which will be selected in accordance with the conclusions of the preliminary cohort study, selecting those offering the best optimisation opportunities for ASP intervention. The study period is estimated to last 3 years (2018–2020): 9 months for start-up activities, 1 year for the cohort study (6 months of patient recruitment, 6 months for analysis) and 15 months for the CRT (9 months of recruitment, 6 months for analysis and dissemination of results) (table 1).

The second phase of this study will be a CRT involving a cluster-level public health intervention. The subjects of this educational intervention will be health professionals in participating clinical units. Inclusion and exclusion criteria are included in table 2.

The institutional review boards involved (online supplementary file) and the Spanish Regulatory Agency have granted a waiver of informed consent for the study intervention. The study involves no more than minimal risk to patients in the care of participating health professionals, and patients will be verbally informed of their participation in the study and treated according to good clinical practice.^{10–12}

	ASSIGNMENT PHASE			CROSS-OVER PHASE		
	Departments A-B	Departments C-D	Departments E-F	Departments A-B	Departments C-D	Departments E-F
	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Hospital 1	A1	C1	E1	A1	C1	E1
	B1	D1	F1	B1	D1	F1
Hospital 2	A2	C2	E2	A2	C2	E2
	B2	D2	F2	B2	D2	F2
Hospital 3	A3	C3	E3	A3	C3	E3
	B3	D3	F3	B3	D3	F3

Figure 1 Crossover design of the NO-BACT study.

Recruitment process

Cohort study

Patients who have had BCx taken will be detected via entries made by the microbiology laboratory in the hospital clinical records. Clinical and treatment-related data will be obtained via a prospective review of clinical records and electronic prescription programmes.

Cluster-randomised trial

Patients will be identified by the microbiology laboratory. Each week a list will be generated of all negative BCx performed on patients in the participating cluster 2 days previously. Prescriptions for antibiotic treatment 2 days after extraction will be confirmed through the electronic prescription programme.

Randomisation and allocation concealment

Assignment to intervention will be made at the cluster level. Each hospital will participate with six clinical units (A, B, C, D, E, F), making 18 clusters in all. Selection of these units will be based on the conclusions of the cohort study, selecting those offering the best optimisation opportunities.

Randomisation will be based on a centralised, computerised random number generator, specifically designed for the purpose. A copy of the randomisation list will be kept in a safe place in the event that technical problems arise. Allocation to the control or experimental intervention will be announced just before implementation to avoid selection bias.

There will be six interventional periods of 6 weeks each. In the three first periods, the assignment to intervention phase, each cluster will be randomly assigned to the control or experimental arm on day 1 (figure 1). Cross-reassignment will be made (crossover phase) in the fourth, fifth and sixth periods. Each cluster will have a 'washout' period of 3 months between phases.

Interventions

The intervention will be made at the cluster level.

Experimental group

In clusters assigned to the experimental intervention, the antibiotic prescriptions of selected cases will be evaluated on day 3 of treatment. The evaluation will be by peer review of two physicians participating in the ASP to assess the suitability of the treatment prescribed based on local hospital guidelines (figure 2). On the basis of this evaluation, recommendations will be made for: withdrawal of antibiotic treatment if it is considered that there are no indications for it; de-escalation, in light of clinically significant microbiology results in other biological samples, or empirical de-escalation, based on local guidelines and depending on the syndrome and baseline characteristics of the patient; and/or evaluation of a switch to oral therapy if possible. Recommendations will be recorded on a specific form designed for the study. In patients who continue antibiotic treatment after the intervention on day 3, a new physician peer review process will be

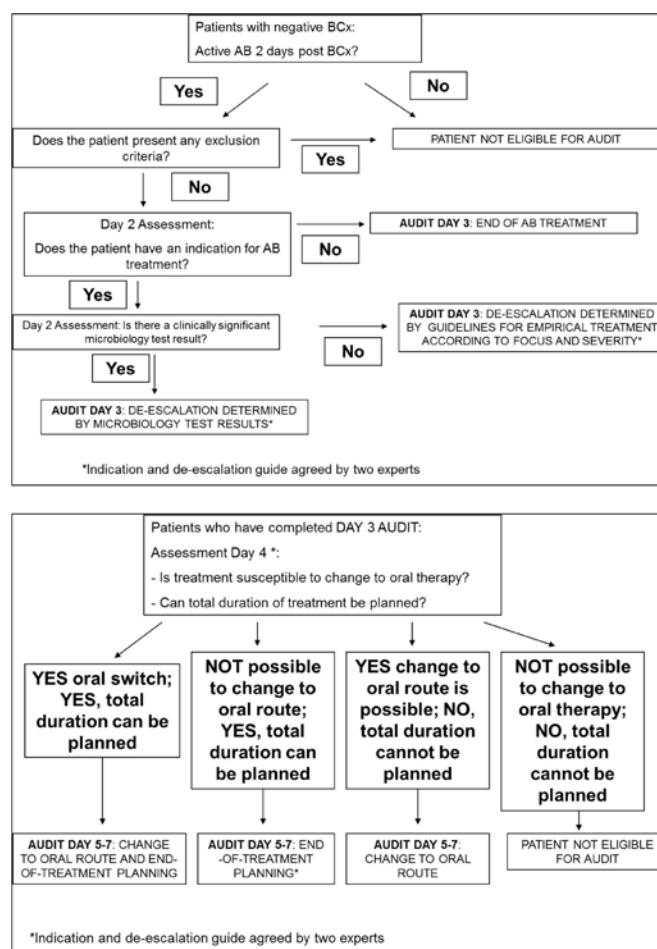


Figure 2 Experimental intervention—NO-BACT.

implemented on day 5 to assess the possibility of a switch to oral therapy if this has not been done previously, or to plan for end of treatment, based on the recommendations of the antibiotic reference guide. Based on the day 5 evaluation, an intervention will be performed on days 5–7 recommending a switch to oral treatment and/or treatment finalisation, as indicated.

Control group

Antibiotic treatment of patients with negative BCx will be prescribed by the physician in charge as per clinical judgement.

Schedule of visits

The schedule of visits and assessments for the cohort study and cluster-randomised trial are described in table 1.

With respect to the CRT, patients included will be followed for 28 days after BCx extraction. Follow-up will be organised in five scheduled visits: visit 0 (2 days after BCx extraction), visit 1 (3 days after BCx extraction), visit 2 (4 days after BCx extraction), visit 3 (between day 5 and day 7 after BCx extraction), visit 4, or end-of-treatment visit (if antibiotic treatment remains active after previous visits; if treatment finished at visits 1 or 3, those visits will be considered end-of-treatment visits) and visit 5 (day 30 after BCx extraction).

Evaluation of results

Cohort study

The primary outcome measure will be the percentage of patients with inadequate treatment at predefined evaluation timepoints (day 2 and days 5–7 following BCx extraction), depending on medical indication, coverage, route of administration and treatment duration.

Secondary outcomes include mortality at 30 days following BCx extraction and length of hospital stay.

Explanatory variables will be analysed (1) to investigate whether the prognosis of patients with negative BCx differs from those with positive BCx; (2) to identify prognostic factors in patients with negative BCx susceptible to intervention and compare them with prognostic predictors in patients with positive BCx; (3) to compare the quality of antibiotic use in patients with negative and positive BCx.

Cluster-randomised trial

The CRT was designed to evaluate the efficacy and safety of a specific ASP to reduce the consumption of antibiotics (using days of treatment (DoT) as primary outcome) in patients with negative BCx. Secondary outcomes include defined daily doses of antibiotics (analysed weekly from randomisation to day 28), all-cause mortality (from day 4 to day 30 following BCx extraction), readmissions in the next 90 days (from day 4 to day 90 following BCx extraction), rate of reinfection by multidrug-resistant bacteria (in the first 3 months after the negative BCx),¹³ rate of patients presenting with confirmed *Clostridium difficile*-associated diarrhoea (in the first 3 months after the negative BCx). Secondary objectives are the evaluation of the impact of a specific ASP in patients with negative BCx aimed at: (1) reducing the use of broad-spectrum antibiotics, (2) reducing the incidence of *Clostridium difficile* colitis.

An interim analysis is planned after 50% of the sample size has been included and monitored in order to ensure that there are no efficacy or safety reasons to prevent the trial from running to completion.

Evaluation of the results will be made in consensus by an independent committee blinded to the intervention assignment, made up of two experts from the Spanish Network for Research in Infectious Diseases (REIPI).

Sample size

Cohort study

Calculation of sample size was based on the proportion of positive and negative BCx. We estimate that at least 100 episodes of positive BCx will be needed to compare the two populations. Since the proportion of positive/negative BCx in the participating hospitals is 1:10 on average, a sample size of 1000 was estimated. The average number of BCx taken in the participating hospitals is around 8000 per year per hospital. It is expected that 50 BCx per month, per hospital will be included every month for six consecutive months in order to obtain the total of 1000 BCx (120–160 positives).

Cluster-randomised trial

The following parameters were used for calculation of sample size: beta error (<80%), alpha error (<5%), mean duration of antibiotic treatment in the control group (10.8 days±4.56). The estimate was based on an analysis of patients with pneumonia and negative BCx in an intervention study conducted in 2016 at two of the participating hospitals. The acceptable margin of error between groups is ≤20%. Considering that 18 clusters will participate and taking into account a high intra-cluster interaction coefficient of 0.4, the estimated sample size is 756 patients (378 to intervention or control). In order to anticipate loss to follow-up, a total of 800 patients should be included, 22 per period and participating cluster.

Statistical analysis

Cohort study

Descriptive statistics will be used to analyse demographic data. Univariate and multivariate analysis with binary logistic regression will be used to evaluate the variables associated with inadequate treatment. Logistic regression will be used to analyse differences in mortality rate up to 30 days. Subgroup analyses will be performed for the main outcome (percentage of inadequate treatment) and secondary outcomes (mortality, readmissions, length of stay and admission to ICU). Subgroups will be: critically ill patients, immunocompromised patients, neutropenic patients, depending on the main syndromes/specific foci, type of infection acquisition and whether or not the micro-organisms isolated were present in other biological samples.

Cluster-randomised trial

For the main outcome, absolute differences in means between the two arms of the intervention will be calculated with 95% CIs. Multivariate analysis using linear regression will be performed to ensure the independence of the effect of the intervention on the main variable (DoT). An analysis stratified by focus and severity of infection will be carried out at the time of BCx extraction.

An interim analysis will be performed when 50% of the population has been recruited. The interim analysis will be evaluated by a Data Monitoring and Safety Board made up of three independent infectious disease physicians. The study will be stopped if a >15% difference in mortality is found. Nevertheless, any differences in mortality will be carefully assessed for potential causality.

The Desirability of Outcome Ranking (DOOR)/Response Adjusted for Duration of Antibiotic Risk (RADAR) methodology will be applied to analyse the effect of the intervention.¹⁴ Analyses of data and feedback reports will be circulated to the study teams on a quarterly basis.

The following populations will be considered: the intention-to-treat population (includes all randomised patients; the per protocol population includes all randomised patients who have been evaluated during the

full intervention (visit 1 day 3 audit and visit 3 days 5–7 audit).

A small proportion of patients is likely to go on to have a positive culture after the intervention on day 3. This population will be considered for subgroup analysis. The ‘having a late positive culture’ variable will also be considered as a possible predictor of outcome (in both the efficacy and the safety analyses).

Legal and ethical considerations

The agreement of the directors of the institutions (who signed the clinical study agreement with the study sponsor) and the authorisation of the Spanish Regulatory Agency (Agencia Española del Medicamento y Productos Sanitarios) was also obtained. The study will be conducted in compliance with the protocol, regulatory requirements, the International Council of Harmonization (ICH) E6 Good Clinical Practice guidelines, and the ethical principles of the latest version of the Declaration of Helsinki adopted by the World Medical Association. The relevant ethics committee(s) will be notified of each substantial protocol amendment for their approval prior to implementation. All data collected will be kept strictly confidential in accordance with all relevant legislation on the control and protection of personal information. Participants will be identified on documentation by a unique ID number, not by name. All study-related information will be stored securely at the study sites.

Patient and public involvement

No patient involved.

DISCUSSION

The aim of this study is to assess the impact of an antimicrobial stewardship intervention on patients with negative BCx. To do this, we designed a two-step study: an exploratory cohort of patients who have had BCx taken, followed by a cluster-randomised trial in which an ASP intervention will be implemented in a population of subjects with negative BCx.

It has been widely demonstrated that management and clinical outcomes in patients presenting bacteraemia improve when infectious diseases specialists participate.¹⁵ Furthermore, interventions on patients with sepsis have also been shown to be effective in terms of clinical results.¹⁶ However, no literature can be found focused specifically on ASP interventions in patients with negative BCx. These patients may represent different clinical scenarios. First, a patient with a negative blood culture may be an individual with no infectious syndrome, in which case antibiotic treatment would be unnecessary and should be avoided to prevent unintended consequences such as toxicity or resistance selection. At the same time, a negative BCx can be found in patients with severe infection and serious clinical conditions, in which case, the previous antibiotic treatment may invalidate the blood culture results. The idea of an exploratory cohort

therefore is to select the subgroup of susceptible patients with negative BCx where an ASP intervention may be more effective in terms of outcome.

The study methodology was selected in order to minimise confusion and ensure its feasibility, given that it is an educational intervention in which it is possible to control contamination by prescribers. In an individual intervention in which the assigned unit is the patient, situations may arise where the same prescriber treats patients in both the intervention group and the control group. If the intervention unit is the set of prescribing doctors, clinicians from the same department can interact with each other, thus affecting the impact of the intervention. A cluster-crossover design where all participating clusters (clinical units) receive both intervention and control assignment minimises these limitations, reduces the total number of clusters required and consequently, the study duration.¹⁷

The NO-BACT study has several strengths. It was designed with daily clinical practice in mind and with a robust design to control for potential confounding factors. The findings could make a notable contribution to achieving good control of severe infectious syndromes in patients not included in sepsis or bacteraemia programmes, in other words, patients without typical syndromes at presentation, such as neutropenia or elderly people in which optimised antimicrobial management could help achieve better clinical outcomes.

There are several limitations in this study that should be taken into account. First is the risk of selection bias, or how the use of a cluster randomisation introduces bias through the way patients are differentially recruited across study groups. Although the most suitable candidates for the intervention will be selected on the basis of the exploratory cohort, patients included in the participating clinical units may present with different underlying characteristics. In this context, the crossover design may help partially control selection bias since the same cluster will participate in both the interventional and control groups.

Second, the nature of the ASP intervention may consist basically of an unsolicited advice programme by an ASP expert. Although a standard methodology will be implemented, based on a predetermined system and with previous training given, the intervention is inherently subjective because the quality of antibiotic use will be assessed by an ASP physician. Hence, peer evaluation based on an antimicrobial reference guide has been implemented.

Since the intervention is not blinded, the main outcome could be affected. To minimise this, a robust primary outcome, ‘DoT’, was selected, and external assessment by a blinded committee added.

Third, the study is powered to determine whether there is a difference in duration of antibiotic use, but not powered to ascertain whether there is a difference in important clinical outcomes such as mortality, ICU admission or length of stay. So, unless there is a dramatically

negative impact on clinical outcomes (such as mortality), a positive result will indicate that this approach can be used. Statistically, speaking, this can only be ensured with a primary outcome of clinical efficacy, and a secondary outcome of duration of antibiotics. In order to mitigate this commonly observed limitation of previous antimicrobial stewardship trials, a mortality threshold of $\pm 15\%$ will be allowed, in addition to the performance of multivariate and subgroup analyses focused on safety outcomes.

Another major concern is associated with informed consent. The latest update of the European Union Regulation (536/2014) on clinical trials in medicinal products for human use includes some of the issues involved in obtaining informed consent in cluster trials, in which groups of subjects rather than individuals are assigned to receive different interventions.^{11 18} In our study, a CRT involves a cluster-level public health intervention in which the health professionals in the participating clinical units are the subjects of this educational intervention. The study involves no more than minimal risk to the patients treated. Patients will be verbally informed of their participation in the study and treated according to good clinical practice. A waiver of informed consent for the study intervention was granted by the institutional review boards involved and the Spanish Regulatory Agency.

In conclusion, the findings of our study could support implementation in clinical practice of an antimicrobial stewardship intervention to optimise use of antibiotics in patients in the selected population with negative BCx.

Trial status

The status of the trial at submission is 486 patients recruited in the cohort study (49% of the estimated recruitment per protocol); CRT will begin after the cohort study.

Current protocol approved is V.1.0 dated 26 February 2018.

Date recruitment began: 8 October 2018 (Cohort); expected start for the CRT, October 2019.

Approximate date when recruitment will be completed: June 2019 (Cohort), June 2020 (CRT).

Author affiliations

¹Clinical Research and Clinical Trials Unit, Hospital Universitario Virgen del Rocío, Seville, Spain

²Infectious Diseases and Clinical Microbiology Department, Hospital Universitario Virgen Macarena. Instituto de Biomedicina de Sevilla (IBIS), Hospital Universitario Virgen Macarena, Seville, Spain

³Department of Clinical Pharmacology, Virgen del Rocío University Hospital, Seville, Spain

⁴Internal Medicine Department, Hospital Universitario Virgen Macarena, Seville, Spain

Twitter Pilar Retamar @PilarRetamar

Contributors PR and JR-B conceived, designed the study and obtained funding for the research. CMR-F and SJ-J collaborated in obtaining funding for the research and in the methodological aspects of the study. SJ-J wrote the first draft of the manuscript. PR and ZRP-B are the coordinating investigators and PR is the leader of the Coordination Team. CMR-F and SJ-J collaborated in the coordination of the study. JAG-O collaborated in the methodological aspects of the study and

the organisation of the study. All authors reviewed, edited and approved the final version.

Funding This work is being supported by the Spanish Clinical Research and Clinical Trials Platform, SCReN (Spanish Clinical Research Network), funded by the ISCIII-General Subdirectorate for Evaluation and Promotion of Research, through project PT17/0017/0012 integrated in the State R & D Plan 2013-2016 and co-financed by and the European Regional Development Fund (FEDER). In addition, is being supported by the Project "PI17/01809", funded by Instituto de Salud Carlos III, integrated in the national I+D+i Plan 2017-2020 and co-funded by European Union (ERDF/ESF, "Investing in your future").

Competing interests ZRP-B reports personal fees from Gilead, outside the submitted work. JR-B and PR participated in accredited educational activities supported by Merck through unrestricted grants, outside the submitted work.

Patient consent for publication Not required.

Ethics approval The study was approved in May 2018 by the reference ethics committee (Comité de Ética de la Investigación con medicamentos Provincial de Sevilla, 2018/119).

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Silvia Jiménez-Jorge <https://orcid.org/0000-0003-2944-6711>

Zaira R Palacios-Baena <http://orcid.org/0000-0002-1713-6807>

REFERENCES

- Turner RB, Valcarlos E, Won R, *et al*. Impact of infectious diseases consultation on clinical outcomes of patients with *Staphylococcus aureus* bacteremia in a community health system. *Antimicrob Agents Chemother* 2016;60:5682-7.
- Menu E, Gouriet F, Casalta J-P, *et al*. Evaluation of empirical treatment for blood culture-negative endocarditis. *J. Antimicrob. Chemother.* 2017;72:290-8.
- Cercenado Mansilla E, Cantón Moreno R. Diagnóstico microbiológico de la bacteriemia y la fungemia: hemocultivos y métodos moleculares. In: *Procedimientos en Microbiología Clínica, Sociedad Española de Enfermedades Infecciosas Y Microbiología Clínica*. 62. SEIMC, 2017. <https://seimc.org/contenidos/documentoscientificos/procedimientosmicrobiologia/seimc-procedimientosmicrobiologia62.pdf>. (Accessed 04 February 2019).
- Jover F, Cuadrado J-M, Andreu L, *et al*. A comparative study of bacteremic and non-bacteremic pneumococcal pneumonia. *Eur J Intern Med* 2008;19:15-21.
- Kim Y, Seo M-R, Kim S-J, *et al*. Usefulness of blood cultures and radiologic imaging studies in the management of patients with community-acquired acute pyelonephritis. *Infect Chemother* 2017;49:22-30.
- Rodríguez-Baño J, Paño-Pardo JR, Alvarez-Rocha L, *et al*. Programs for optimizing the use of antibiotics (proA) in Spanish hospitals: GEIH-SEIMC, SEFH and SEMPSPH consensus document. *Enferm Infecc Microbiol Clin* 2012;30:22.e1-22.e23.
- Tamma PD, Avdic E, Keenan JF, *et al*. What is the more effective antibiotic stewardship intervention: Preprescription authorization or Postprescription review with feedback? *Clin Infect Dis* 2017;64:537-43.
- Davey P, Marwick CA, Scott CL, *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017;39.
- Campbell MK, Piaggio G, Elbourne DR, *et al*. Consort 2010 statement: extension to cluster randomised trials. *BMJ* 2012;345:e5661.
- Weijer C, Grimshaw JM, Eccles MP, *et al*. The Ottawa statement on the ethical design and conduct of cluster randomized trials. *PLoS Med* 2012;9:e1001346.
- Sim J, Dawson A. Informed consent and cluster-randomized trials. *Am J Public Health* 2012;102:480-5.
- McRae AD, Weijer C, Binik A, *et al*. When is informed consent required in cluster randomized trials in health research? *Trials* 2011;12:202.

- 13 Magiorakos A-P, Srinivasan A, Carey RB, *et al.* Multidrug-Resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clinical Microbiology and Infection* 2012;18:268–81.
- 14 Evans SR, Rubin D, Follmann D, *et al.* Desirability of outcome ranking (door) and response adjusted for duration of antibiotic risk (radar). *Clin Infect Dis.* 2015;61:800–6.
- 15 López-Cortés LE, del Toro MD, Gálvez-Acebal J, *et al.* Impact of an evidence-based bundle intervention in the quality-of-care management and outcome of *Staphylococcus aureus* bacteremia. *Clinical Infectious Diseases* 2013;57:1225–33.
- 16 Schorr C, Odden A, Evans L, *et al.* Implementation of a multicenter performance improvement program for early detection and treatment of severe sepsis in general medical-surgical wards. *J. Hosp. Med.* 2016;11:S32–9.
- 17 Turner RM, White IR, Croudace T, *et al.* Analysis of cluster randomized cross-over trial data: a comparison of methods. *Stat Med* 2007;26:274–89.
- 18 Sim J. Addressing conflicts in research ethics: consent and risk of harm. *Physiother. Res. Int.* 2010;15:80–7.