

BMJ Open Daptomycin plus fosfomycin versus daptomycin monotherapy in treating MRSA: protocol of a multicentre, randomised, phase III trial

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ABSTRACT

Introduction: Despite the availability of new antibiotics such as daptomycin, methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia continues to be associated with high clinical failure rates. Combination therapy has been proposed as an alternative to improve outcomes but there is a lack of clinical studies. The study aims to demonstrate that combination of daptomycin plus fosfomycin achieves higher clinical success rates in the treatment of MRSA bacteraemia than daptomycin alone.

Methods and analysis: A multicentre open-label, randomised phase III study. Adult patients hospitalised with MRSA bacteraemia will be randomly assigned (1:1) to group 1: daptomycin 10 mg/kg/24 h intravenous; or group 2: daptomycin 10 mg/kg/24 h intravenous plus fosfomycin 2 gr/6 g intravenous. The main outcome will be treatment response at week 6 after stopping therapy (test-of-cure (TOC) visit). This is a composite variable with two values: Treatment success: resolution of clinical signs and symptoms (clinical success) and negative blood cultures (microbiological success) at the TOC visit. Treatment failure: if any of the following conditions apply: (1) lack of clinical improvement at 72 h or more after starting therapy; (2) persistent bacteraemia (positive blood cultures on day 7); (3) therapy is discontinued early due to adverse effects or for some other reason based on clinical judgement; (4) relapse of MRSA bacteraemia before the TOC visit; (5) death for any reason before the TOC visit. Assuming a 60% cure rate with daptomycin and a 20% difference in cure rates between the two groups, 103 patients will be needed for each group (α :0.05, β : 0.2). Statistical analysis will be based on intention to treat, as well as per protocol and safety analysis.

Ethics and dissemination: The protocol was approved by the Spanish Medicines and Healthcare Products Regulatory Agency (AEMPS). The sponsor commits itself to publishing the data in first quartile

peer-review journals within 12 months of the completion of the study.

Trial registration number: NCT01898338.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia is of concern to healthcare systems worldwide because of its high incidence rates and poor outcomes. Mortality rates range between 20% and 30%, which are higher than those associated with methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia.¹ During the past decade, several epidemiological changes have been observed among patients with MRSA bacteraemia, such as an upward trend in patient age, more severe comorbidities, non-nosocomial healthcare acquisition and a non-intravascular catheter source.² These factors may be contributing to the high-mortality rate. In addition, one recent multicentre observational study in 21 Spanish hospitals, which focused on MRSA bacteraemia and included almost 600 episodes, found a mortality rate in excess of 30%, regardless of the type of antibiotic treatment administered.³

Vancomycin is still considered to be the standard treatment for MRSA bacteraemia, despite its association with poor patient outcomes such as persistent bacteraemia, treatment failure and nephrotoxicity.⁴ The higher mortality rates associated with MRSA as compared with MSSA bacteraemia have been attributed to differences in host conditions, microbial pathogenicity and especially to the

inferior antistaphylococcal killing effect of glycopeptides when compared with β -lactam antibiotics.⁵

The approval of daptomycin for treating MRSA bacteraemia and right-sided endocarditis has expanded the therapeutic options for treating MRSA bacteraemia. Daptomycin is a cyclic lipopeptide antibiotic with clinical efficacy at least as effective as that of vancomycin for treating MRSA bacteraemia,⁶ and at the same time it offers significant advantages over the latter, such as a more rapid bactericidal effect and less nephrotoxicity.⁴ Daptomycin exhibits concentration-dependent bactericidal killing activity and is generally safe and well tolerated at higher doses,⁷ although mortality rates, particularly in patients with persistent or complicated bacteraemia, have not declined significantly.³ In one multicentre randomised clinical trial that compared daptomycin 6 mg/kg/d with vancomycin plus gentamicin for the treatment of MRSA bacteraemia or right-sided endocarditis, the success rate among patients treated with daptomycin was 44%, compared to 32% in the vancomycin–gentamicin group.⁸

There are increasingly favourable opinions concerning the use of high-dose daptomycin, although no randomised studies have been performed to support this change. Based on expert opinion, current Infectious Diseases Society of America (IDSA) clinical practice guidelines recommend higher doses of daptomycin (8–10 mg/kg/d) for the treatment of MRSA bacteraemia or infective endocarditis. The Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) also recommends high-dose daptomycin (10 mg/kg/d) for treating left-sided infective endocarditis.^{9 10} At present, a daptomycin dosage of 8 mg/kg/day or more is safe for patients with complicated MRSA infections.¹¹

Failures of therapy with daptomycin due to persistent or relapsing infection have been reported, especially in complicated bacteraemia, and in some of these cases an increase in daptomycin minimum inhibitory concentration (MIC) was also observed.⁶ Recent *in vitro* data suggest that combination therapies might be an alternative to achieve better outcomes.^{12 13} Among them, daptomycin in combination with rifampin or gentamicin has not been associated with a better response in the experimental model of endocarditis,^{14 15} while daptomycin plus antistaphylococcal β -lactams, nafcillin or cloxacillin was effective for treating patients with refractory MRSA bacteraemia. The *in vitro* study showed that β -lactams enhanced daptomycin bactericidal activity by means of a reduction in membrane surface charges.¹⁶

Fosfomycin is a phosphonic acid derivative that exhibits bactericidal antimicrobial activity by binding to and subsequently inhibiting uridine diphosphate (UDP)-N-acetylglucosamine enolpyruvyl transferase, an enzyme involved in early-stage peptidoglycan synthesis. This unique mechanism of action of fosfomycin makes cross-resistance to other antibiotics highly unusual; furthermore, fosfomycin retains activity against the majority of MRSA strains.¹⁷

However, it cannot be used alone because of the rapid development of resistance.

There is limited experience of *in vitro* synergistic activity of fosfomycin in combination with β -lactams, although it has been observed.¹⁸ *In vitro* and *in vivo* synergy have also been observed between daptomycin and fosfomycin in an MRSA experimental endocarditis model,^{19 20} and the combination of daptomycin plus fosfomycin was at least as active as daptomycin plus cloxacillin in the same MRSA experimental endocarditis model.²⁰ Indeed, some clinical cases of MRSA bacteraemia/endocarditis have been successfully treated with the combination of daptomycin plus fosfomycin.^{19 21}

In spite of these encouraging data, there is no controlled clinical study comparing the efficacy and safety of daptomycin plus fosfomycin versus daptomycin alone.

Rationale

Despite the availability of new antibiotics such as daptomycin, MRSA bacteraemia continues to be associated with high clinical failure rates and poor outcomes. Recent data suggest that combination therapies might be an alternative to achieve better outcomes.^{12 13} Fosfomycin and daptomycin have recently been associated with good clinical response.^{19 21} We hypothesize that fosfomycin plus daptomycin will obtain higher clinical response than a therapy with daptomycin alone.

Investigators chose daptomycin as a comparator instead of vancomycin, which is still the standard therapy, because in the last decades MRSA bacteraemia affects elderly patients with more severe comorbidities² who have higher risk to renal impairment. In addition, vancomycin has been associated with poorer outcomes in bacteraemia with MRSA with elevated vancomycin MICs.^{22 23} MRSA strains with vancomycin MIC ≥ 2 $\mu\text{g/mL}$ have risen from 5.6% in 2004 to 11.1% in 2009, especially in some countries.²⁴

Primary objective

To demonstrate that high-dose daptomycin combined with fosfomycin achieves a better response than therapy with high-dose daptomycin alone, measured in terms of clinical success plus microbiological success (treatment success) at week 6 after end of therapy (test-of-cure visit, TOC).

Secondary objectives

Clinical secondary objectives

1. To compare the clinical success of daptomycin plus fosfomycin versus daptomycin alone at end of therapy (EOT).
2. To evaluate the safety of the daptomycin plus fosfomycin combination compared with daptomycin alone.
3. To evaluate overall mortality between the two treatment arms, daptomycin plus fosfomycin versus daptomycin alone, at EOT and at week 6 after TOC.

Microbiological secondary objectives

1. To determine the frequency of persistent and relapsing bacteraemia between the two treatment arms.

2. To determine the emergence of daptomycin-resistant strains during therapy in the two treatment arms.
3. To determine the emergence of fosfomicin-resistant strains in the arm with fosfomicin treatment.

METHODS AND ANALYSIS

Study design

A multicentre, open-label, randomised, phase 3, interventional clinical trial stratified by centre with parallel allocation (1:1). The trial has a superiority design.

Study population

Patients with complicated or uncomplicated MRSA bacteraemia hospitalised in participating hospitals.

Inclusion criteria

1. Patients must be ≥ 18 years old
2. Must have at least one blood culture positive for MRSA in the 72 h up to randomisation
3. Written informed consent
4. Mandatory use of contraception methods for fertile participants during the study period and for 6 months after stopping antibiotic therapy.

Exclusion criteria

1. Polymicrobial bacteraemia (more than one microorganism in blood cultures)
2. Participants with pneumonia
3. Severe clinical status with expected survival of less than 24 h
4. Allergic to daptomycin or fosfomicin
5. A positive pregnancy test at the time of inclusion
6. Any clinical condition that requires additional antibiotic therapy with microbiological activity against MRSA (specific forbidden antibiotics are named in page 10, section: drugs accepted during the trial)
7. Patient is already included in another clinical trial
8. Severe liver disease (Child-Pugh score class C)
9. Prior history of eosinophilic pneumonia

Note: ≤ 72 h of active antibiotic therapy for MRSA bacteraemia will not be considered a criterion for exclusion

Setting

Patients will be recruited among different academic hospitals of Spain located in Barcelona; Madrid; Seville; Granada; Mallorca; Tarragona; Lleida; Barakaldo, Valencia and Lugo.

List of study sites: Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Barcelona; Hospital Universitari Clínic de Barcelona; Hospital Universitari Santa Creu i Sant Pau, Barcelona; Hospital Universitari Vall d'Hebron, Barcelona; Hospital Universitari Parc de Salut Mar, Barcelona; Hospital Universitari Joan XXIII, Tarragona; Hospital Universitari Arnau de Vilanova, Lleida; Hospital Universitari Mutua de Terrassa, Barcelona; Hospital de Terrassa, Terrassa, Barcelona, Corporació Sanitària Parc Taulí, Sabadell, Barcelona; Hospital Universitario Gregorio Marañón, Madrid, Hospital Universitario 12 de

Octubre, Madrid; Hospital Universitario Ramón y Cajal, Madrid; Hospital Universitario Virgen Macarena, Sevilla; Hospital Universitario Virgen de las Nieves, Granada; Hospital Universitario de Cruces, Barakaldo; Hospital Universitari i Politècnic la Fe, Valencia; Hospital Universitari Son Espases, Mallorca; Hospital Universitario Lucus Augusti, Lugo.

Recruitment of patients

Patients will be identified at each participating hospital by checking daily for all blood cultures positive for MRSA. Microbiologists will alert trial researchers to assess for recruitment. Patients fulfilling all inclusion criteria and none of the exclusion criteria will be assigned in a randomised fashion to one of the treatment arms.

Randomisation and allocation concealment

A centralised electronic computer system will generate random lists based on randomly permuted blocks. Allocation sequences will be concealed by the system. The programme will randomly assign participants on a 1:1 basis to two parallel groups in two treatment arms, stratified by centre; 24 h web-based randomisation will be provided.

Intervention

Patients will be randomly assigned to one of the following arms:

1. Arm 1: Daptomycin 10 mg/kg intravenous, q/24 h
2. Arm 2: Daptomycin 10 mg/kg intravenous, q/24 h plus fosfomicin 2 gr/6 h intravenous

Note: No more than 24 h must elapse between randomisation and start of therapy.

Treatment of patients

Patients will receive the standard care of treatment for MRSA bacteraemia from the attending physician and study investigators will carry out extra scheduled visits.

Prescription of therapy

Daptomycin: 10 mg/kg, by intravenous infusion over a period of 30 min, once a day. The recommended dosage regimen for patients with creatinine clearance (CrCl) < 30 mL/min, including patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD), will be 10 mg/kg once every 48 h.²⁵

Note: Whenever possible on haemodialysis days, daptomycin will be administered following completion of haemodialysis.

Fosfomicin: 2 gr, by intravenous infusion over a period of 2 h, every 6 h a day. If there is renal impairment, the dose should remain constant (2 gr), with the interval between administrations varying according to creatinine clearance.²⁶ (table 1).

Duration of therapy

Duration of therapy will be 10–14 days for uncomplicated bacteraemia and 28 days and up to 42 days for

Table 1 Prescription of therapy

Creatinine clearance	Doses
40–20 mL/min	2 g every 12 h
20–10 mL/min	2 g every 24 h
≤10 mL/min	2 g every 48 h
Dialysis	2 gr following haemodialysis session

complicated bacteraemia. Cases of complicated bacteraemia considered by the PI to need 42-day therapy should be discussed previously with the sponsor.

Drugs accepted during the trial

Concomitant use of any kind of drug is accepted during the patient's participation in the clinical trial, except for antibiotics with activity against MRSA (rifampin, clindamycin, trimethoprim-sulfamethoxazole, doxycycline, gentamicin, linezolid, tigecycline and β -lactam antibiotics with proven in vitro activity against MRSA in combination with daptomycin as meropenem, piperacillin-tazobactam, cloxacillin, ampicillin or cefepime).

In addition, temporary suspension of agents associated with rhabdomyolysis, such as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, should be considered for patients receiving daptomycin.

Definitions

Complicated bacteraemia: will be defined as patients with MRSA in at least one blood culture with evidence of spread of infection (metastatic infection), suspected endocarditis, infection involving a foreign material that cannot be removed in less than 4 days, or persistence of a positive blood culture at 72–96 h from start of antimicrobial therapy.

Uncomplicated bacteraemia: will be defined as patients with MRSA in at least one blood culture with exclusion of endocarditis and no evidence of

haematogenous spread of infection at follow-up, plus negative results for blood culture at 72–96 h from start of antimicrobial therapy.

Participant timeline

All participants will be followed up by the study team for 6 weeks after stopping the study therapy. To assess outcome, all patients will be visited on day 3, day 7 (only if blood cultures at day 3 remain positive), weekly until the EOT (EOT: at days 10–14, day 28 or day 42), then a visit 6 weeks after stopping therapy (TOC). All data will be recorded on electronic eCRF (see figure 1; online supplementary appendix 1 shows the clinical trial assessment).

OUTCOMES

Primary end point

Treatment response at the TOC visit. This is a composite variable with two values.

Treatment success will be defined as the resolution of all clinical signs and symptoms (clinical success) plus negative blood culture (microbiological success) at the TOC visit.

Treatment failure will be defined as any of the following situations: (1) lack of clinical improvement at 72 h or more after the start of therapy; (2) persistent bacteraemia (positive blood culture on day 7 after the start of therapy); (3) premature discontinuation of therapy due to adverse effects or for any other reason based on clinical judgement; (4) relapsing MRSA bacteraemia before the TOC visit; (e) death for any reason before the TOC visit.

Secondary end point

- ▶ Treatment success at EOT visit (clinical success + microbiological success)
- ▶ Mortality at EOT and the TOC visit
- ▶ Severe adverse effects

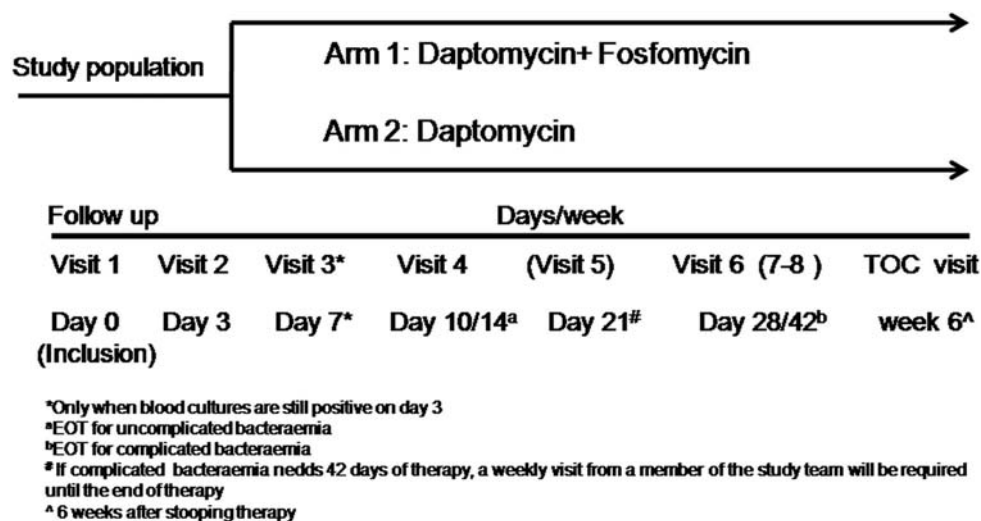


Figure 1 Participant timeline.

- ▶ Persistent MRSA bacteraemia
- ▶ Recurrence of MRSA bacteraemia (positive blood culture when previous ones were negative)
- ▶ Emergence of daptomycin resistance
- ▶ Emergence of fosfomycin resistance
- ▶ Days until negative results of blood culture
- ▶ Days to death
- ▶ Days to treatment failure

Note: Eucast Clinical break points have been considered to define daptomycin and fosfomycin susceptibility that were above 1 and 32 mg/L, respectively.

Criteria for withdrawing a patient from the study

Patients must be withdrawn from the study in any of the following situations:

- ▶ The criteria for clinical failure are fulfilled at 72 h after start of therapy (worsening of sepsis signs or symptoms).
- ▶ The criteria for treatment failure are fulfilled (positive MRSA blood culture on day 7 after start of therapy).
- ▶ The patient asks to be withdrawn from the study (at any time during the patient's participation in the study).
- ▶ A new clinical condition makes it necessary to add a new antimicrobial (different from those used in the study) with activity against MRSA.
- ▶ The principal investigator (PI) considers that there has been a serious protocol violation.
- ▶ The following occur during therapy: CPK values are >5, the upper limit of normal (ULN) plus muscle symptoms (cramps, muscle pain, weakness); signs or symptoms of peripheral neuropathy or suspicion of eosinophilic pneumonia.
- ▶ Any adverse event for which the clinicians consider that it is necessary to withdraw antibiotic therapy.
- ▶ Lost to follow-up.
- ▶ Pregnancy during the study.

Note: The following will not be considered a cause for withdrawal: any surgical intervention, such as debridement of an abscess, device removal and prosthesis valve replacement during therapy, since these are considered part of the standard care for complicated MRSA bacteraemia.

Managing withdrawals

When a patient has been withdrawn from the study, the investigator will record the reason/s for withdrawal on the clinical chart and the eCRF. If possible, all early withdrawal patients will be assessed up to the EOT visit. If the reason for withdrawal was a serious adverse event, the patient must be followed until the resolution or stabilisation of the event.

Note: Patients who withdraw early will not be replaced.

STATISTICAL ANALYSIS PLAN

Sample size and power calculations

We have assumed a 60% treatment success rate in the daptomycin group (based on success rates at the end of

therapy shown in Fowler's clinical trial). Accepting an α risk of 0.05 and a β risk of 0.2 in a two-sided test, 103 patients per group would be necessary to find a statistically significant difference of 20% between treatment groups. A dropout rate of 20% has been anticipated.

Type of analysis

To assess differences between study groups in baseline variables and other efficacy end points, two independent sample procedures will be employed. Continuous variables will be compared using parametric t tests or non-parametric Mann-Whitney U tests, depending on whether the distribution can be assumed to be normal (after performing tests for normality). Categorical data will be compared by the χ^2 or Fisher's exact tests, as appropriate. Survival curves will be compared by means of the log-rank test. Logistic or Cox regression models will be used to explore associations between different efficacy end points, interventions and relevant baseline conditions, using two-sided tests and a 5% significance level.

A logistic regression model will be used to assess the effect of important prognostic factors on response to treatment. Covariates at a 0.10 level of significance in the univariate analysis will be included in the multivariate analysis. In addition, each component of the composite end point treatment response will be analysed separately.

Efficacy analyses will be performed for the intention-to-treat (ITT) population. Given that patients will be hospitalised during antibiotic treatment and close follow-up is expected, this population will consist of all randomised participants. To account for dropouts between end-of-therapy and TOC visits, we will explore the various dropout patterns and their impact on response. Appropriate multiple imputation procedures will be employed to account for missing data for treatment response. When analysing survival analysis end points (time to death, time to negative blood culture, time to treatment failure), relevant patients will be censored at the time of withdrawal. Safety analyses will be performed on all randomised patients.

MONITORING

Monitoring plans

The data monitoring board will ensure the correct progress of the research and the efficacy of the data towards achieving the goals of the study

A safety monitoring committee with independent investigators will review safety data and provide advice about the continuation, modification and/or termination of the study.

ADVERSE EVENTS REPORTING AND QUANTIFICATION

Definitions

Adverse event: any injury related to medical management (including all aspects of care) that occurs during the patient's participation in the clinical trial will be considered an adverse event. An adverse event may be related to the study medication or be non-related.

Adverse drug event: any medication-related adverse event occurring during the patient's participation in the clinical trial will be considered an adverse drug event.

Adverse drug reaction: any 'adverse drug event' that occurs when the medication is used as directed and in the usual dosage will be considered an adverse drug reaction.

Serious adverse event or reaction will be defined as an event or reaction that:

- ▶ Results in death
- ▶ Is life-threatening
- ▶ Causes persistent or significant disability
- ▶ Causes a congenital anomaly/birth defect
- ▶ Requires in-patient hospitalisation or prolongation of existing hospitalisation (not related to basal diseases)

Grading of adverse event or reaction: will be performed in accordance with the Division of Microbiology and Infection Diseases (DMID) adult toxicity table, May 2001.

Adverse drug event of particular interest for the study

- ▶ **Diarrhoea:** A stool test for detecting *Clostridium difficile*-associated diarrhoea should be considered if the patient develops diarrhoea during the study. The occurrence of this adverse event will not lead to discontinuation of the drug, unless the PI considers it necessary.
- ▶ **Elevated creatine phosphokinase (CPK):** CPK levels >5 times the upper limit of normal (ULN)+symptoms (cramps, muscle pain, weakness) should lead to discontinuation of study medication and early patient withdrawal. For asymptomatic patients, a CPK >10 times the upper limit of normal (ULN) will be required for drug discontinuation. These adverse events should be notified to the sponsor.

Reporting

Any adverse event and its relationship to the study drug occurring during the patient's participation in the clinical trial should be recorded by the PI on the clinical chart at every scheduled visit.

On the electronic eCRE, there should only be recorded: serious adverse drug events; adverse events of any grade related to the study medication, in the opinion of the PI; adverse events of any grade leading to modification of study drug dosage, its interruption/early discontinuation.

All serious adverse events should be notified to the sponsor within 24–48 h of the investigator becoming aware of the event.

ETHICAL ISSUES

The trial will be conducted according to the principles of the Declaration of Helsinki (2008) and current Spanish legislation (Real decreto 223/2004). The principal investigator or collaborator at each site will obtain written informed consent from all patients, or their legal representatives (LRs) if they lack capacity, before enrolment. Patients (or their LRs) are free to withdraw from the trial at any time and this will be explicitly stated on the patient's information sheets (see online supplementary appendix 2).

The data collected for the study will be identified by a code and only the study doctor and collaborators will be

able to link those data with patients and their clinical history. Consequently, the patient's identity will not be revealed to any other person, except in cases of medical emergency or if required to do so by law.

Access to patient information will be restricted to the study doctor and collaborators, the health authorities (Spanish Medicines and Healthcare Products Regulatory Agency (AEMPS)), the Clinical Research Ethics Committee, and personnel authorised by the sponsor when they need to check the data and procedures used in the study, but always maintaining the confidentiality of the said information in accordance with current legislation.

The trial protocol received research ethics committee approval in July 2013. Amendment was approved in June 2014 (V.4. 30th April 2014).

The informed consent form and information sheet received research ethics committee approval in July 2013 and AEMPS approval in September 2013.

Indemnities

In accordance with Spanish legislation governing clinical trials (RD 223/2004), this study has liability insurance covering possible damages to patients during their participation in the study, Zurich Insurance PLC, Spanish branch, policy number 70383054.

Publication plans

The sponsor commits itself to publishing the data within 12 months of the completion of the study. Results will be analysed and reported in accordance with CONSORT guidelines.

Protocol amendments

For communicating important protocol modifications, we will first notify the Clinical Research Ethics Committee and Spanish Medicines and Healthcare Products Regulatory Agency (AEMPS) in accordance with Spanish legislation. After their approval, all the Ethics Committee members and investigators of the participating sites will be informed.

DISCUSSION

Currently, there is a need to improve cure rates of patients with MRSA bacteraemia. Some in vitro studies showed a synergistic activity of fosfomycin in combination with β -lactams.¹⁸ In addition, some patients with MRSA bacteraemia have recently been successfully treated with the combination of daptomycin and fosfomycin.^{19–21}

We designed this open-label randomised study to demonstrate the hypothesis that fosfomycin (2 gr every 6 h a day) in combination with daptomycin (10 mg/kg once a day) will be better therapy for treating patients with MRSA bacteraemia than therapy with daptomycin alone. Therefore, the study design includes patients with uncomplicated and complicated MRSA bacteraemia, and the main end point includes clinical success plus microbiological success at week 6 after EOT (TOC visit)

Expected impact: this trial will help provide a response to the priority clinical question of whether treatment with daptomycin plus fosfomycin reduces mortality rates and also improves clinical outcomes associated with MRSA bacteraemia.

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Contributors MP and JC were the study sponsors; took part in study design and recruitment of patients. ES participated in study design; review of the protocol and recruitment of patients. JMM participated in study design and review of the protocol. CC, MPA, CP, JLC, MM, GGP, FB, EC, EE, OG, BP, AGR, VP, JRB, JP, MM, MS, JM and MJGP took part in review of the protocol and recruitment of patients.

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Competing interests None.

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REFERENCES

1. Cosgrove SE, Sakoulas G, Perencevich EN, *et al.* Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis* 2003;36:53–9.
2. Gasch O, Ayats J, Dominguez MA, *et al.* Epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection: secular trends over 19 years at a university hospital. *Medicine (Baltimore)* 2011;90:319–27.
3. Gasch O, Camoez M, Dominguez MA, *et al.* Predictive factors for mortality in patients with methicillin-resistant *Staphylococcus aureus* bloodstream infection: impact on outcome of host, microorganism and therapy. *Clin Microbiol Infect* 2013;19:1049–57.
4. Chang FY, Peacock JE Jr, Musher DM, *et al.* *Staphylococcus aureus* bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. *Medicine* 2003;82:333–9.
5. Schweizer ML, Furuno JP, Harris AD, *et al.* Comparative effectiveness of nafcillin or ceftazolin versus vancomycin in methicillin-susceptible *Staphylococcus aureus* bacteremia. *BMC Infect Dis* 2011;11:279.
6. Fowler VG, Boucher HW, Corey GR, *et al.* Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med* 2006;355:653–65.
7. Wu G, Abraham T, Rapp J, *et al.* Daptomycin: evaluation of a high-dose treatment strategy. *Int J Antimicrob Agents* 2011;38:192–6.
8. Rehm SJ, Boucher H, Levine D, *et al.* Daptomycin versus vancomycin plus gentamicin for treatment of bacteraemia and endocarditis due to *Staphylococcus aureus*: subset analysis of patients infected with methicillin-resistant isolates. *J Antimicrob Chemother* 2008;62:1413–21.
9. Liu C, Bayer A, Cosgrove SE, *et al.* Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis* 2011;52:285–92.
10. Gudiol F, Aguado JM, Pacual A, *et al.* Consensus document for the treatment of bacteremia and endocarditis caused by methicillin-resistant *Staphylococcus aureus*. *Enferm Infecc Microbiol Clin* 2009;27:105–15.
11. Kullar R, Davis SL, Levine DP, *et al.* High-dose daptomycin for treatment of complicated Gram-positive infections. *Pharmacotherapy* 2011;31:527–36.
12. Yang SJ, Xiong YQ, Boyle-Vavra S, *et al.* Daptomycin-oxacillin combinations in treatment of experimental endocarditis caused by daptomycin-nonsusceptible strains of methicillin-resistant *Staphylococcus aureus* with evolving oxacillin susceptibility (the "seesaw effect"). *Antimicrob Agents Chemother* 2010;54:3161–9.
13. Mehta S, Singh C, Plata KB, *et al.* β -Lactams increase the antibacterial activity of daptomycin against clinical methicillin-resistant *Staphylococcus aureus* strains and prevent selection of daptomycin-resistant derivatives. *Antimicrob Agents Chemother* 2012;56:6192–200.
14. LaPlante KL, Woodmansee S. Activities of daptomycin and vancomycin alone and in combination with rifampin and gentamicin against biofilm-forming methicillin-resistant *Staphylococcus aureus* isolates in an experimental model of endocarditis. *Antimicrob Agents Chemother* 2009;53:3880–6.
15. Miró JM, Garcia de la Maria C, Armero Y, *et al.* Addition of gentamicin or rifampin does not enhance the effectiveness of daptomycin in treatment of experimental endocarditis due to methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2009;53:4172–7.
16. Dhand A, Bayer AS, Pogliano J, *et al.* Use of antistaphylococcal beta-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant *Staphylococcus aureus*: role of enhanced daptomycin binding. *Clin Infect Dis* 2011;53:158–63.
17. Popovic M, Steinort D, Pillai S, *et al.* Fosfomycin: an old, new friend? *Eur J Clin Microbiol Infect Dis* 2010;29:127–42.



18. Kastoris AC, Rafailidis PI, Vouloumanou EK, *et al.* Synergy of fosfomycin with other antibiotics for Gram-positive and Gram negative bacteria. *Eur J Clin Pharmacol* 2010;66: 359–68.
19. Miró J, Entenza JM, del Rio A, *et al.* High-dose daptomycin plus fosfomycin was safe and effective in treating methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* endocarditis: from bench to bedside. *Antimicrob Agents Chemother* 2012;56:4511–15.
20. Combination of daptomycin plus fosfomycin has synergistic, potent and rapid bactericidal activity against methicillin-resistant *Staphylococcus aureus* (MRSA) in a rabbit model of experimental endocarditis (EE). P0088. 24th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) Barcelona, Spain 10–13 May 2014.
21. Chen LY, Huang CH, Kuo SC, *et al.* High-dose daptomycin and fosfomycin treatment of a patient with endocarditis caused by daptomycin non susceptible *Staphylococcus aureus*: case report. *BMC Infect Dis* 2011;26:152.
22. Soriano A, Marco F, Martinez JA, *et al.* Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2008;46:193–200.
23. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. *Clin Infect Dis* 2012;54:755–71.
24. Hawser SP, Bouchillon SK, Hoban DJ, *et al.* Rising incidence of *Staphylococcus aureus* with reduced susceptibility to vancomycin and susceptibility to antibiotics: a global analysis 2004–2009. *Int J Antimicrob Agents* 2011;37:219–24.
25. Daptomycin. Summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000637/WC500036049.pdf [cited 24 Nov 2014].
26. Fosfomicina disódica. Agencia española de medicamentos y productos sanitarios. Ministerio de sanidad política social y Igualdad. 2003. http://www.aemps.gob.es/cima/pdfs/es/ft/54165/FT_54165.pdf [cited 24 Nov 2014].