A case study on *Staphylococcus aureus* bacteraemia: available treatment options, antibiotic R&D and responsible antibiotic-use strategies

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Objectives: This case study addresses: (i) antibiotic treatment options for *Staphylococcus aureus* bacteraemia (SAB), for both empirical and targeted therapy; (ii) the current status of and priorities for the antibiotic pipeline to ensure access of effective antibiotics for SAB; and (iii) strategies for responsible antibiotic use relevant to the clinical management of SAB.

Methods: Evidence to address the aims was extracted from the following information sources: (i) EUCAST and CLSI recommendations, summaries of product characteristics (SPCs), antibiotic treatment guidelines and the textbook *Kucers’ The Use of Antibiotics*; (ii) the www.clinicaltrial.gov database; and (iii) quality indicators for responsible antibiotic use.

Results: Current monotherapy treatment options for SAB include only three drug classes (β-lactams, glycopeptides and lipopeptides), of which two also cover MRSA bacteraemia (glycopeptides and lipopeptides). The analysis of the antibiotic pipeline and ongoing clinical trials revealed that several new antibiotics with *S. aureus* (including MRSA) coverage were developed in the past decade (2009–19). However, none belonged to a new antibiotic class or had superior effectiveness and their added clinical value for SAB remains to be proven. Responsible antibiotic use for the treatment of SAB was illustrated using 11 quality indicators.

Conclusions: Awareness of the problem of a limited antibiotic arsenal, together with incentives (e.g. push incentives), is needed to steer the R&D landscape towards the development of novel and effective antibiotics for treating SAB. In the meantime, responsible antibiotic use guided by quality indicators should preserve the effectiveness of currently available antibiotics for treating SAB.

Introduction

*Staphylococcus aureus*, a Gram-positive bacterium that is both a human commensal and an opportunistic pathogen, is a frequent cause of bacteraemia in industrialized nations.1–3 The mortality associated with *S. aureus* bacteraemia (SAB), estimated at 20%–25%, is considerable.4,5 Furthermore, the burden of SAB is increasing over time.6–8 SAB is a common healthcare-associated infection, often linked to the use of intravascular catheters, but can also be acquired in the community.

Over the past 60 years, *S. aureus* has shown great aptitude for becoming resistant to antibiotics, thereby posing challenges for clinical management of *S. aureus* infections. Currently, MRSA strains are resistant to several β-lactam antibiotics, including penicillins, cephalosporins, carbapenems,9,10 quinolones11 and even vancomycin.12 The epidemiology of MRSA is continuously changing and shows a wide variation within and between geographical regions.13 For example, methicillin resistance rates among *S. aureus* invasive isolates range from 1.2% to 50.5% in European countries.3

The development of resistance by bacteria is a natural phenomenon and all use of antimicrobial drugs drives the development of resistance by selection pressure. At the level of healthcare facilities, strategies to reduce the emergence of resistance should thus focus on limiting antibiotic use to appropriate clinical situations. These responsible antibiotic-use strategies are the core focus of antibiotic stewardship. Containing the spread of MRSA is in the...
interests of both patient health and hospital finances. The quantity of hospital antibiotic use has previously been associated with the frequency of MRSA acquisition. Over recent years, remarkable decreases in MRSA rates were observed following infection control and stewardship activities in France and the UK.

Aims

This case study addresses: (i) available antibiotic treatment options for SAB including both empirical and targeted therapy; (ii) current status of and priorities for the antibiotic pipeline to ensure access of effective antibiotics for SAB; and (iii) strategies for responsible antibiotic use relevant to the clinical management of SAB. The case study focuses on the management of SAB in the hospital setting and does not address other treatment options such as source control, vaccines or antibodies against S. aureus.

Case study methodology

Definition

A case study can be defined as an intensive study about a person, a group of people or a unit, which is aimed to generalize over several units. A case study is typically characterized by its subject (i.e. a phenomenon of scientific interest or ‘unit’) and its object (i.e. the analytical frame within which the case subject is understood). The present case study addresses: (i) the available antibiotic arsenal; (ii) the current status of and priorities for antibiotic R&D; and (iii) responsible antibiotic-use strategies (objects) for the treatment of SAB (subject) in the hospital setting.

I. SAB: current antibiotic treatment options

Empirical treatment options (Table 1) and targeted treatment options for SAB and/or endocarditis (Table 2) were compiled using the information sources listed below:

- Clinical breakpoints were extracted from EUCAST. When no clinical breakpoint was described in the EUCAST database, the CLSI library was searched.
- Clinical-use sections of the textbook Kucers’ The Use of Antibiotics (7th edition) (2018) were searched for relevant human data on severe infections, bacteraemia and/or endocarditis, or empirical treatment of febrile neutropenic patients. Kucers’ The Use of Antibiotics is considered a leading source of information in the field of infectious diseases.
- An illustrative sample of guidelines from Europe, the USA and Australia, accessible in English, were searched for recommendations:
  - Clinical practice guidelines for the treatment of MRSA infections in adults and children by IDSA (2011).
  - Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection by IDSA (2009).
  - European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia (ECIL) (2013).
  - Guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC) (2015).
- Staphylococcus aureus Bacteraemia (SAB) Management Clinical Guideline developed by the South Australian expert Advisory Group on Antimicrobial Resistance (SAAGAR) (2019).
- Antibacterial therapy of adult patients with sepsis guideline by the Dutch Working Party on Antibiotic Policy (SWAB) (2010) (revisions have been announced).
- Guidelines for the prophylaxis and treatment of MRSA infections in the UK (2009).
- UpToDate chapter ‘Clinical approach to Staphylococcus aureus bacteremia in adults’ by Holland & Fowler (last updated in July 2019).
- When available, the Summary of Product Characteristics (SPC) of antibiotics approved by the regulatory agencies (EMA and/or FDA) were accessed online. When no harmonized EMA indication was available (e.g. for drugs already widely in use before the creation of the EMA in 1995 and not undergoing referral procedures at EMA afterwards), SPVs from EU National Regulatory Agencies (EU NRAs) were searched. The sections ‘therapeutic indications’ and ‘posology’ were screened for one of the following indications: bacteraemia, sepsis, septicemia, severe infections or endocarditis.

Additional information on the data extraction process:

- Antibiotics for which no literature on use as monotherapy was reviewed in Kucers’ The Use of Antibiotics were not included (e.g. fosfomycin, rifampicin, aminoglycosides and ertapenem).
- The level of evidence of the recommendations is not provided. However, the UpToDate chapter on SAB was included as an information source and the recommendations from UpToDate have previously been shown to adhere to the Grading of Recommendations Assessment Development and Evaluation (GRADE) framework.
- No distinction was made between first or second choice of therapy. This case study should not be seen as clinical practice guidance but rather as a reflection on the current antibiotic arsenal for SAB. Of note, antibiotics mentioned as alternative, third-line (i.e. very weak evidence) or salvage treatment options were not included.

II. SAB: current status of and priorities for antibiotic R&D

Ongoing and recently completed (≤5 years) clinical trials for antibiotics for the treatment of SAB and/or endocarditis (Table 3) were searched for in the www.clinicaltrial.gov database. Clinical trials were not included in the table when: trial status was ‘unknown’; the trial was completed before January 2014; trial results were already published; the interventions were not limited to the use of antibiotics (e.g. algorithm-based therapy, adjunctive immunotherapeutics or other novel approaches); or when trials did not study any specific (combination of) antibiotics. Utilization registry trials, observational and retrospective studies are not presented in Table 3.

III. SAB: responsible antibiotic-use strategies

Fifty-one generic inpatient quality indicators (IQIs) for antibiotic use were recently developed by the Driving ReInVEstment in R&D and responsible Antibiotic use (DRIVE-AB) consortium through an international and multidisciplinary consensus. While we recognize that all 51 IQIs are relevant to the management of SAB, we...
Table 1. Options for broad-spectrum initial empirical antibiotic therapy of severe infections (i.e. suspected bacteraemia, sepsis and/or endocarditis) including coverage of *S. aureus*.

| Antibiotic class | Antibiotic agent | Clinical breakpoint for *S. aureus* (MIC) | Source | MSSA bacteraemia | MSSA endocarditis | MRSA bacteraemia | MRSA endocarditis | References |
|------------------|------------------|------------------------------------------|--------|------------------|------------------|------------------|------------------|------------|
| β-Lactams        |                  |                                          |        |                  |                  |                  |                  |            |
| Cephalosporins   | cefuroxime       | ≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin) | mentioned in Kucers' | no               | no               | no               | no               | 21         |
| (2nd generation) |                  |                                          |        | recommended by guideline(s) | yes             | no               | no               | no               | 28         |
|                  |                  |                                          |        | EMA harmonized indication | no              | no               | no               | no               | 80         |
|                  |                  |                                          |        | FDA indication    | yes             | no               | no               | no               | 81         |
| Cephalosporins   | cefotaxime       | ≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin) | mentioned in Kucers' | no               | yes              | no               | no               | 21         |
| (3rd generation) |                  |                                          |        | recommended by guideline(s) | yes             | yes              | yes              | no               | 26,28      |
|                  |                  |                                          |        | EU NRA indicationc (e.g. France) | yes             | yes              | no               | no               | 82         |
|                  |                  |                                          |        | FDA indication    | yes             | no               | no               | no               | 83         |
|                  | ceftriaxone      | ≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin) | mentioned in Kucers' | no               | yes              | no               | no               | 21         |
|                  |                  |                                          |        | recommended by guideline(s) | yes             | yes              | no               | no               | 28         |
|                  |                  |                                          |        | EMA harmonized indication | yes             | yes              | no               | no               | 84         |
|                  |                  |                                          |        | FDA indication    | yes             | no               | no               | no               | 85         |
| Cephalosporins   | ceftazidime      | —                                        | mentioned in Kucers' | yes             | no               | no               | no               | 21         |
| (4th generation) |                  |                                          |        | recommended by guideline(s) | no              | no               | no               | no               | 86         |
|                  |                  |                                          |        | EMA harmonized indication | no              | no               | no               | no               | 87         |
|                  |                  |                                          |        | FDA indication    | no              | no               | no               | no               | 88         |
| Cephalosporins   | ceftazidime      | —                                        | no     | no               | no               | no               | no               | no               | 89         |
| (5th generation) |                  |                                          |        | no               | no               | no               | no               | no               | 90         |
|                  |                  |                                          |        | no               | no               | no               | no               | no               | 91         |
| Cephalosporins   | cefepime         | ≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin) | mentioned in Kucers' | yes             | no               | no               | no               | 21         |
| (4th generation) |                  |                                          |        | recommended by guideline(s) | yes             | no               | no               | no               | 25         |
|                  |                  |                                          |        | EU NRA indicationc (e.g. UK) | yes             | no               | no               | no               | 88         |
|                  |                  |                                          |        | FDA indication    | yes             | no               | no               | no               | 89         |
| Cephalosporins   | ceftaroline      | ≤1 mg/L (S); >2 mg/L (R) | mentioned in Kucers' | no             | no               | no               | no               | 21         |
| (5th generation) |                  |                                          |        | recommended by guideline(s) | no              | no               | no               | no               | 90         |
|                  |                  |                                          |        | EMA harmonized indication | no              | no               | no               | no               | 91         |
|                  |                  |                                          |        | FDA indication    | no              | no               | no               | no               | 92         |
| Cephalosporins   | ceftobiprole     | ≤2 mg/L (S); >2 mg/L (R) | mentioned in Kucers' | no             | no               | no               | no               | 21         |
|                  |                  |                                          |        | recommended by guideline(s) | no              | no               | no               | no               | 93         |
|                  |                  |                                          |        | EU NRA indicationc,d (e.g. UK) | no              | no               | no               | no               | 94         |
|β-Lactam/β-lacta- | piperacillin/ta- | ≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin) | mentioned in Kucers' | yes             | no               | no               | no               | 21         |
| mase inhibitor   | zobactam         |                                          |        | recommended by guideline(s) | yes             | no               | no               | no               | 25,28      |
| combinations     |                  |                                          |        | EMA harmonized indication | yes             | no               | no               | no               | 92         |
| Carbapenems      | imipenem/cilastatin | ≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin) | mentioned in Kucers' | yes             | yes              | no               | no               | 21         |
|                  |                  |                                          |        | recommended by guideline(s) | yes             | yes              | no               | no               | 28         |
|                  |                  |                                          |        | EMA harmonized indication | yes             | yes              | no               | no               | 94         |
|                  |                  |                                          |        | FDA indication    | yes             | yes              | no               | no               | 95         |
| Carbapenems      | meropenem        | ≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin) | mentioned in Kucers' | yes             | yes              | no               | no               | 21         |
|                  |                  |                                          |        | recommended by guideline(s) | yes             | yes              | no               | no               | 28         |
|                  |                  |                                          |        | EMA harmonized indication | yes             | yes              | no               | no               | 96         |
|                  |                  |                                          |        | FDA indication    | yes             | no               | no               | no               | 97         |

Continued
highlight here a selection of themes and associated quality indicators considered to be particularly pertinent to measuring responsible antibiotic use for SAB. The original codes for the addressed IQIs are shown in the text.32

Study limitations

The limitations of case study research include bias toward verification (i.e. the tendency to confirm the researcher's preconceived notions).33 The data extraction performed among different international information sources and the collaboration with researchers from different backgrounds (including medical specialists, a health economist and a regulator) is expected to reduce risks for verification biases.

I. SAB: current antibiotic treatment options

The clinical management of SAB requires a combination of effective antibiotic therapy and prompt removal of the source of infection such as catheter removal or abscess drainage. As with most infectious diseases, there is no 'one size fits all' antibiotic treatment for SAB, as the appropriate dosage regimen is determined by a combination of pathogen-related factors (e.g. antibiotic susceptibility), patient-related factors (e.g. antibiotic allergies, immune factors, comorbidities and concomitant therapy) and the source of infection (e.g. skin and skin tissue versus pulmonary).

SAB can be classified as 'complicated' or 'uncomplicated'.23 One of the criteria used for this severity classification is whether endocarditis is suspected or diagnosed. Indeed, S. aureus is the major causative pathogen of infective endocarditis in many regions of the world.34 This distinction between complicated and uncomplicated SAB has a significant impact on clinical management by guiding the diagnostic procedures, the duration of antibiotic treatment and the overall prognosis.35

Terminology: empirical versus targeted therapy

A crucial aspect of the clinical management of bacterial infections is the distinction between empirical therapy (also called initial therapy) and targeted therapy (or definitive therapy).36 While the first should be based on clinical presentation and local epidemiology (i.e. a ‘bacteriological educated guess’ covering all suspected causative pathogens including S. aureus), the latter should be based on microbiology results (i.e. identification of S. aureus as the causative pathogen and antimicrobial susceptibility data). In this case study, initial empirical therapy refers to the first days of therapy, i.e. 48–72 h before the cultures identify the causative pathogen.

Antibiotic treatment options for SAB and S. aureus endocarditis

Current treatment options for SAB and S. aureus endocarditis are shown in Table 1 and Table 2. Coverage of S. aureus infections should be guided by local epidemiology; however, there is no generally accepted consensus on an appropriate methicillin resistance threshold for bacteraemia. A threshold of 10% resistance rate in bacteria has been recommended previously.29 However, some argued that this 10% resistance threshold is too low.37 A threshold of 20% has been advised to guide the choice of empirical therapy for non-bacteraemia infections when MRSA is suspected.38

| Antibiotic class | Antibiotic agent | MSSA bacteremia, endocarditis | MSSA bacteremia, endocarditis | References |
|------------------|------------------|-----------------------------|-----------------------------|------------|
| Glycopeptides    | vancomycin       | yes                         | yes                         | 21, 23-25, 29-30 |
|                   | teicoplanin      | yes                         | yes                         | 19, 21, 24, 29, 30 |
| Source           | Source mentioned in Kucers, no human clinical data reviewed, yes means no human clinical data reviewed. Recommended by guideline(s), yes means the antibiotic was recommended by at least one of the searched guidelines. EMA indication, yes means regulatory indication available. | yes                         | yes                         | 23, 24, 26, 27, 29, 30 |
| Clinical breakpoint for S. aureus (MIC) | Clinical breakpoint for S. aureus (MIC) | ≤2 mg/L (S) ≤2 mg/L (R) | ≤2 mg/L (S) ≤2 mg/L (R) | 19, 21, 24, 29, 30 |

S, susceptible; R, resistant; –, missing data.
Table 2. Options for targeted antibiotic therapy of SAB and S. aureus endocarditis

| Antibiotic class | Antibiotic agent | Clinical breakpoint for S. aureus (MIC) | Source<sup>a</sup> | MSSA | MRSA | References |
|------------------|------------------|----------------------------------------|---------------------|------|------|------------|
| **β-Lactams**    |                  |                                        |                     |      |      |            |
| Penicillins      | isoxazolyl penicillins, e.g. oxacillin, doxacillin, dicloxacillin, flucloxacillin | ≤2 mg/L (S); >2 mg/L (R) (MIC of oxacillin)<sup>19</sup> | mentioned in Kucers’ recommended by guideline(s) | yes  | yes  | no  | no  | 21     |
|                  |                  |                                        | EU NRA indication<sup>c</sup> (e.g. The Netherlands) | yes  | yes  | no  | no  | 101    |
|                  |                  |                                        | FDA indication      |      |      |      |      |        |
|                  | nafcillin        | ≤2 mg/L (S); >4 mg/L (R) (inferred from MIC of oxacillin)<sup>20</sup> | mentioned in Kucers’ recommended by guideline(s) | yes  | yes  | no  | no  | 21     |
|                  |                  |                                        | EU NRA/EMA harmonized indication | yes  | yes  | no  | no  | 24,30  |
|                  |                  |                                        | FDA indication      |      |      |      |      |        |
| Cephalosporins (1st generation) | cefalotin | —                                      | mentioned in Kucers’ recommended by guideline(s) | yes  | yes  | no  | no  | 21     |
|                  |                  |                                        | EU NRA indication<sup>c</sup> (e.g. Belgium) | no   | no   | no  | no  |        |
|                  |                  |                                        | FDA indication      |      |      |      |      |        |
|                  | cefazolin        | ≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin)<sup>19</sup> | mentioned in Kucers’ recommended by guideline(s) | yes  | no   | no  | no  | 21,24,26,27,30 |
|                  |                  |                                        | EU NRA indication<sup>c</sup> (e.g. Belgium) | yes  | yes  | no  | no  | 104    |
|                  |                  |                                        | FDA indication      | yes  | yes  | no  | no  | 105    |
| Glycopeptides    | vancomycin       | ≤2 mg/L (S); >2 mg/L (R)<sup>19</sup> | mentioned in Kucers’ recommended by guideline(s) | yes  | yes  | yes | yes | 21     |
| Lipoglycopeptides | oritavancin     | ≤0.125 mg/L (S); >0.125 mg/L (R)<sup>19</sup> | mentioned in Kucers’ recommended by guideline(s) | yes  | no   | no  | no  | 21     |
|                  |                  |                                        | EMA harmonized indication | yes  | yes  | yes | yes | 23,24,26,27,29,30 |
|                  |                  |                                        | FDA indication      | yes  | yes  | yes | yes | 98     |
|                  |                  |                                        |                  |      |      |      |      |        |
|                  | teicoplanin      | ≤2 mg/L (S); >2 mg/L (R)<sup>19</sup> | mentioned in Kucers’ recommended by guideline(s) | yes  | yes  | yes | yes | 21     |
|                  |                  |                                        | EMA harmonized indication | yes  | yes  | yes | yes | 29,30  |
|                  |                  |                                        | FDA indication      | yes  | yes  | yes | yes | 100    |
|                  |                  |                                        |                  |      |      |      |      |        |
|                  | dalbavancin      | ≤0.125 mg/L (S); >0.125 mg/L (R)<sup>19</sup> | mentioned in Kucers’ recommended by guideline(s) | yes  | no   | no  | no  | 21     |
|                  |                  |                                        | EMA harmonized indication | no  | no   | no  | no  | 106    |
|                  |                  |                                        | FDA indication      | no   | no   | no  | no  | 107    |

Continued
| Antibiotic class   | Antibiotic agent                        | Clinical breakpoint for S. aureus (MIC) | Source<sup>a</sup> | MSSA bacteraemia | MSSA endocarditis<sup>b</sup> | MRSA bacteraemia | MRSA endocarditis<sup>b</sup> | References |
|-------------------|----------------------------------------|----------------------------------------|---------------------|------------------|-------------------|------------------|-------------------|------------|
|                   | telavancin                             | ≤0.125 mg/L (S) (MIC for MRSA)<sup>19</sup> | mentioned in Kucers’ recommended by guideline(s) EU NRA/EMA harmonized indication | yes              | yes               | yes              | yes               | 21         |
|                   |                                        |                                        |                     |                  |                   |                  |                   |            |
| Lipopeptides      | daptomycin                             | ≤1 mg/L (S); >1 mg/L (R)<sup>19</sup>  | mentioned in Kucers’ recommended by guideline(s) EMA harmonized indication FDA indication | yes              | no                | yes              | no                | 21         |
|                   |                                        |                                        |                     |                  |                   |                  |                   |            |
| Other antibiotics | linezolid                               | ≤4 mg/L (S); >4 mg/L (R)<sup>19</sup>  | mentioned in Kucers’ recommended by guideline(s) EU NRA indication<sup>c</sup> (e.g. The Netherlands) FDA indication | yes              | no                | yes              | yes               | 21         |
| Oxazolidinones    |                                        |                                        |                     |                  |                   |                  |                   |            |
|                   | tedizolid                               | ≤0.5 mg/L (S); >0.5 mg/L (R)<sup>19</sup> | mentioned in Kucers’ recommended by guideline(s) EMA harmonized indication FDA indication | no                | no                | no                | no                | 21         |
| Macrolide-lincosamide-streptogramins | quinupristin/ dalfopristin           | ≤1 mg/L (S); >2 mg/L (R)<sup>19</sup> | mentioned in Kucers’ recommended by guideline(s) EU NRA indication<sup>c</sup> FDA indication | yes              | no                | yes              | no                | 21         |
| Lincosamides      | clindamycin                             | ≤0.25 mg/L (S); >0.5 mg/L (R)<sup>19</sup> | mentioned in Kucers’ recommended by guideline(s) EU NRA (e.g. The Netherlands)<sup>c</sup> FDA indication | yes              | yes               | no                | no                | 21         |
| Combination of dihydrofolate reductase inhibitor and a sulphonamide | trimethoprim/sulfa- methoxazole (co-trimoxazole) | ≤2 mg/L (S); >4 mg/L (R)<sup>19</sup> | mentioned in Kucers’ recommended by guideline(s) EU NRA indication<sup>c</sup> (e.g. UK) FDA indication | yes              | yes               | no                | no                | 21         |

<sup>S</sup>, susceptible; <sup>R</sup>, resistant; <sup>–</sup>, missing data.

<sup>a</sup>Sources: Mentioned in Kucers’, ‘yes’ means human clinical data reviewed; ‘no’ means no human clinical data reviewed. Recommended by guideline(s): ‘yes’ means the antibiotic was recommended in at least one of the searched guidelines; specific guideline references are shown in the column ‘references’; ‘no’ means the antibiotic was not recommended by any of the searched guidelines. EMA/EU NRA indication or FDA indication: ‘yes’ means regulatory indication available; ‘no’ means no regulatory indication available.

<sup>b</sup>No distinction was made between prosthetic and native valve endocarditis or between right- and left-sided endocarditis.

<sup>c</sup>No harmonized EMA indication.

<sup>d</sup>Specific clinical indications (e.g. bacteraemia, sepsis, severe infections) were not documented.

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Table 3. Ongoing and recently completed (≤5 years) clinical trials for antibiotics for the treatment of SAB and/or S. aureus endocarditis

| Antibiotic class              | Drug name                      | MRSA coverage | Endocarditis | Trial phase | Drug comparatora | Number of patients | Trial status                        | Trial period          | Countries                          | Clinical Trials.gov identifier and other reference |
|-------------------------------|--------------------------------|---------------|--------------|-------------|------------------|--------------------|-------------------------------|---------------------|------------------------------------|------------------------------------------------------|
| **β-Lactams, cephalosporins** |                               |               |              |             |                  |                    |                               |                     |                                    |                                                      |
|                               | cefazolin                      | no            | no           | IV          | cloxacillin      | 300 (estimated)    | recruiting         | Sept 2018–estimated Sept 2022 | France               | NCT0324806321                                      |
|                               | cefotaxime                     | no            | ND           | IV          | NA               | 60 enrolled        | completed terminated (due to slow enrolment) | Nov 2015–Sept 2016  | The Netherlands USA                    | NCT02560207 NCT02424734                                 |
|                               | ceftaroline fosamil + ampicillin + optiona!l aminoglycoside | no            | ND           | II          | NA               | 11 participants    | NA               | Aug 2015–Dec 2017      | USA                                  | NCT02424734                                           |
|                               | ceftaroline fosamil             | yes           | yes          | IV          | NA               | 56 enrolled        | recruiting         | May 2013–July 2014       | USA, Argentina, Brazil, Bulgaria, Germany, Israel, Italy, Russia, Spain, Ukraine | NCT0313873322                                                   |
|                               | ceftobiprole medocaril          | yes           | yes          | III         | daptomycin       | 390 (estimated)    | completed recruiting | Jan 2013–Aug 2021       | USA                                  | NCT01701219                                           |
| **β-Lactams, penicillins**    |                               |               |              |             |                  |                    |                               |                     |                                    |                                                      |
|                               | cloxacillin + levofloxacin      | no            | no           | III          | cloxacillin      | 1 enrolled (154 estimated) | terminated (not participants inclusion) not yet recruiting | May 2013–Nov 2014 | Spain                              | NCT01875263                                           |
|                               | cloxacillin + fosfomycin        | no            | yes          | IV          | cloxacillin      | 366 (estimated)    | recruiting         | May 2019–estimated Aug 2021 | Spain                              | NCT03959345                                           |
|                               | daptomycin                     | yes           | no           | II          | NA               | 20 (estimated)     | recruiting         | Dec 2018–estimated May 2021 | Japan                              | NCT03643952                                           |
|                               | daptomycin + fosfomycin         | yes           | yes          | III         | daptomycin       | 14 enrolled (50 estimated) | terminated (slow accrual of participants) terminated (lack of inclusion) completed | Jan 2014–Dec 2015 | Singapore                           | NCT01975662                                           |
|                               | vancomycin or daptomycin        | yes           | yes          | III         | NA               | not provided       | completed terminated (recommendation of the Data Safety Monitoring Committee) | March 2014–Sept 2015 | France, Australia, New Zealand, Singapore, Israel | NCT01424075 NCT0236549324                                   |
|                               | vancomycin or daptomycin with β-lactam | yes          | yes          | IV          | placebo + β-lactam | 102 (estimated)    | active, not recruiting | Nov 2016–Sept 2019       | Canada                              | NCT0297298325                                           |
| **Glycopeptides**             |                               |               |              |             |                  |                    |                               |                     |                                    |                                                      |
|                               | daptomycin                     | yes           | yes          | IV          | placebo + β-lactam | 300 (estimated)    | recruiting         | Feb 2017–estimated Feb 2019 | Estonia, Greece, Italy, Spain, UK Australia | NCT02790996 NCT04044703                                    |
|                               | vancomycin                     | yes           | ND           | IV          | NA               | 28 (estimated)     | recruiting         | Aug 2019–estimated Aug 2020 | Brazil                              | NCT03438214                                           |
|                               | vancomycin + gentamicin         | yes           | ND           | IV          | NA               | 222 (estimated)    | recruiting         | Apr 2018–estimated Dec 2022   | Egypt                               | NCT03688659                                           |
| **Lipoglycopeptides**         |                               |               |              |             |                  |                    |                               |                     |                                    |                                                      |
|                               | dalbavancin                     | yes           | yes          | II          | standard of care | 2 enrolled (150 estimated) | stopped ‘due to business reasons’ recruiting | Jul 2019–estimated Dec 2019 | USA                                  | NCT03148756                                           |
|                               | oritavancin                     | yes           | yes          | IV          | NA               | 15 enrolled (estimated) | recruiting         | Jan 2014–Aug 2017       | USA                                  | NCT03761953                                           |
Table 3.  Continued

| Antibiotic class | Drug name     | MRSA coverage | Endocarditis | Trial phase | Drug comparator\(^a\) | Number of patients | Trial status | Trial period          | Countries | Clinical Trials.gov identifier and other reference |
|------------------|---------------|---------------|--------------|-------------|------------------------|--------------------|--------------|-----------------------|-----------|--------------------------------------------------|
|                  |               | yes           | yes          | III         | vancomycin, daptomycin, synthetic penicillin, cefazolin | 121 enrolled (248 estimated) | terminated (halted due to lack of statistical power; no safety concerns identified) | Dec 2014–Apr 2018 | USA | NCT0208063 |
| Telavancin       | telavancin    | yes           | no           | II          | —                     | 40 enrolled | completed | Mar 2011–Dec 2016 | USA | NCT01321879 |
| Oxazolidinones   | tedizolid phosphate | yes           | unspecified  | III         | linezolid             | 125 enrolled | completed | Nov 2013-Oct 2016 | Japan | NCT01967225 |
| Other antibiotics | fosfomycin + imipenem | yes           | yes          | IV          | vancomycin            | 50 enrolled | completed | Jun 2009–Apr 2015 | Spain | NCT00871104 |
| Early oral switch | trimethoprim/ sulfamethoxazole, clindamycin, linezolid, flucloxacillin, clavulanic, vancomycin, daptomycin, cefazolin | yes           | no           | III         | NA                    | 215 (estimated) | recruiting | Dec 2013–Oct 2019 | Germany | NCT01792804\(^b\) |
|                  | levofloxacin + rifampicin | yes           | yes          | III         | doxycillin, oxacillin, gentamicin, vancomycin, rifampicin\(^c\) | 324 (estimated) | recruiting | Feb 2016–estimated Oct 2021 | France | NCT02701608 |

From www.clinicaltrials.gov, accessed December 2019.
NA, not applicable; ND, not documented.
\(^a\)Not all the trials used a comparator drug (e.g. single-arm trial, pharmacokinetics trial, Phase IV trial).
\(^b\)Exclusion criteria: left-sided endocarditis.
\(^c\)Exclusion criteria: prosthetic endocarditis.
\(^d\)Conventional IV treatment of staphylococci in infective endocarditis following European guidelines.\(^e\)
percentages overlap with previous recommendations for a 10%–
20% threshold by IDSA and the American Thoracic Society for
pneumonia. Coverage of MRSA should also be opted for in the
presence of one or more risk factors, such as recent antibiotic use
or use of central venous catheters in settings where MRSA is preva-
lent, known nasal MRSA colonization or prior MRSA infection.40,41

Empirical therapy of SAB

Twelve β-lactams and one glycopeptide antibiotic are described as
empirical treatment options for SAB (Table 1). Ten antibiotics are
recommended by at least one guideline or have an indication
(from an EU NRA, EMA or FDA). Of these antibiotic options, eight
have only MSSA coverage (β-lactams, including cephalosporins
and carbapenems) and two also have MRSA coverage (vanco-
mycin and teicoplanin). Two more recent extended-spectrum β-
lactam antibiotics, ceftaroline and ceftobiprole, for which there is
no recommendation for the treatment of SAB to date, are dis-

cussed more in detail later.

Targeted therapy of SAB

Fifteen antibiotics are described as targeted treatment options for
SAB (Table 2). Seven antibiotics are recommended by at least one
guideline or have an indication (from an EU NRA, EMA or FDA). Of
these antibiotic options, three have only MSSA coverage (isoxazolyl
penicillins, nafcillin and cefazolin) and four also have MRSA cover-
age (vancomycin, teicoplanin, daptomycin and linezolid). Of note,
linezolid has no regulatory indication from the FDA or EMA for bac-
teraemia and is only recommended for uncomplicated bacteraemia
with confirmed MRSA by one guideline.29

Combination antibiotic therapy

There are two major rationales for combination therapy. The first
is broadening the antibiotic spectrum of the empirical therapy. The
second purpose of combinations is improving targeted therapy.
This case study does not address the options for combination ther-
apy. Recommendations for initial empirical combination treat-
ments for SAB are made in several guidelines.25,26,28,30 The available
evidence and clinical added value for combination therapy

Oral step-down antibiotic therapy

Advantages of (early) oral step-down include a reduced duration
of the need for intravenous lines, with their associated complica-
tions, a reduced need for prolonged hospitalization or professional
home care and improved patient comfort, e.g. quality of life.46,47
The appropriateness of oral therapy depends on both the oral bio-
availability of the antibiotic as well as patient factors.29 Currently,
there is only scarce clinical evidence to support an oral step-down
approach for the treatment of SAB or endocarditis. However, new
insights are likely on their way, with an ongoing trial assessing
whether early oral switch therapy is safe and effective for patients
with SAB (Table 3).48 Also, a recently approved project of the
Antibacterial Resistance Leadership Group (ARLG) is testing new
strategies for step-down therapy for MRSA bloodstream infections
( BSIs).49 A recent trial performed by Iversen et al.50 showed non-
iinferiority of oral switch compared with continued IV antibiotic

treatment of stable patients with left-sided endocarditis.

II. SAB: current status of and priorities for
antibiotic R&D

Our review of the current monotherapy treatment options for SAB
showed a limited arsenal, with only three drug classes (β-lactams,
glycopeptides and lipopeptides) for SAB, of which two have MRSA
coverage (glycopeptides and lipopeptides) (Table 2).

Output of the antibiotic pipeline in the past decade

The current antibiotic pipeline is not as productive and dynamic as
it once was. However, 18 new antibiotics received FDA approval51
and 12 received EMA approval in the past decade (2009–19). Of
these new antibiotics, none belonged to a new drug class or
involved a (likely) new mechanism of action. Of note, daptomycin
was the last discovery of a new class for the treatment of SAB, with
initial FDA approval in 2003.52

Eight of these new antibiotics could potentially be relevant to
the treatment of SAB: ceftaroline fosamil (Table 1); dalbavancin,
oritavancin, telavancin and tedizolid (Table 2); and delafloxacin,
omadacycline and lefamulin.

Ceftaroline fosamil was approved by the FDA in 2011 for the
treatment of acute bacterial skin and skin structure infections
(ABSSSIs) and community-acquired pneumonia (CAP).53 The
approved indication covers CAP caused by Streptococcus pneumoniae,
including cases with concurrent bacteraemia. Regardless,
ceftaroline fosamil remains of interest for the empirical treatment
of SAB because of its rapid clearance of MSSA and MRSA BSIs.54
New trials should provide further insights into its clinical relevance
for SAB therapy.

Some new targeted treatment options for MRSA bacteraemia
(dalbavancin, oritavancin and telavancin), approved for the treat-
ment of ABSSSIs, have been reviewed in Table 2. In addition, recent
trial activities involving these new agents are listed in Table 3.
Tedizolid is a fourth new agent that might have therapeutic poten-
tial for MRSA bacteraemia.55 However, so far no clinical trial has
been registered to evaluate tedizolid for the treatment of SAB
(Table 3).

A relatively new antibiotic with treatment potential for SAB
(both MSSA and MRSA coverage) is ceftobiprole (Table 2).
Ceftobiprole received refusals by the FDA in 2008 and consecutively
in 2010 by the EMA, based on lack of Good Clinical Practice com-
pliance of the conducted trials and reliability of the yielded
data.56,57 Currently, following re-submission with new clinical data
to national agencies in the EU, ceftobiprole is approved for sale in
13 European countries (e.g. Germany, Italy, the UK, France, Austria
and Switzerland) and several non-European countries for the
treatment of adult patients with CAP and hospital-acquired pneu-
monia (HAP), excluding ventilator-associated pneumonia (VAP).58
In 2017, the manufacturer announced two studies of ceftobiprole
for the treatment of SAB and ABSSSIs that would support regula-
tory approval for these indications.59

More recently, the FDA approved delafloxacin,59 a new fluoro-
quinolone for ABSSSIs, and omadacycline, a semisynthetic tetra-
cycline derivative, for ABSSSIs and CAP.60 The most recent FDA
approval was for lefamulin, a pleuromutilin antibiotic for CAP.61
Additional clinical trials are anticipated and should determine their clinical role for other indications. However, currently no trials for these new antibiotics are registered for SAB or endocarditis (Table 3).

The newly developed antibiotics ceftaroline, ceftobiprole, delafloxacin and omadacycline all have a very broad spectrum. Regardless of their activity, this feature makes them less suitable for targeted SAB treatment.

**Current SAB trials**

Ongoing and recently (<5 years) completed but not yet published clinical trials for SAB are shown in Table 3. Interestingly, several trials are being conducted with young infants (e.g. NCT04044703 and NCT02790996) and children (e.g. NCT03688659 and NCT03643952) (Table 3). It is expected that these trials should yield improved dosing regimens for these specific patient populations. Another observation is that 7 trials out of 26 have ended prematurely over the past few years (Table 3). The reasons provided for early termination of the SAB trials included recruitment-related issues (n = 4), ‘business reasons’ (n = 1), lack of statistical power (n = 1) and following a safety recommendation (n = 1). Exploring the barriers (e.g. financial, recruitment logistics, ethical and trial design related) that led to the discontinuation of antibiotic trials would be valuable to help work towards facilitating antibiotic R&D. Results of recently completed or ongoing trials should be used to inform clinical practice guidelines in a timely manner.

**What should guide R&D priorities for antibiotics against S. aureus?**

The driving forces of antibiotic R&D should not be market based but rather based on unmet public health needs. SAB is a life-threatening condition. Even in cases with adequate source control, patients treated with available antibiotics are having positive blood cultures for several days. Therefore, there is a need for superior antibiotics (in terms of effectiveness and safety) for treating SAB, regardless of resistance to available antibiotics. Previous developments have mainly targeted resistance (MRSA), which led to expanding the number of drugs that target MRSA from classes that show no superior activity against MSSA. The added value of recently developed drugs can be considered related mainly to some minor improvement in aspects such as ease of use within known antibiotics classes, e.g. once-only dose oritavancin or the oral formulation of tedizolid.

Incontestable positive developments are the increased awareness of the urgency of the antimicrobial resistance issue as well as the ‘high priority’ label for MRSA and vancomycin-resistant S. aureus from the WHO on its priority pathogen list (PPL) for antibiotic-resistant bacteria.62 In addition, MSSA infections remain an important burden. Currently, it is unclear whether MRSA bacteraemia is more dangerous than infections caused by MSSA.63-65 Thus, there is a need for new potent drugs for both MSSA and MRSA bacteraemia. Decreases in MRSA colonization and/or infections can be achieved through implementing antibiotic stewardship and infection control policies and need more consideration as well.

In conclusion, progress has been made to address the coverage of MRSA as the antibiotic pipeline has yielded multiple new regulatory approvals; we call for awareness of the potentially overshadowed severe MSSA infections that do not require a broader spectrum but more potent molecules for treatment.

**What could benefit the R&D strategy for antibiotics against SAB?**

A few potential facilitators of SAB R&D that should speed up the process of drug development and lead to more efficient resource allocation are addressed here.

**Push incentives**

The effective stimulation of antibiotic R&D calls for both push incentives (those designed to support R&D directly) and pull incentives (those designed to reward successful outcomes from R&D).66 The value of two push incentives, as proposed by the DRIVE-AB consortium, are discussed here.

- Pipeline coordinators (i.e. governmental or non-profit organizations) act as monitors of the progress, or lack thereof, of the antibiotic pipeline.67 By closely following new developments, they can steer R&D projects to address potential gaps (assessed through unmet public health priorities and the PPL) and thereby ideally avoiding duplication. In addition, they may finance development activities or themselves advance specific programmes. Examples of pipeline coordinators include Global Antibiotic Research and Development Partnership (GARDP), BARDA (Biomedical Advanced Research and Development Authority) and CARB-X.

- A grant framework has been proposed as a second push incentive to stimulate R&D. This framework consists of four financial incentives to support early- and mid-stage R&D, complemented by two highly focused incentives: priority and clinical development grants.68 Here again, the focus is to steer new development towards unmet public health needs in antimicrobial R&D.

**Regulatory aspects of SAB**

Registration for the indication of bacteraemia is not common as it needs to rely on prior demonstration of efficacy at the infection source covering different body sites. A clear indication pathway defined by the regulatory agencies is expected to facilitate regulatory approval of new antibiotics. While the FDA recognizes SAB as a unique severe infection, regardless of the presence of an infection source, which is often not found, the EMA currently does not consider that an indication for treatment of bacteraemia can, in principle, be substantiated by a trial that enrols patients with bacteraemia due to a specific pathogen, regardless of the primary focus of infection.69 However, it can be considered that the FDA position specifically for SAB has its rationale and therefore sponsors are encouraged to still discuss the options with the EMA.

**Marketing incentives**

An example of a marketing incentive to stimulate antibiotic R&D is the status of Qualified Infectious Disease Product (QIDP) offered by the FDA since the Generating Antibiotic Incentives Now Act (GAIN) from 2012. This status promises manufacturers an accelerated review of the drug application and five additional years of...
marketing exclusivity. Unfortunately, GAIN has not set stringent requirements to ensure that qualifying antibiotics address unmet public health need.\textsuperscript{70} Dalbavancin, tedizolid and oritavancin are novel antibiotics that benefited from these marketing incentives, even if not having a major impact on unmet needs. More promising incentives that are expected to improve the profitability of the market are subscription-based payment models that will soon be piloted in Sweden and the UK.\textsuperscript{71,72} These models will test the concept of delinkage, i.e. paying to maintain access to an essential antibiotic rather than strictly reimbursing unit sales.

**Clinical trial designs**

Regulatory agencies can assist sponsors in the clinical development of new antibacterial drugs by developing guidance documents on innovative clinical trial designs. In 2013, the EMA issued a new guidance document that described examples of streamlined clinical programmes that could allow granting approval for pathogen-specific indications in areas of unmet medical needs.\textsuperscript{73} In 2017, the FDA issued guidance on ‘Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases’.\textsuperscript{74} In addition, Holland et al.\textsuperscript{75} recently addressed key features to consider in designing an SAB trial for the different stakeholders, including investigators, sponsors and regulators. An example of an innovative trial design is the *Staphylococcus aureus* Network Adaptive Platform Trial, which aims to optimize management of SAB via the implementation of adaptive trials, in which design modifications (e.g. response-adaptive randomization) are made based on the results of interim analyses. Such trials are expected to help allocate resources more efficiently without lowering scientific and regulatory standards.\textsuperscript{76,77}

### III. SAB: responsible antibiotic-use strategies

A selection of quality indicators for responsible antibiotic use considered particularly pertinent to measuring responsible antibiotic use for SAB are addressed.

**Resistance surveillance**

The European Antimicrobial Resistance Surveillance Network (EARS-Net) provides insights into the evolving epidemiology of MRSA and largely relies on data input from national focal points of EU/European Economic Area member states. Therefore, surveillance practice at the hospital level (IQI-41) is essential to inform upstream national focus points. Compliance with this IQI is key to monitor the epidemiology of MRSA and subsequently guide the selection of optimal antibiotic therapy for SAB.

**Access/availability**

A selection of both empirical and targeted antibiotic drugs for SAB should be part of the hospital formulary and present at the hospital to facilitate optimal patient care. (IQI-1)

**Microbiological diagnostic**

Blood cultures are needed to perform antibiotic susceptibility testing (AST), which in turn will allow de-escalation from empirical to targeted therapy of SAB. (IQI-31). Harmonization of AST methods should be pursued. EUCAST provides guidelines for harmonization of clinical breakpoints to guide AST reporting. In addition, rapid molecular tests such as the T2Bacteria magnetic resonance assay can be performed to identify MRSA and steer treatment choice for SAB.\textsuperscript{78}

**Expertise and resources**

Over the past decades, studies performed around the world have repeatedly shown that a bedside consultation from infectious disease specialists largely benefits patient outcomes (IQI-27).

**Antibacterial activity and spectrum**

Depending on the local epidemiology, empirical therapy should cover MRSA in patients with risk factors (IQI-3). In order to reduce broad-spectrum antibiotic selection pressure on the commensal microbiome, the antibiotic therapy should be changed to be pathogen directed as soon as the results of the microbiological diagnostic become available, i.e. de-escalation of antibiotic therapy (IQI-5 and IQI-7).

Furthermore, a useful tool to stimulate the use of narrow-spectrum antibiotics is the selective reporting of antibiotic susceptibilities by the microbiology laboratory. Indeed, limiting the numbers of effective formulary drugs shown in the antibiotic susceptibility reports (e.g. showing only very few treatment options with a narrow activity spectrum) should improve the quality of antibiotic prescribing (IQI-4).

**Evidence-based guidelines**

Only a few authoritative (i.e. endorsed by professional societies) English written clinical practice guidelines addressing BSI are available. This lack of guidelines for SAB may result in variation in clinical practice as well as in deviations from published evidence.\textsuperscript{79} The few available evidence-based and graded guidelines available in English for SAB should be used in national (and possibly even more local) guideline developments based on geographical epidemiology (IQI-18). The ESCMID/IDSA guideline on SAB that is currently under preparation will contribute to improved evidence-based clinical practice as well as steer the development of more local guidelines within the European region.

**Toxicity**

Antibiotics are a common cause of drug allergies. To avoid unnecessary complications in patients with SAB, allergies to penicillins, cephalosporins and glycopeptides should be taken into account (IQI-47).

**Timing**

In view of the severity of SAB, timely administration of initial empirical therapy is required. Following the recommendation of the SWAB guideline on sepsis, antibiotics should be started as soon as possible, preferably within the first hour of diagnosis for patients with severe sepsis and septic shock (IQI-45).\textsuperscript{28}
Conclusions

Case study research allows for the study of complex issues in real-world settings. Consultation of different information sources and involvement of researchers with various backgrounds should limit verification bias. While much research attention is given to (multi-)resistant Gram-negative bacteria, it is important not to underestimate the burden of Gram-positive species. With the ageing of the world population, the burden of SAB is expected to expand further. Another important development is the increased incidence of MSSA bacteraemia independently from the epidemiological evolution of MRSA bacteraemia. The analysis of the antibiotic pipeline and ongoing clinical trials revealed that several new antibiotics with S. aureus coverage (including MRSA) were developed in the past decade (2009–19). However, none belonged to a new antibiotic class or had superior effectiveness and their added clinical value for SAB remains to be proven. Clinical trials are needed to fill current gaps and to inform best practices for the clinical management of SAB. Awareness of the limited antibiotic arsenal, together with incentives, is needed to steer the R&D landscape towards the development of novel and effective drugs for SAB. In the meantime, responsible antibiotic use guided by the use of quality indicators should preserve the effectiveness of currently available antibiotics for treating SAB.

Transparency declarations

None to declare.

Author contributions

This case study was conceived during the DRIVE-AB project. A.A.M. and I.C.G designed and drafted the manuscript. A.A.M. performed the data extraction. E.T., C.A. and M.C. contributed to the finalization of the manuscript. All authors have critically reviewed and approved the final manuscript.

Disclaimer

The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or by any committee or working party.

Supplementary data

The Reviewer report is available as Supplementary data at JAC-AMR Online.

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