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

Annelie A. Monnier [1,2], Evelina Tacconelli[3], Christine Årdal[4], Marco Cavaleri[5] and Inge C. Gyssens [1,2]*

[1]*Department of Internal Medicine and Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands;* [2]*Faculty of Medicine, Research group of Immunology and Biochemistry, Hasselt University, Hasselt, Belgium;* [3]*Infectious Diseases, Department of Diagnostic and Public Health, University of Verona, Verona, Italy;* [4]*Norwegian Institute of Public Health, Antimicrobial Resistance Centre, Oslo, Norway;* [5]*European Medicines Agency, Amsterdam, The Netherlands*

*Corresponding author. E-mail: inge.gyssens@radboudumc.nl

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] quinolones[11] 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.[14] The quantity of hospital antibiotic use has previously been associated with the frequency of MRSA acquisition.[15] Over recent years, remarkable decreases in MRSA rates were observed following infection control and stewardship activities in France and the UK.[16]

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.[17] 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 and illustrated).[18] 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.[19] When no clinical breakpoint was described in the EUCAST database, the CLSI library was searched.[20]
- 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.[21] *Kucers' The Use of Antibiotics* is considered a leading source of information in the field of infectious diseases.[22]
- 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).[23]
  - Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection by IDSA (2009).[24]
  - 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).[25]
  - Guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC) (2015).[26]
  - *Staphylococcus aureus* Bacteraemia (SAB) Management Clinical Guideline developed by the South Australian expert Advisory Group on Antimicrobial Resistance (SAAGAR) (2019).[27]
  - Antibacterial therapy of adult patients with sepsis guideline by the Dutch Working Party on Antibiotic Policy (SWAB) (2010) (revisions have been announced).[28]
  - Guidelines for the prophylaxis and treatment of MRSA infections in the UK (2009).[29]
  - UpToDate chapter 'Clinical approach to *Staphylococcus aureus* bacteremia in adults' by Holland & Fowler (last updated in July 2019).[30]
- 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), SPCs 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, septicaemia, 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).[21]
- The level of evidence of the recommendations is not provided. However, the UpToDate chapter on SAB[30] 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.[31]
- 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 ($\leq$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.[32] 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[a]	MSSA		MRSA		References
				bacteraemia	endocarditis[b]	bacteraemia	endocarditis[b]	
β-Lactams								
Cephalosporins (2nd generation)	cefuroxime	≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin)[19]	mentioned in Kucers'	no	no	no	no	21
			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 (3rd generation)	cefotaxime	≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin)[19]	mentioned in Kucers'	no	yes	no	no	21
			recommended by guideline(s)	yes	yes	no	no	26,28
			EU NRA indication[c] (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)[19]	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
	ceftazidime	—	mentioned in Kucers'	yes	no	no	no	21
			recommended by guideline(s)	no	no	no	no	
			EMA harmonized indication	no	no	no	no	86
			FDA indication	yes	no	no	no	87
Cephalosporins (4th generation)	cefepime	≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin)[19]	mentioned in Kucers'	yes	no	no	no	21
			recommended by guideline(s)	yes	yes	no	no	25
			EU NRA indication[c] (e.g. UK)	yes	no	no	no	88
			FDA indication	yes	no	no	no	89
Cephalosporins (5th generation)	ceftaroline	≤1 mg/L (S); >2 mg/L (R)[19]	mentioned in Kucers'	no	no	no	no	21
			recommended by guideline(s)	no	no	no	no	
			EMA harmonized indication	no	no	no	no	90
			FDA indication	no	no	no	no	53
	ceftobiprole	≤2 mg/L (S); >2 mg/L (R)[19]	mentioned in Kucers'	no	no	no	no	21
			recommended by guideline(s)	no	no	no	no	
			EU NRA indication[c,d] (e.g. UK)	no	no	no	no	91
			FDA indication	not available in the USA				
β-Lactam/β-lactamase inhibitor combinations	piperacillin/tazobactam	≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin)[19]	mentioned in Kucers'	yes	no	no	no	21
			recommended by guideline(s)	yes	no	no	no	25,28
			EMA harmonized indication	yes	no	no	no	92
			FDA indication	yes	yes	no	no	93
Carbapenems	imipenem/cilastatin	≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin)[19]	mentioned in Kucers'	yes	yes	no	no	21
			recommended by guideline(s)	yes	yes	no	no	28
			EMA harmonized indication	yes	no	no	no	94
			FDA indication	yes	yes	no	no	95
	meropenem	≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin)[19]	mentioned in Kucers'	yes	yes	no	no	21
			recommended by guideline(s)	yes	yes	no	no	28
			EMA harmonized indication	yes	no	no	no	96
			FDA indication	yes	no	no	no	97

Continued

Table 1. *Continued*

Antibiotic class	Antibiotic agent	Clinical breakpoint for *S. aureus* (MIC)	Source[a]	MSSA		MRSA			References
				bacteraemia	endocarditis[b]	bacteraemia	endocarditis[b]		
Glycopeptides									
	vancomycin	≤2 mg/L (S); >2 mg/L (R)[19]	mentioned in Kucers'	yes	yes	yes	yes		21
			recommended by guideline(s)	yes	yes	yes	yes		23,24,26,27,29,30
			EMA harmonized indication	yes	yes	yes	yes		98
			FDA indication	yes	yes	yes	yes		99
	teicoplanin	≤2 mg/L (S); >2 mg/L (R)[19]	mentioned in Kucers'	yes	yes	yes	yes		21
			recommended by guideline(s)	yes	yes	yes	no		24,29,30
			EMA harmonized indication	yes	yes	yes	yes		100
			FDA indication	not available in the USA					

S, susceptible; R, resistant; –, missing data.
[a]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.
[b]No distinction was made between prosthetic and native valve endocarditis or between right- and left-sided endocarditis.
[c]No harmonized EMA indication.
[d]Refused authorization for use in the EU by the EMA: https://www.ema.europa.eu/en/medicines/human/EPAR/zeftera-previously-zevtera.

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] These

Table 2. Options for targeted antibiotic therapy of SAB and *S. aureus* endocarditis

Antibiotic class	Antibiotic agent	Clinical breakpoint for *S. aureus* (MIC)	Source[a]	MSSA		MRSA		References
				bacteraemia	endocarditis[b]	bacteraemia	endocarditis[b]	
β-Lactams								
Penicillins	isoxazolyl penicillins, e.g. oxacillin, cloxacillin, dicloxacillin, flucloxacillin	≤2 mg/L (S); >2 mg/L (R) (MIC of oxacillin)[19]	mentioned in Kucers'	yes	yes	no	no	21
			recommended by guideline(s)	yes	yes	no	no	24,26–28,30
			EU NRA indication[c] (e.g. The Netherlands)	yes	yes	no	no	101
			FDA indication	all susceptible infections[d]	all susceptible infections[d]	no	no	102
	nafcillin	≤2 mg/L (S); >4 mg/L (R) (inferred from MIC of oxacillin)[20]	mentioned in Kucers'	yes	yes	no	no	21
			recommended by guideline(s)	yes	yes	no	no	24,30
			EU NRA/EMA harmonized indication	not available in Europe				
			FDA indication	all susceptible infections[d]	all susceptible infections[d]	no	no	103
Cephalosporins (1st generation)	cefalotin	—	mentioned in Kucers'	yes	yes	no	no	21
			recommended by guideline(s)	no	no	no	no	
			EU NRA indication[c]	—		—		
			FDA indication	not available in the USA				
	cefazolin	≤4 mg/L (S); >4 mg/L (R) (inferred from MIC of cefoxitin)[19]	mentioned in Kucers'	yes	no	no	no	21
			recommended by guideline(s)	yes	no	no	no	24,26,27,30
			EU NRA indication[c] (e.g. Belgium)	yes	yes	no	no	104
			FDA indication	yes	yes	no	no	105
Lipo(glyco)peptides								
Glycopeptides	vancomycin	≤2 mg/L (S); >2 mg/L (R)[19]	mentioned in Kucers'	yes	yes	yes	yes	21
			recommended by guideline(s)	yes	yes	yes	yes	23,24,26,27,29,30
			EMA harmonized indication	yes	yes	yes	yes	98
			FDA indication	yes	yes	yes	yes	99
	teicoplanin	≤2 mg/L (S); >2 mg/L (R)[19]	mentioned in Kucers'	yes	yes	yes	yes	21
			recommended by guideline(s)	yes	yes	yes	no	24,29,30
			EMA harmonized indication	yes	yes	yes	yes	100
			FDA indication	not available in the USA				
Lipoglycopeptides	oritavancin	≤0.125 mg/L (S); >0.125 mg/L (R)[19]	mentioned in Kucers'	yes	no	no	no	21
			recommended by guideline(s)	no	no	no	no	
			EMA harmonized indication	no	no	no	no	106
			FDA indication	no	no	no	no	107
	dalbavancin	≤0.125 mg/L (S); >0.125 mg/L (R)[19]	mentioned in Kucers'	yes	no	yes	no	21
			recommended by guideline(s)	no	no	no	no	
			EMA harmonized indication	no	no	no	no	108
			FDA indication	no	no	no	no	109

Continued

Table 2. *Continued*

Antibiotic class	Antibiotic agent	Clinical breakpoint for *S. aureus* (MIC)	Source[a]	MSSA		MRSA		References
				bacteraemia	endocarditis[b]	bacteraemia	endocarditis[b]	
	telavancin	≤0.125 mg/L (S) (MIC for MRSA)[19]	mentioned in Kucers'	yes	yes	yes	yes	21
			recommended by guideline(s)	no	no	no	no	
			EU NRA/EMA harmonized indication	not available in Europe				
			FDA indication	no	no	no	no	110
Lipopeptides								
	daptomycin	≤1 mg/L (S); >1 mg/L (R)[19]	mentioned in Kucers'	yes	no	yes	no	21
			recommended by guideline(s)	yes	no	yes	yes	23,30
			EMA harmonized indication	yes	yes	yes	yes	111
			FDA indication	yes	yes	yes	yes	52
Other antibiotics								
Oxazolidinones	linezolid	≤4 mg/L (S); >4 mg/L (R)[19]	mentioned in Kucers'	yes	no	yes	yes	21
			recommended by guideline(s)	no	no	yes	yes	29
			EU NRA indication[c] (e.g. The Netherlands)	no	no	no	no	112
			FDA indication	no	no	no	no	113
	tedizolid	≤0.5 mg/L (S); >0.5 mg/L (R)[19]	mentioned in Kucers'	no	no	no	no	21
			recommended by guideline(s)	no	no	no	no	
			EMA harmonized indication	no	no	no	no	114
			FDA indication	no	no	no	no	115
Macrolide-lincosamide-streptogramins	quinupristin/dalfopristin	≤1 mg/L (S); >2 mg/L (R)[19]	mentioned in Kucers'	yes	no	yes	no	21
			recommended by guideline(s)	no	no	no	no	
			EU NRA indication[c]	–		–		
			FDA indication	no	no	no	no	116
Lincosamides	clindamycin	≤0.25 mg/L (S); >0.5 mg/L (R)[19]	mentioned in Kucers'	yes	yes	no	no	21
			recommended by guideline(s)	no	no	no	no	
			EU NRA (e.g. The Netherlands)[c]	no	no	no	no	117
			FDA indication	no	no	no	no	118
Combination of dihydrofolate reductase inhibitor and a sulphonamide	trimethoprim/sulfamethoxazole (co-trimoxazole)	≤2 mg/L (S); >4 mg/L (R)[19]	mentioned in Kucers'	yes	yes	no	no	21
			recommended by guideline(s)	no	no	no	no	
			EU NRA indication[c] (e.g. UK)	no	no	no	no	119
			FDA indication	no	no	no	no	120

S, susceptible; R, resistant; –, missing data.
[a]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 searches guidelines. EMA/EU NRA indication or FDA indication: 'yes' means regulatory indication available; 'no' means no regulatory indication available.
[b]No distinction was made between prosthetic and native valve endocarditis or between right- and left-sided endocarditis.
[c]No harmonized EMA indication.
[d]Specific clinical indications (e.g. bacteraemia, sepsis, severe infections) were not documented.

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 comparator[a]	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	NCT03248063[121]
	cefotaxime	no	ND	IV	NA	60 enrolled	completed	Nov 2015–Sept 2016	The Netherlands	NCT02560207
	ceftaroline fosamil + ampicillin + optional aminoglycoside	no	ND	II	NA	11 participants	terminated (due to slow enrolment)	Aug 2015–Dec 2017	USA	NCT02424734
	ceftaroline fosamil	yes	yes[b]	IV	NA	56 enrolled	completed	Jan 2013–July 2014	USA	NCT01701219
	ceftobiprole medocaril	yes	yes[b]	III	daptomycin	390 (estimated)	recruiting	Jun 2018–*estimated* Aug 2021	USA, Argentina, Brazil, Bulgaria, Georgia, Germany, Israel, Italy, Russia, Spain, Ukraine	NCT03138733[122]
β-Lactams, penicillins	cloxacillin + levofloxacin	no	no	III	cloxacillin	1 enrolled (154 estimated)	terminated (not participants inclusion)	May 2013–Nov 2014	Spain	NCT01875263
	cloxacillin + fosfomycin	no	yes[c]	IV	cloxacillin	366 (estimated)	not yet recruiting	May 2019–*estimated* Aug 2021	Spain	NCT03959345
Glycopeptides	daptomycin	yes	no	II	NA	20 (estimated)	recruiting	Dec 2018 *estimated* May 2021	Japan	NCT03643952
	daptomycin	yes	ND	II	vancomycin	14 enrolled (50 estimated)	terminated (slow accrual of participants)	Jan 2014–Dec 2015	Singapore	NCT01975662
	daptomycin	yes	ND	III	vancomycin	10 enrolled (332 estimated)	terminated (lack of inclusion)	May 2012–July 2014	France	NCT01515020
	daptomycin + fosfomycin	yes	yes	III	daptomycin	167 enrolled	completed	Dec 2013–Jan 2018	Spain	NCT01898338[123]
	daptomycin	yes	yes	III	NA	not provided	completed	March 2014–Sept 2015	France	NCT02142075
	vancomycin or daptomycin	yes	yes	III	vancomycin or daptomycin + β-lactam	358 enrolled (440 estimated)	terminated (recommendation of the Data Safety Monitoring Committee)	Aug 2015–Oct 2018	Australia, New Zealand, Singapore, Israel	NCT02365493[124]
	daptomycin + β-lactam	yes	yes	IV	placebo + β-lactam	102 (estimated)	active, not recruiting	Nov 2016–Sept 2019	Canada	NCT02972983[125]
	vancomycin	ND	yes	II	NA	300 (estimated)	recruiting	Feb 2017–*estimated* Feb 2019	Estonia, Greece, Italy, Spain, UK	NCT02790996
	vancomycin	yes	ND	IV	NA	28 (estimated)	recruiting	Aug 2019–*estimated* Aug 2020	Australia	NCT04044703
	vancomycin	yes	ND	IV	NA	222 (estimated)	recruiting	Apr 2018–*estimated* Dec 2022	Brazil	NCT03438214
	vancomycin + gentamicin	yes	yes	ND	NA	30 (estimated)	not yet recruiting	Jan 2019–*estimated* Jan 2021	Egypt	NCT03688659
Lipoglycopeptides	dalbavancin	yes	yes	II	standard of care	2 enrolled (150 estimated)	stopped 'due to business reasons'	May 2017–Aug 2017	USA	NCT03148756
	oritavancin	yes	yes	IV	NA	15 estimated	recruiting	Jul 2019–*estimated* Dec 2019	USA	NCT03761953

Continued

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
	telavancin	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	NCT02208063
	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, cloxacillin, vancomycin, daptomycin, cefazolin	yes	no	III	NA	215 (estimated)	recruiting	Dec 2013–Oct 2019	Germany	NCT01792804[48]
	levofloxacin + rifampicin	yes	yes	III	cloxacillin, oxacillin, gentamicin, vancomycin, rifampicin[d]	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.[26]

percentages overlap with previous recommendations for a 10%–20% threshold by IDSA and the American Thoracic Society for pneumonia.[39] 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 prevalent, 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 (vancomycin 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 discussed 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 coverage (vancomycin, teicoplanin, daptomycin and linezolid). Of note, linezolid has no regulatory indication from the FDA or EMA for bacteraemia and is only recommended for uncomplicated bacteraemia with confirmed MRSA by one guideline.[29]

Combination antibiotic therapy

There are two major rationales for combination therapies. 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 therapy. Recommendations for initial empirical combination treatments for SAB are made in several guidelines.[25,26,28,30] The available evidence and clinical added value for combination therapies for targeted SAB are reviewed elsewhere.[13,42–45]

Oral step-down antibiotic therapy

Advantages of (early) oral step-down include a reduced duration of the need for intravascular lines, with their associated complications, 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 bioavailability 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-inferiority 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 approval[51] 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 treatment 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 potential 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 compliance 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 pneumonia (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 regulatory approval for these indications.[58]

More recently, the FDA approved delafloxacin,[59] a new fluoroquinolone for ABSSSIs, and omadacycline, a semisynthetic tetracycline 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.[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.[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.[73] In 2017, the FDA issued guidance on 'Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases'.[74] In addition, Holland *et al.*[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.[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.[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.[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).[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 reflecting the position of the European Medicines Agency or one of its committees or working parties.

Supplementary data

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

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