



## Hot Topic

## An update on *Staphylococcus aureus* infective endocarditis from the International Society of Antimicrobial Chemotherapy (ISAC)



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### 1. Introduction

*Staphylococcus aureus* remains one of the dominant pathogens in infective endocarditis (IE) causing 25–30% of all cases [1,2] including healthcare-associated IE, which comprises ca. 30% of IE [3]. Most IE cases involve the aortic or mitral valves, with tricuspid valve involvement accounting for <10% of cases, often in association with injection drug use [1,4,5]. Prosthetic valve IE (PVE) and IE related to cardiovascular implantable electronic devices account for approximately one-third of all cases and are most commonly caused by coagulase-negative staphylococci [1,5].

*Staphylococcus aureus* is equipped with microbial surface components recognising adhesive matrix molecules (MSCRAMMs), which are well-defined adhesion molecules on the bacterial surface able to promote adherence to cardiac endothelial cells. *Staphy-*

*lococcus aureus* can multiply and persist within cardiac cells, further promoting vegetation growth via activation of cytokines and thrombotic pathways [6]. Moreover, in *S. aureus* PVE, surface biofilm formation complicates eradication of the infection. *Staphylococcus aureus* has been identified as an independent predictor of poor outcome in IE [7,8]. In this review, an expert group from the International Society of Antimicrobial Chemotherapy (ISAC) will present recent data, evidence and personal experience on *S. aureus* IE.

### 2. Recent evidence related to the diagnosis of *Staphylococcus aureus* infective endocarditis

Despite advances in medical provision and interdisciplinary approaches to management, diagnostic latency of *S. aureus* IE remains a challenge. Both for native valve IE and PVE diagnosis is still based on major and minor modified Duke criteria [7], entailing microbiology and other laboratory results, echocardiography, and clinical

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appearances or features. Liesman et al. recently published a review on laboratory diagnostics in IE, including the importance of culture and histological examination (if a microbial diagnosis has not been established at the time of surgery, including intraoperative valvular tissue) and molecular techniques [8]. Still, in clinically suspected cases, traditional blood cultures (at least three sets, properly filled, ideally taken when the patient is febrile and/or prior to commencing antimicrobial therapy) remain central to the diagnosis in most cases [4,9]. However, because the time required for blood culture results may delay diagnosis, novel molecular techniques for pathogen detection, identification and antimicrobial susceptibility testing may be useful in the future [10].

*Staphylococcus aureus* bacteraemia (SAB) in patients with prosthetic valves is a strong predictor of PVE [11]. The British Society for Antimicrobial Chemotherapy (BSAC) recommends echocardiography in all patients with SAB, ideally within the first week of treatment or within 24 h if there is other evidence to suggest IE [9]. Transthoracic echocardiography (TTE) should be primarily performed in each patient with clinical suspicion of IE; the current European guidelines recommend transoesophageal echocardiography (TOE or TEE) in all patients with negative or non-conclusive TTE findings. An oscillating mass compatible with vegetation is not well visualised by TTE in PVE, with a relatively significant lower sensitivity than in native valve IE [12]. If a prosthetic heart valve or an intracardiac device, e.g. pacemaker, is present, TOE should be performed as first choice. The only situation in which TTE is equal to TOE with respect to sensitivity of IE detection is right heart IE in patients with a good acoustic window [4]. In addition, novel imaging technologies such as white blood cell single-photon emission computed tomography/computed tomography (SPECT/CT) and <sup>18</sup>F-FDG positron emission tomography (PET)/CT are generally recommended for complex clinical situations [4,13] but are not widely used for a variety of reasons including cost, availability and the experience of interpreting cardiologists.

### 3. Recent evidence related to the treatment of *Staphylococcus aureus* infective endocarditis

Guidelines for the treatment of IE were updated in 2015, both in the USA [14] and Europe [4]. Treatment of coagulase-negative staphylococcal IE follows exactly the same principles, based on drug susceptibility testing, as for *S. aureus*. The first-line backbone treatments are quite similar in both guidelines: intravenous (i.v.) antistaphylococcal penicillin or cefazolin for methicillin-susceptible staphylococcal IE, and i.v. vancomycin or daptomycin for methicillin-resistant staphylococcal IE. Likewise, there is a general agreement that we should not systematically use aminoglycosides in the treatment of native valve staphylococcal IE, regardless of the susceptibility to methicillin, for the following reasons: (i) the added value of aminoglycosides has never been proven in staphylococcal IE, even when evaluated in randomised studies [15]; and (ii) conversely, recent data demonstrated their deleterious effect even when administered only for a few days [16].

For staphylococcal PVE, both guidelines recommend gentamicin during the first 2 weeks of treatment: two or three injections/day in the USA [14] and one or two injections/day in Europe [4], in association with the backbone regimen (see above), and rifampicin, which must be prolonged for  $\geq 6$  weeks. Of note, daptomycin is not supported for PVE by current guidelines despite available relevant data and experience with this agent [14]. Although the systematic use of gentamicin and rifampicin in staphylococcal PVE is based on a low level of evidence, it could be justified by the requirement for highly bactericidal regimens to eradicate staphylococci on biofilms, taking into account that: (i) rifampicin use has been associated with a lower risk of relapses in other foreign device-related staphylococcal infections (e.g. prosthetic joint infections) [17]; and

(ii) the early bactericidal effect of aminoglycosides may protect from the emergence of rifampicin-resistant isolates, especially during the first days of treatment when the bacterial inoculum is large and the effect of the backbone regimen is not fully established (especially with slowly bactericidal agents such as vancomycin).

According to large epidemiological studies, methicillin-resistant *S. aureus* (MRSA) is more prevalent in PVE than in native valve IE. Early PVE (<1 year from valve implantation) is more often caused by hospital-acquired MRSA strains, some with reduced susceptibility to vancomycin. Late PVE demonstrates a microbiological profile similar to community-acquired native IE [14,18]. Moreover, complications such as valve abscess and embolisation are more frequent in PVE. Patients with *S. aureus* PVE require individualised assessment for valve surgery [14,18].

The presence of a prosthetic valve is a major predictor of mortality in *S. aureus* IE. Valve dehiscence, re-operations, and in-hospital or 6-month mortality is further increased to 30–50% in patients with MRSA PVE. This difference may also reflect a higher Charlson comorbidity index score and older age in patients with PVE compared with native valve IE [18].

European guidelines promoted as an alternative the high-dose combination of trimethoprim/sulfamethoxazole (TMP/SMX) (960 mg/day of TMP and 4800 mg/day of SMX) for 6 weeks, in combination with clindamycin (1800 mg/day) for 1 week, in the treatment of native valve *S. aureus* IE, regardless of methicillin resistance. However, this should be discouraged in light of the two large randomised trials showing that TMP/SMX is inferior to vancomycin in the treatment of SAB [19,20]. Likewise, European guidelines suggested cefotaxime as an alternative to cefazolin in penicillin-allergic patients with methicillin-susceptible staphylococcal IE, but this is probably suboptimal in light of different in vitro, experimental and cohort studies suggesting that third-generation cephalosporins are significantly less active than cefazolin for methicillin-susceptible staphylococci [21].

Despite these limitations, the updates of these guidelines are useful, enabling the optimisation of staphylococcal IE treatment.

### 4. Timing of valvular surgery for *Staphylococcus aureus* infective endocarditis

The optimal time for valvular surgery in patients with *S. aureus* IE is still unclear [4]. *Staphylococcus aureus* is the most common pathogen in right-sided valve IE (RVIE), but surgical treatment is required much less often (5–16%) than for left-sided valve IE (LVIE), which generally could reach 50%. Cardiac surgery in RVIE is most often for prosthetic tricuspid valve *S. aureus* IE. For a damaged tricuspid valve in native IE, early valve surgery (EVS) within 7 days with valve repair is preferable to valve replacement, especially in intravenous drug users [22].

Indications for surgery in LVIE include heart failure, paravalvular complications, persistent infection and *S. aureus* PVE, the latter with level of evidence IIaC [4]. *Staphylococcus aureus* PVE is often complicated (stroke, valve dehiscence) and might require EVS; however, candidates for and timing of surgery are not well defined. In a large international cohort of IE, *S. aureus* IE patients were treated more conservatively than non-*S. aureus* IE (odds ratio = 0.5, 95% confidence interval 0.37–0.66) [23]. Mortality was significantly lower in patients treated both with surgery and antibiotics compared with those treated only medically (33.7% vs. 59%;  $P = 0.001$ ). However, a propensity score analysis, adjusted for survival bias, failed to demonstrate an overall significant survival benefit at 1 year of EVS in *S. aureus* PVE [23]. These results corroborate a previous study of *S. aureus* PVE in which >50% of the patients, especially younger patients without systemic IE complications, were successfully treated only with antibiotics [24].

Regarding the impact of MRSA on prognosis and outcome of surgery, data are limited. In one study, all patients with methicillin-susceptible *S. aureus* (MSSA) IE without indications for surgery survived, but one-third of patients with MSSA IE who were operated upon indication died. Most MRSA patients were treated only with antibiotics (i.e. without surgery), and 6-month mortality was higher among MRSA than MSSA IE cases [25].

In conclusion, the optimal timing of surgery in *S. aureus* IE should be individualised, taking into account the patient's health status, IE complications, LVIE, PVE and evolution of the disease under antimicrobial therapy. Overall, surgery is recommended if the benefits outweigh the operative risk. A tailored approach regarding timing of surgery, type of valve and surgical techniques is recommended [4].

### 5. New antimicrobials and their role in methicillin-resistant *Staphylococcus aureus* infective endocarditis

Several new antimicrobials active against *S. aureus* from a variety of drug classes have been approved during the past decade. There are reports documenting successful off-label use of the new agents for bacteraemia, IE and other invasive infections (Table 1) [26–47]. Further studies are needed to address the efficacy and cost effectiveness of these new anti-MRSA antibiotics in IE and other invasive infections.

### 6. Special considerations for infective endocarditis in children

Despite significant advances, IE in children continues to have a high mortality of up to 10%, although this compares favourably with mortality in adults. Whilst the basic principles of management of IE in the paediatric age group are broadly similar to those in adults, there are some significant differences. For example, TTE has a sensitivity of 80% in children and so, unlike in adults, TOE is rarely indicated [48]. Echocardiography should always be performed in children with SAB as a significant proportion of children have IE [49]. Staphylococci and streptococci are the major causes of IE in children. Staphylococci predominate in children without congenital heart disease. For example, in a recent epidemiological investigation in Italy, *S. aureus* emerged as the leading cause of IE in children without predisposing cardiac ailments, with an overwhelming majority (85.7%) of *S. aureus* isolates being MRSA [50].

The incidence of IE in neonates is increasing as a result of improved diagnostic techniques and enhanced levels of intervention such as the use of central venous catheters (CVCs). Septic emboli are common in neonates leading to signs of metastatic illness, such as seizures [51].

$\beta$ -Lactamase-stable penicillins are the mainstay of treatment for staphylococcal IE on native valves, with the option of adding gentamicin for the first 3–5 days. For IE caused by MRSA, vancomycin remains the favoured agent, with daptomycin as an alternative. High-dose daptomycin (10 mg/kg once daily instead of the standard 6 mg/kg) is recommended in children aged  $\leq 6$  years to compensate for rapid clearance of this agent from the bloodstream [51], although an even higher dosage (12 mg/kg) has been used [52]. Combination of  $\beta$ -lactamase-stable penicillins and vancomycin is an attractive option for staphylococcal infections until MRSA is ruled out, particularly in units where the prevalence of MRSA is high [48]. The recommended duration of treatment for staphylococcal IE is  $\geq 4$  weeks (6 weeks for MRSA and PVE). As in adults, addition of rifampicin and gentamicin is recommended for PVE [51]. Experience with newer antibiotics is limited, although linezolid has been successfully used in a neonate with IE caused by MRSA following failure of vancomycin therapy [53]. Dosing strategies for antibiotics may need to be individualised in order to optimise pharmacokinetic/pharmacodynamic targets. Nichols et al.

have published a useful commentary in relation to dose optimisation in the paediatric age group in patients with IE [54].

### 7. Antibiotic prophylaxis to prevent infective endocarditis

Recent reviews of endocarditis prophylaxis in the UK and the USA [55,56] have challenged the practice of giving antibiotic prophylaxis to prevent IE in a range of minor invasive procedures, highlighting the frequency of transient bacteraemia in everyday activities such as brushing teeth and the lack of association of many procedures with endocarditis, and have questioned the efficacy of antibiotic prophylactic regimens.

The perceived risk of IE among patients with cardiac conditions undergoing interventions is now felt to be minimal, and lower than the risks of severe adverse events, or indeed loss of life, from the adverse events and volume of prophylactic antibiotics used. For example, antibiotic prophylaxis against IE for dental procedures may lead to a greater number of deaths through fatal anaphylaxis than a strategy of no antibiotic prophylaxis, and is not cost effective.

The following cardiac conditions are regarded as being at higher risk of IE: acquired valvular heart disease with stenosis or regurgitation; valve replacement; structural congenital heart disease; previous IE; and hypertrophic cardiomyopathy. Emphasis is now placed on giving patients clear advice on oral hygiene and dental care, awareness of symptoms of IE, and the importance of early medical intervention.

Prophylaxis for IE remains a contentious issue. The UK National Institute for Health and Care Excellence (NICE) guideline published in 2008 and revised in 2015 does not recommend antibiotic prophylaxis even for patients at high risk of IE [57]. Prophylaxis with amoxicillin (clindamycin in penicillin-allergic patients) is, however, recommended by the European Society of Cardiology (ESC) guidelines for patients undergoing high-risk dental procedures [4]. Studies conducted following the restriction of antibiotic prophylaxis provided some evidence of an increasing incidence of IE, but there was no microbiological information to support the view that oral streptococci were responsible for the rise in the number of cases. Amoxicillin, which is the most commonly used prophylactic agent in the dental setting, is not active against a vast majority of isolates of *S. aureus* and consequently the debate on prophylaxis is mainly relevant to streptococcal infections. Prevention of *S. aureus* IE focuses mainly on healthcare-associated infections rather than those resulting from community dental procedures.

Prevention of SAB is the key to prevent subsequent IE. Preventing healthcare-associated infection goes beyond the confines of antibiotic prophylaxis. A reduction in the incidence of CVC-related bacteraemia can be achieved by improving adherence to infection control practices such as hand hygiene and barrier precautions, full coverage of which is beyond the scope of this review. Guidelines for prevention of intravascular catheter-related infections have been published [58]. Borg et al. found that hospitals with competency programmes in insertion of peripheral venous cannulae and CVCs have a lower prevalence of SAB. Root cause analysis of bacteraemia, hand hygiene audits and antibiotic stewardship all contribute to lowering of rates of bacteraemia [59].

Vaccines against *S. aureus* have been investigated but failed to demonstrate efficacy in clinical trials. Vaccination is likely to be of benefit in select groups of patients at high risk of bacteraemia and its complications, e.g. patients on chronic haemodialysis. A sustained immune response to the V710 vaccine was demonstrated in clinical trials [60]. However, a phase 3 trial of this vaccine did not demonstrate a reduction in the rate of *S. aureus* infections in the vaccine group. There was also higher mortality in the vaccine group compared with the control group in patients who developed *S. aureus* infection [61]. Much additional research is thus necessary

**Table 1**  
Summary of some novel antibiotics with a potential role in methicillin-resistant *Staphylococcus aureus* (MRSA) infective endocarditis (IE).

Antimicrobial agents	Comments including experience in IE
<p><b>Cephalosporins</b> Ceftaroline and ceftobiprole, both active against MRSA, are bactericidal with favourable safety profiles. Both are currently only approved [ceftaroline (FDA) and ceftobiprole (Europe)] for ABSSSIs and community-acquired pneumonia</p>	<p>There have been case reports and series documenting the successful use of ceftaroline for IE [26], including successful treatment of VISA and daptomycin-non-susceptible <i>S. aureus</i> [27]. Ceftaroline was reported to be non-inferior to vancomycin in the treatment of MRSA bacteraemia in a retrospective study in Michigan [38], and was studied in a retrospective multicentre cohort of 211 MRSA bacteraemia patients [41]. An observational study from France of left-sided IE treated with ceftaroline either as monotherapy or in combination with another agent reported a cure in 5 of 8 patients [42]. Several other case reports have been published on the successful use of ceftaroline in combination with daptomycin for MRSA, VISA and daptomycin-non-susceptible <i>S. aureus</i> IE [27,43,44], but this approach requires further study. To our knowledge, there are no published reports of ceftobiprole being used for IE therapy.</p>
<p><b>Lipoglycopeptides</b> Over the last decade, three new lipoglycopeptides have been approved by the FDA for ABSSSI (telavancin, dalbavancin and oritavancin). The long half-lives and extended dosing regimen of the latter two make them especially appealing for future use in MRSA IE. However, the long half-lives may complicate their use for empirical therapy</p>	<p>Telavancin is a bactericidal once-daily agent that achieved a similar cure rate compared with standard therapy in SAB in a small randomised trial [45]. In a retrospective study of 14 patients with refractory MRSA bacteraemia and IE, the response rate to telavancin was similar to daptomycin or vancomycin; 8 subjects survived to hospital discharge, 5 of whom had IE. The 6 who did not survive all had IE, and 5 of these were deemed not to be surgical candidates [46]. Telavancin is relatively contraindicated in patients with renal dysfunction as it is associated with increased mortality in this population.</p> <p>Dalbavancin is a lipoglycopeptide with once-weekly dosing. In a phase 2 study of catheter-related MSSA and MRSA bloodstream infections, dalbavancin had a higher success rate than vancomycin [47]. In a recently published paper, the clinical outcomes and safety of dalbavancin as primary and sequential treatment of Gram-positive bacteraemia with IE were evaluated in a single centre. Clinical success with dalbavancin was high (92.6%), but in the majority of patients (24/27) dalbavancin was only used after clearance of bacteria from the bloodstream [28]. Another recent retrospective study from Spain assessing dalbavancin therapy for a variety of invasive infections, including bacteraemia, demonstrated clinical success in 84.1% of cases and also a reduction in the number of hospitalisation days and cost [29]. Despite these encouraging results, there was a recent case report documenting failure of therapy in a pregnant patient with MRSA IE after 4 weeks of dalbavancin [30]. Treatment failed due to re-infection with VISA, perhaps due to inadequate dalbavancin exposure. Another reason for a cautious approach to using this drug for IE is that it was not bactericidal in a rabbit model of IE [31].</p> <p>Oritavancin is another lipoglycopeptide approved for ABSSSI with a very long half-life, ranging from 245–393 h. In a recent case series of 17 patients treated with oritavancin for invasive, complicated, Gram-positive infections, including 2 patients with MRSA pneumonia, all improved, although 4 had an adverse reaction [32]. In another case series, 7 of 10 patients with invasive bacterial infections treated with oritavancin were cured, although only one of these patients had an MRSA infection [33]. A notable recent report documented success of therapy with oritavancin for a case of refractory MRSA IE [34]. Oritavancin may thus be useful for MRSA IE although more data are needed before it is recommended.</p>
<p><b>Oxazolidinones</b> Tedizolid is the newest oxazolidinone antibiotic approved for ABSSSI. As for linezolid, it is considered a bacteriostatic rather than a bactericidal drug and is not likely to become a first-line agent for bacteraemia or IE. However, it has high oral bioavailability and only requires once-daily dosing [35]</p>	<p>Currently there are no published case reports of tedizolid use in the therapy of IE; however, a 2015 study of a rabbit model of <i>S. aureus</i> IE compared tedizolid, daptomycin and vancomycin. Tedizolid had modest bactericidal <i>in vivo</i> activity but was less active than the other two drugs [36]. Also, the combination of tedizolid and daptomycin in simulated endocardial vegetations suggested an antagonistic relationship that impeded antimicrobial activity [37]. Additional investigation is thus required before tedizolid is used to treat IE</p>
<p><b>Other novel drugs</b> There are several new drugs that may be feasible options for MRSA IE treatment in the future, including delafloxacin and iclaprim</p>	<p>Delafloxacin, a fluoroquinolone approved by the FDA in 2017 for the treatment of ABSSSI with activity against MRSA, demonstrates lower MICs compared with other fluoroquinolones, a higher barrier to resistance and good activity against biofilms [39]. However, there are no current studies or reports regarding delafloxacin use in IE or bacteraemia.</p> <p>Iclaprim is a diaminopyrimidine that inhibits bacterial dihydrofolate reductase. The drug completed phase 3 trials for ABSSSI that demonstrated it was non-inferior to vancomycin and had a favourable safety profile [40]. Whilst iclaprim is still new to the field, future exploration is warranted for indications for invasive infections</p>

FDA, US Food and Drug Administration; ABSSSI, acute bacterial skin and skin-structure infection; VISA, vancomycin-intermediate *S. aureus*; SAB, *S. aureus* bacteraemia; MSSA, methicillin-susceptible *S. aureus*; MIC, minimum inhibitory concentration.

to develop an effective vaccine and to determine the appropriate target population.

## 8. Role of Pantone–Valentine leukocidin (PVL) and other toxins in *Staphylococcus aureus* infective endocarditis incidence and outcome

A range of *S. aureus* virulence factors have been implicated in IE. Most studies have proposed a relationship between IE and expression of secreted virulence factor superantigens in *S. aureus*. Superantigens include staphylococcal enterotoxins (SE), staphylococcal enterotoxin-like (SEL) molecules and toxic shock syndrome toxin-1 (TSST-1 encoded by *tstH*). Whilst three of these superanti-

gens (TSST-1, SEB and SEC) are associated with toxic shock syndrome, others may primarily contribute to local effects such as vegetation formation in IE. A prospective study showed that MSSA clonal complex 30 (CC30) IE isolates were significantly more likely to contain genes for TSST-1 as well as some staphylococcal enterotoxins (*sea*, *sed*, *see*) and SEL molecules (*sei*) [62]. The frequency of *sed* was significantly higher in MRSA compared with MSSA IE isolates in a small retrospective study, notwithstanding the absence of association with mortality [63]. A more recent experimental study has emphasised the role in IE of an operon comprising one SE gene (*seg*) and SE-like genes (*selo*, *selm*, *sei*, *selu*, *seln* and *seg*) known as the enterotoxin gene cluster (*egc*) that is highly prevalent in *S. aureus* [64]. Stach et al. showed that while TSST-1 contributes to both

**Table 2**  
Evidence to support the role of Pantone–Valentine leukocidin (PVL) in the pathogenesis of *Staphylococcus aureus*-related infective endocarditis (IE).

Background	Risk factor(s)	Reference
IE related to PVL+ CA-MRSA was initially reported in five previously healthy patients	Following development of furunculosis	[67]
PVL+ MRSA IE, five cases caused by USA300 CA-MRSA clone and two cases of HA-MRSA	Intravenous drug use	[68]
In a cohort of 131 HIV-infected patients with <i>S. aureus</i> bacteraemia, patients with USA300 PVL+ CA-MRSA infections had significantly greater odds of IE (OR = 2.73)	HIV+ patients with USA300 PVL+ CA-MRSA infections	[69]
A case of IE related to the PVL+ CA-MRSA ST93 (Queensland) strain	Intravenous drug use in one of two cases; the second case had no reported risk factors	[70]
First and only case of IE relating to PVL+ CA-MSSA (to the best of our knowledge), reported in a 76-year-old man in Japan who was treated with ceftriaxone and gentamicin followed by cardiac surgery	None known, apart from age	[71]

PVL+, Pantone–Valentine leukocidin positive; CA, community-associated; MRSA, methicillin-resistant *S. aureus*; HA, healthcare-associated; HIV, human immunodeficiency virus; OR, odds ratio; MSSA, methicillin-susceptible *S. aureus*.

IE and sepsis, the effect of *egc* superantigens is limited to vegetation formation in IE [64]. Population-based epidemiological studies to further support the role of *S. aureus* superantigens in IE are not available.

Other studies have focused on the role of regulatory networks such as the quorum-sensing operon *agr* (accessory gene regulator) implicated in induction of expression of virulence factors. In a rabbit model of IE, infection persistence after treatment with vancomycin correlated with early *agr* activation [65]. However, other experimental studies suggest that *agr* is not a key regulator of virulence factor gene expression and instead attributed this role to gene regulator MgrA [66]. Epidemiological data are required to confirm the importance of these two global regulatory elements in the establishment and progression of IE as well as failure of vancomycin therapy.

Evidence to support the role of PVL in the pathogenesis of *S. aureus* IE is limited to small studies and case series/reports (Table 2).

## 9. Conclusion

*Staphylococcus aureus* IE is a common clinical infection with a high mortality. To prevent infection and to decrease mortality from *S. aureus* IE, further research is required to define its molecular epidemiology, the importance of bacterial toxins and other virulence factors, modifiable host risk factors, the optimal choice of empirical and definitive antimicrobial therapies, and the timing and indications for valvular surgery. Whilst awaiting these research studies, native valve staphylococcal IE should be treated with a 4–6-week course of a single agent, i.v. antistaphylococcal penicillin or cefazolin for methicillin-susceptible staphylococci, and vancomycin or daptomycin for methicillin-resistant staphylococci. For staphylococcal PVE, this must be reinforced with the addition of gentamicin during the first 2 weeks, and rifampicin during the whole duration (i.e. 6 weeks). Timing of surgery in *S. aureus* IE should be individualised. Further studies are also needed regarding the use of ceftobiprole and ceftaroline as single agents in the management IE.

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## References

- [1] Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis—Prospective Cohort Study. *Arch Intern Med* 2009;169:463–73. doi:10.1001/archinternmed.2008.603.
- [2] Raoult D, Casalta JP, Richet H, Khan M, Bernit E, Rovero C, et al. Contribution of systematic serological testing in diagnosis of infective endocarditis. *J Clin Microbiol* 2005;43:5238–42. doi:10.1128/JCM.43.10.5238-5242.2005.
- [3] Selton-Suty C, Célaro M, Le Moing V, Doco-Lecompte T, Chirouze C, Lung B, et al. Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based survey. *Clin Infect Dis* 2012;54:1230–9. doi:10.1093/cid/cis199.
- [4] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, Del Zotti F, et al. 2015 ESC guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;36:3075–128. doi:10.1093/eurheartj/ehv319.
- [5] Fournier P, Thuny F, Richet H, Lepidi H, Casalta J, Arzouni J, et al. Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases. *Clin Infect Dis* 2010;51:131–40. doi:10.1086/653675.
- [6] Moreillon P, Que Y-A. Infective endocarditis. *Lancet* 2004;363:139–49. doi:10.1016/S0140-6736(03)15266-X.
- [7] Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633–8. doi:10.1086/313753.
- [8] Liesman RM, Pritt BS, Maleszewski JJ, Patel R. Laboratory diagnosis of infective endocarditis. *J Clin Microbiol* 2017;55:2599–608. doi:10.1128/JCM.00635-17.
- [9] Gould FK, Denning DW, Elliott TSJ, Foweraker J, Perry JD, Prendergast BD, et al. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* 2012;67:269–89. doi:10.1093/jac/dkr450.
- [10] Poole S, Kidd SP, Saeed K. A review of novel technologies and techniques associated with identification of bloodstream infection etiologies and rapid antimicrobial genotypic and quantitative phenotypic determination. *Expert Rev Mol Diagn* 2018;18:543–55. doi:10.1080/14737159.2018.1480369.
- [11] Tubiana S, Duval X, Alla F, Selton-Suty C, Tattevin P, Delahaye F, et al. The VIRSTA score, a prediction score to estimate risk of infective endocarditis and determine priority for echocardiography in patients with *Staphylococcus aureus* bacteremia. *J Infect* 2016;72:544–53. doi:10.1016/j.jinf.2016.02.003.
- [12] Habib G, Badano L, Tribouilloy C, Vilacosta I, Zamorano JL, Galderisi M, et al. Recommendations for the practice of echocardiography in infective endocarditis. *Eur J Echocardiogr* 2010;11:202–19. doi:10.1093/ejechocard/jeq004.
- [13] Hoerr V, Franz M, Pletz MW, Diab M, Niemann S, Faber C, et al. *S. aureus* endocarditis: clinical aspects and experimental approaches. *Int J Med Microbiol* 2018;308:640–52. doi:10.1016/j.ijmm.2018.02.004.
- [14] Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation* 2015;132:1435–86. Erratum in: *Circulation* 2016;134:e113. doi:10.1161/CIR.000000000000029610.1161/CIR.0000000000000427.
- [15] Ribera E, Gómez-Jiménez J, Cortes E, del Valle O, Planes A, Gonzalez-Alujas T, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided *Staphylococcus aureus* endocarditis. A randomized, controlled trial. *Ann Intern Med* 1996;125:969–74.

- [16] Cosgrove SE, Vigiiani GA, Campion M, Fowler VG Jr, Abrutyn E, Corey GR, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. *Clin Infect Dis* 2009;48:713–21. doi:10.1086/597031.
- [17] Saeed K, Dryden M, Bassetti M, Bonnet E, Bouza E, Chan M, et al. Prosthetic joints: shining lights on challenging blind spots. *Int J Antimicrob Agents* 2017;49:153–61. doi:10.1016/j.ijantimicag.2016.10.015.
- [18] Wang A, Athan E, Pappas PA, Fowler VG, Olaison L, Paré C, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA* 2007;297:1354–61. doi:10.1001/jama.297.12.1354.
- [19] Paul M, Bishara J, Yahav D, Goldberg E, Neuberger A, Ghanem-Zoubi N, et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by methicillin resistant *Staphylococcus aureus*: randomised controlled trial. *BMJ* 2015;350:h2219. doi:10.1136/bmj.h2219.
- [20] Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. *Ann Intern Med* 1992;117:390–8.
- [21] Tattevin P, Mainardi J-L. Analysis of the 2015 American and European guidelines for the management of infective endocarditis. *Med Mal Infect* 2016;46:406–10. doi:10.1016/j.medmal.2016.05.008.
- [22] Hussain ST, Witten J, Shrestha NK, Blackstone EH, Pettersson GB. Tricuspid valve endocarditis. *Ann Cardiothorac Surg* 2017;6:255–61. doi:10.21037/acs.2017.03.09.
- [23] Chirouze C, Alla F, Fowler VG, Sexton DJ, Corey GR, Chu VH, et al. Impact of early valve surgery on outcome of *Staphylococcus aureus* prosthetic valve infective endocarditis: analysis in the International Collaboration of Endocarditis-Pro prospective Cohort Study. *Clin Infect Dis* 2015;60:741–9. doi:10.1093/cid/ciu871.
- [24] Sohaii MR, Martin KR, Wilson WR, Baddour LM, Harmsen WS, Steckelberg JM. Medical versus surgical management of *Staphylococcus aureus* prosthetic valve endocarditis. *Am J Med* 2006;119:147–54. doi:10.1016/j.amjmed.2005.09.037.
- [25] Hill EE, Peetermans WE, Vanderschueren S, Claus P, Herregods M-C, Herjigs P. Methicillin-resistant versus methicillin-sensitive *Staphylococcus aureus* infective endocarditis. *Eur J Clin Microbiol Infect Dis* 2008;27:445–50. doi:10.1007/s10096-007-0458-2.
- [26] Lin JC, Fierer J, Aung G, Johns S, Thomas A, Jahng M, et al. The use of ceftaroline fosamil in methicillin-resistant *Staphylococcus aureus* endocarditis and deep-seated MRSA infections: a retrospective case series of 10 patients. *J Infect Chemother* 2013;19:42–9. doi:10.1007/s10156-012-0449-9.
- [27] Ho TT, Cadena J, Childs LM, Gonzalez-Velez M, Lewis JS. Methicillin-resistant *Staphylococcus aureus* bacteraemia and endocarditis treated with ceftaroline salvage therapy. *J Antimicrob Chemother* 2012;67:1267–70. doi:10.1093/jac/dks006.
- [28] Tobudic S, Forstner C, Burgmann H, Lagler H, Ramharter M, Steininger C, et al. Dalbavancin as primary and sequential treatment for Gram-positive infective endocarditis: 2-year experience at the General Hospital of Vienna. *Clin Infect Dis* 2018;67:795–8. doi:10.1093/cid/ciy279.
- [29] Bouza E, Valerio M, Soriano A, Morata L, Carus EG, Rodríguez-González C, et al. Dalbavancin in the treatment of different Gram-positive infections: a real-life experience. *Int J Antimicrob Agents* 2018;51:571–7. doi:10.1016/j.ijantimicag.2017.11.008.
- [30] Steele JM, Seabury RW, Hale CM, Mogle BT. Unsuccessful treatment of methicillin-resistant *Staphylococcus aureus* endocarditis with dalbavancin. *J Clin Pharm Ther* 2018;43:101–3. doi:10.1111/jcpt.12580.
- [31] Lefort A, Pavie J, Garry L, Chau F, Fantin B. Activities of dalbavancin in vitro and in a rabbit model of experimental endocarditis due to *Staphylococcus aureus* with or without reduced susceptibility to vancomycin and teicoplanin. *Antimicrob Agents Chemother* 2004;48:1061–4. doi:10.1128/AAC.48.3.1061-1064.2004.
- [32] Schulz LT, Dworkin E, Dela-Pena J, Rose WE. Multiple-dose oritavancin evaluation in a retrospective cohort of patients with complicated infections. *Pharmacotherapy* 2018;38:152–9. doi:10.1002/phar.2057.
- [33] Stewart CL, Turner MS, Frens JJ, Snider CB, Smith JR. Real-world experience with oritavancin therapy in invasive Gram-positive infections. *Infect Dis Ther* 2017;6:277–89. doi:10.1007/s40121-017-0156-z.
- [34] Ruggero MA, Ziegler MJ, Tebas P, Binkley A, Kelly BJ. Successful treatment of methicillin-resistant *Staphylococcus aureus* vertebral osteomyelitis with outpatient oritavancin therapy. *Infect Dis Clin Pract* 2018;26:141–4. doi:10.1097/IPC.0000000000000599.
- [35] Zhanel GG, Love R, Adam H, Golden A, Zelenitsky S, Schweizer F, et al. Tedizolid: a novel oxazolidinone with potent activity against multidrug-resistant Gram-positive pathogens. *Drugs* 2015;75:253–70. doi:10.1007/s40265-015-0352-7.
- [36] Chan LC, Basuino L, Dip EC, Chambers HF. Comparative efficacies of tedizolid phosphate, vancomycin, and daptomycin in a rabbit model of methicillin-resistant *Staphylococcus aureus* endocarditis. *Antimicrob Agents Chemother* 2015;59:3252–6. doi:10.1128/AAC.04376-14.
- [37] Smith JR, Yim J, Rice S, Stamper K, Kebriaei R, Rybak MJ. Combination of tedizolid and daptomycin against methicillin-resistant *Staphylococcus aureus* in an in vitro model of simulated endocardial vegetations. *Antimicrob Agents Chemother* 2018;62 pii: e00101-18. doi:10.1128/AAC.00101-18.
- [38] Arshad S, Huang V, Hartman P, Perri MB, Moreno D, Zervos MJ. Ceftaroline fosamil monotherapy for methicillin-resistant *Staphylococcus aureus* bacteremia: a comparative clinical outcomes study. *Int J Infect Dis* 2017;57:27–31. doi:10.1016/j.ijid.2017.01.019.
- [39] Jorgensen SCJ, Mercuro NJ, Davis SL, Rybak MJ. Delafloxacin: place in therapy and review of microbiologic, clinical and pharmacologic properties. *Infect Dis Ther* 2018;7:197–217. doi:10.1007/s40121-018-0198-x.
- [40] Holland TL, O'Riordan W, McManus A, Shin E, Borghei A, File TM, et al. A phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of intravenous iclaprim versus vancomycin for treatment of acute bacterial skin and skin structure infections suspected or confirmed to be due to Gram-positive pathogens (REVIVE-2 Study). *Antimicrob Agents Chemother* 2018;62:e02580–e02517. doi:10.1128/AAC.02580-17.
- [41] Zasowski EJ, Trinh TD, Claeys KC, Casapao AM, Sabagha N, Lagnf AM, et al. Multicenter observational study of ceftaroline fosamil for methicillin-resistant *Staphylococcus aureus* bloodstream infections. *Antimicrob Agents Chemother* 2017;61:e02015–16. doi:10.1128/AAC.02015-16.
- [42] Tattevin P, Boutoille D, Vitrat V, Van Grunderbeeck N, Revest M, Dupont M, et al. Salvage treatment of methicillin-resistant staphylococcal endocarditis with ceftaroline: a multicentre observational study. *J Antimicrob Chemother* 2014;69:2010–13. doi:10.1093/jac/dku085.
- [43] Cunha BA, Gran A. Successful treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) aortic prosthetic valve endocarditis with prolonged high-dose daptomycin plus ceftaroline therapy. *Int J Antimicrob Agents* 2015;46:225–6. doi:10.1016/j.ijantimicag.2015.04.006.
- [44] Baxi SM, Chan D, Jain V. Daptomycin non-susceptible, vancomycin-intermediate *Staphylococcus aureus* endocarditis treated with ceftaroline and daptomycin: case report and brief review of the literature. *Infection* 2015;43:751–4. doi:10.1007/s15010-015-0763-0.
- [45] Stryjewski ME, Lentnek A, O'Riordan W, Pullman J, Tambyah PA, Miró JM, et al. A randomized phase 2 trial of telavancin versus standard therapy in patients with uncomplicated *Staphylococcus aureus* bacteremia: the ASSURE study. *BMC Infect Dis* 2014;14:289. doi:10.1186/1471-2334-14-289.
- [46] Ruggero MA, Peaper DR, Topal JE. Telavancin for refractory methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis. *Infect Dis (Lond)* 2015;47:379–84. doi:10.3109/00365548.2014.995696.
- [47] Raad I, Darouiche R, Vazquez J, Lentnek A, Hachem R, Hanna H, et al. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by Gram-positive pathogens. *Clin Infect Dis* 2005;40:374–80. doi:10.1086/427283.
- [48] Dixon G, Christov G. Infective endocarditis in children. *Curr Opin Infect Dis* 2017;30:257–67. doi:10.1097/QCO.0000000000000370.
- [49] Valente AM, Jain R, Scheurer M, Fowler VG, Corey GR, Bengur AR, et al. Frequency of infective endocarditis among infants and children with *Staphylococcus aureus* bacteremia. *Pediatrics* 2004;115:e15–19. doi:10.1542/peds.2004-1152.
- [50] Esposito S, Mayer A, Krzysztofki A, Garazzino S, Lipreri R, Galli L, et al. Infective endocarditis in children in Italy from 2000 to 2015. *Expert Rev Anti Infect Ther* 2016;14:353–8. doi:10.1586/14787210.2016.1136787.
- [51] Baltimore RS, Gewitz M, Baddour LM, Beerman LB, Jackson MA, Lockhart PB, et al. Infective endocarditis in childhood: 2015 update: a scientific statement from the American Heart Association. *Circulation* 2015;132:1487–515. doi:10.1161/CIR.0000000000000298.
- [52] Prabhudesai S, Kanjani A, Nambi PS, Gnanasambandam S, Ramachandran B. Successful use of high-dose daptomycin in a child with *Staphylococcus aureus* endocarditis. *Pediatr Infect Dis J* 2016;35:517–18. doi:10.1097/INF.0000000000000958.
- [53] Sung T-J, Kim H-M, Kim M-J. Methicillin-resistant *Staphylococcus aureus* endocarditis in an extremely low-birth-weight infant treated with linezolid. *Clin Pediatr (Phila)* 2008;47:504–6. doi:10.1177/0009922807311736.
- [54] Nichols KR, Israel EN, Thomas CA, Knoderer CA. Optimizing guideline-recommended antibiotic doses for pediatric infective endocarditis. *Ann Pharmacother* 2016;50:423–7. doi:10.1177/1060028016635660.
- [55] Gould FK, Elliott TSJ, Foweraker J, Fulford M, Pery JD, Roberts GJ, et al. Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* 2006;57:1035–42. doi:10.1093/jac/dkl121.
- [56] Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007;116:1736–54. doi:10.1161/CIRCULATIONAHA.106.183095.
- [57] National Institute for Health and Care Excellence (NICE). Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. London, UK: NICE; 2008.
- [58] O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2011;52:e162–93. doi:10.1093/cid/cir257.
- [59] Borg MA, Hulscher M, Scicluna EA, Richards J, Azanowsky J-M, Xuereb D, et al. Prevention of methicillin-resistant *Staphylococcus aureus* bloodstream infections in European hospitals: moving beyond policies. *J Hosp Infect* 2014;87:203–11. doi:10.1016/j.jhin.2014.05.003.
- [60] Moustafa M, Aronoff GR, Chandran C, Hartzel JS, Smugar SS, Galphin CM, et al. Phase IIa study of the immunogenicity and safety of the novel *Staphylococcus aureus* vaccine V710 in adults with end-stage renal disease receiving hemodialysis. *Clin Vaccine Immunol* 2012;19:1509–16. doi:10.1128/CI.00034-12.

- [61] Fowler VG, Allen KB, Moreira ED, Moustafa M, Isgro F, Boucher HW, et al. Effect of an investigational vaccine for preventing *Staphylococcus aureus* infections after cardiothoracic surgery. *JAMA* 2013;309:1368–78. doi:10.1001/jama.2013.3010.
- [62] Nienaber JJ, Sharma Kuinkel BK, Clarke-Pearson M, Lamletthson S, Park L, Rude TH, et al. Methicillin-susceptible *Staphylococcus aureus* endocarditis isolates are associated with clonal complex 30 genotype and a distinct repertoire of enterotoxins and adhesins. *J Infect Dis* 2011;204:704–13. doi:10.1093/infdis/jir389.
- [63] Chung J-W, Karau MJ, Greenwood-Quaintance KE, Ballard AD, Tilahun A, Khaleghi SR, et al. Superantigen profiling of *Staphylococcus aureus* infective endocarditis isolates. *Diagn Microbiol Infect Dis* 2014;79:119–24. doi:10.1016/j.diagmicrobio.2014.03.009.
- [64] Stach CS, Vu BG, Merriman JA, Herrera A, Cahill MP, Schlievert PM, et al. Novel tissue level effects of the *Staphylococcus aureus* enterotoxin gene cluster are essential for infective endocarditis. *PLoS One* 2016;11:e0154762. doi:10.1371/journal.pone.0154762.
- [65] Abdelhady W, Chen L, Bayer AS, Seidl K, Yeaman MR, Kreiswirth BN, et al. Early *agr* activation correlates with vancomycin treatment failure in multi-clonotype MRSA endovascular infections. *J Antimicrob Chemother* 2015;70:1443–52. doi:10.1093/jac/dku547.
- [66] Gupta RK, Alba J, Xiong YQ, Bayer AS, Lee CY. MgrA activates expression of capsule genes, but not the  $\alpha$ -toxin gene in experimental *Staphylococcus aureus* endocarditis. *J Infect Dis* 2013;208:1841–8. doi:10.1093/infdis/jit367.
- [67] Bahrain M, Vasiliades M, Wolff M, Younus F. Five cases of bacterial endocarditis after furunculosis and the ongoing saga of community-acquired methicillin-resistant *Staphylococcus aureus* infections. *Scand J Infect Dis* 2006;38:702–7. doi:10.1080/00365540500447150.
- [68] Haque NZ, Davis SL, Manierski CL, Vager D, Donabedian SM, Perri MB, et al. Infective endocarditis caused by USA300 methicillin-resistant *Staphylococcus aureus* (MRSA). *Int J Antimicrob Agents* 2007;30:72–7. doi:10.1016/j.ijantimicag.2007.02.007.
- [69] Furuno JP, Johnson JK, Schweizer ML, Uche A, Stine OC, Shurland SM, et al. Community-associated methicillin-resistant *Staphylococcus aureus* bacteremia and endocarditis among HIV patients: a cohort study. *BMC Infect Dis* 2011;11:298. doi:10.1186/1471-2334-11-298.
- [70] Townell NJ, Munchhof WJ, Nimmo G, Bannan A, Holley A, Daniel A, et al. Community-associated methicillin-resistant *Staphylococcus aureus* endocarditis 'down under': case series and literature review. *Scand J Infect Dis* 2012;44:536–40. doi:10.3109/00365548.2012.664779.
- [71] Nakajima H, Dohi K, Tanabe M, Nakamura A, Kanemitsu S, Wada H, et al. Infective endocarditis caused by Panton–Valentine leukocidin-producing methicillin-susceptible *Staphylococcus aureus* identified by the broad-range PCR method. *Intern Med* 2016;55:1871–5. doi:10.2169/internalmedicine.55.5403.