REVIEW ARTICLE

How to prevent infective endocarditis in 2020? Practical issues

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KEY WORDS

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ABSTRACT

The incidence of infective endocarditis (IE) continues to rise in many populations and is typically accompanied by a shift to healthcare-associated staphylococcal species. Despite efforts with aggressive antibiotic therapy and increasing rates of surgical intervention, little progress has been made to reduce mortality. Disease prevention is therefore a crucial part of limiting its effects. Prevention should target each point in the pathogenic triad of IE: initiating bacteremia, adhesion to substrate, and proliferation of pathogenic species. Preventative strategies should focus on at-risk patients undergoing high-risk procedures, and these patients and procedures can now be identified by quantitative risk estimates. The attendant risk resulting from a procedure must then be placed in the perspective of the day-to-day risk, and the resulting balance can inform the benefit of prophylactic antibiotics. Implantable devices are a major risk factor for IE, and novel coatings and designs may be effective in risk reduction. Guidelines differ worldwide and a consensus has yet to be reached on who should receive pre- and periprocedural antibiotics.

Introduction Infective endocarditis (IE) has proven to be a persistent and pervasive problem worldwide. The incidence is increasing in high--income countries, with an estimated rate of 4-15 cases/100000 population/year. Overall, an estimated 0.15% (SD, 0.02%) of deaths is now due to IE (an increase from 0.09% in 1990) and this observation is consistent across all socioeconomic groups (FIGURE 1). In high-income countries, this trend is characterized by higher mean age, higher proportion of men, and an increase in cases of disease acquired in the healthcare setting.² The evolving pattern of IE has been accompanied by microbiological variation: while there is significant geographical variation, staphylococcal species have surpassed streptococci as the predominant causative organism in high-income countries,³ particularly in North America.³

Mortality from IE remains significant, with an in-hospital fatality rate of 20% to 30%. Despite extensive efforts to improve prognosis, there is no clear evidence that mortality has fallen over time. ³⁻⁶ The first challenge is reaching an early definitive diagnosis—a task that

requires a high initial index of suspicion followed by integration of clinical findings, microbiological analysis, and imaging results. The modified Duke criteria provide a useful diagnostic framework, but they have limited sensitivity in patients with suspected prosthetic valve endocarditis, right-sided IE, and cardiac device-related infection.8 Second, there has been little improvement in the efficacy of IE treatment. While antibiotics are the mainstay of therapy, there has been an increase in resistant organisms over time and increasing recognition of the complexity of infected valve flora. Third, surgical repair or replacement remains the definitive treatment for valve damage, but a relatively small proportion of eligible patients undergo surgery in practice. While the number of patients with IE undergoing surgery has increased from 18.7% to 24.6%, a lower rate of patients receiving surgical treatment is reported among those with Staphyloccus aureus IE, which may reflect advanced age or higher prevalence of comorbid conditions. 10

Current healthcare trends and practices have contributed to an unintended rise in

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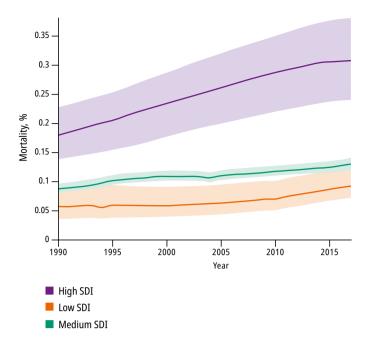


FIGURE 1 Proportion of deaths attributed to infective endocarditis in both male and female patients at all ages worldwide (subgrouped according to the sociodemographic index [SDI])¹

the incidence of IE, now affecting more frail and elderly patients who are often unsuitable for surgery. Prevention is therefore preferable to cure. In this review, we outline the pathogenesis of IE, discuss historical, current, and future attempts at prevention, and identify priorities for research.

Pathogenesis Bacteremia is the initiating factor for IE and occurs after irritation or damage of tissues, resulting in a portal of entry for bacteria to access the bloodstream. Bacteremia is not a rare event and may even be triggered by normal toothbrushing or chewing. 11 Once bacteremia is established, a complex interplay of pathogen and host factors determines whether adhesion within the heart will follow. The risk of IE is increased where there is an abnormal cardiac endothelium or a nidus of prosthetic material for infection, as in patients with prosthetic valves, permanent pacemakers, implantable cardioverter-defibrillators, or pre-existing cardiac disease (particularly rheumatic valve disease and congenital heart disease). 12,13 Furthermore, systemic disease (including chronic kidney disease [particularly dialysis patients], chronic liver disease, malignancy, corticosteroid use, and diabetes), indwelling lines for venous access, and intravenous drug use¹⁴ increase the risk of IE.

The healthy endocardium is normally extremely resistant to bacterial adhesion, but it serves as a substrate for adhesion of pathogenic material when injured or inflamed (such as at sites of valve coaptation).¹²

Successful adhesion may be followed by proliferation of a bacterial aggregate to form a vegetation, which persists with cycles of endothelial

injury and thrombus deposition. Bacteria become embedded within a matrix (or biofilm), mainly consisting of self- and host-produced polysaccharides and proteins. Maturation of the vegetation promotes survival of the colonizing pathogens and evasion of host defences. Streptococci and staphylococci species trigger both platelet activation and endothelial tissue factor production. During this process, microbes benefit from platelet prothrombotic effects, but must also evade platelet-induced killing. This interaction between platelets and *S. aureus* utilizes an array of surface proteins to promote adhesion and aggregation independent of their nutritional state. 12

The precise interactions between circulating bacteria, the heart, and the host immune system, which determine whether a vegetation forms and persists, are poorly understood. One important factor may be immunosenescence—the age-associated decline in immune function. The mechanisms of immunosenescence are complex, but include reduced chemotaxis and defective activation of innate immune cells, alongside diminished phagocytosis and intracellular killing, particularly of Escherichia coli and S. aureus. Elevated proinflammatory mediator levels in the elderly (perhaps mediated by Toll-like receptor 5) may also play a role independent of health status measures, as they are associated with significantly increased mortality. 12,16

Each component of this triad of initiating bacteremia, substrate adhesion, and proliferation ¹⁷ may serve as a point of intervention in the prevention of IE.

Prevention Host factors The first tenet of prevention is to identify groups at risk, and, then, to understand and remove factors predisposing individual patients to IE. Typically, these factors can be classified as cardiac and noncardiac in origin. While a clear pathophysiological mechanism exists for many of them (generally those permitting adhesion and proliferation), others, such as the increased risk in men versus women with a prosthetic valve, have no clear basis. ¹⁸

The major international cardiology societies have attempted to identify at-risk groups since the inception of guidelines in the 1950s. The European Society for Cardiology (ESC), 19 Japanese Cardiology Society,²⁰ and American Heart Association (AHA)21 guidelines identify individuals at high or moderate risk of endocarditis, and a further group at an unknown risk, while the United Kingdom National Institute for Health and Care Excellence (NICE) guidelines indicate a group at increased risk only (TABLE 1). Risk stratification varies geographically and has also changed over time; valvular regurgitation and mitral prolapse with regurgitation were risk factors requiring prophylaxis in the 1997 AHA guidelines, 22 but they were excluded from

TABLE 1 Quantitative risks of developing IE²⁴ compared with qualitative risk ratings provided in international clinical quidelines^{19,20,23,25-27}

Procedure / condition	OR of developing IE in 5 years ²⁴	Risk				
		AHA 2015 (with risk rating from 2007) ^{21,23}	ESC 2015 ¹⁹	NICE 2015 + 2016 amendment ²⁶	SDCEP 2018 ²⁵	JCS 2017 ²⁰
Previous IE	265.5	High	High	Increased	Speciala	High
Prosthetic heart / VAD	124.2	-	-	-	-	-
CHD with a palliative shunt or conduit	86.1	-	High	Increased	Special	High
Valve repair with prosthetic material	76.7	High	High	-	Special	High
Prosthetic valve replacement	70.1	High	High	Increased	Special	High
Congenital valve anomalies	66.4	High	-	-	Increased	Moderate / low
Cyanotic CHD	55.4	High	High	Increased	Special	High
Rheumatic fever	51.4	-	-	_		-
Nonrheumatic valve disease	41.5	-	-	Increased	Increased	Moderate
Hypertrophic cardiomyopathy	32.8	-	-	Increased	Increased	Moderate
CHD repaired with prosthetic material	18.3	High	High	-	Special ^b	High at <6 mo, moderate / low at >6 mo since repair
Implanted pacemaker/ICD	9.7	-	-	-	-	Moderate
Heart transplant	5.5	High	_	-	-	-
English population in 2008	1	-	-	-	-	-

a For special consideration (ie, higher risk than in the group at increased risk)

Abbreviations: AHA, American Heart Association; CHD, congenital heart disease; ESC, European Society of Cardiology; ICD, implantable cardioverter-defibrillator; IE, infective endocarditis; JCS, Japanese Society of Cardiology; NICE, National Institute for Health and Care Excellence; OR, odds ratio; SDCEP, Scottish Dental Clinical Excellence Programme; VAD, ventricular assist device

the high-risk category (alongside several other conditions) in the 2007 AHA update.²³

Given the lack of certainty concerning risk stratification, further investigation has long been warranted. A retrospective analysis of all hospital admissions in England between 2000 and 2008 provided the first quantitative analysis of the risks of developing IE in the presence of pre-existing cardiac conditions. Patients with coded cardiac conditions were followed up to identify hospital admissions or death due to IE over 5 years after the index diagnosis or procedure and compared with a reference population comprising the remainder of the cohort (those without a procedural or cardiac risk factor) (TABLE 1). ²⁴

Beyond cardiac abnormalities, other host factors such as host genetics are likely to be important in determining susceptibility to IE. In a genome-wide association study comparing native valve patients with S. aureus IE (cases) and matched control patients with S. aureus bacteremia but without IE, 4 single-nucleotide polymorphisms with a lower frequency of a minor allele were found in the case group compared with controls. The ex vivo analysis of aortic valve tissues revealed that these single-nucleotide polymorphisms (all found on chromosome 3) were associated with significantly higher mRNA expression levels of the cationic amino acid transporter protein SLC7A14, which the authors infer to ordinarily have a protective effect. 28 Various

b Up to 6 months or lifelong if a significant remaining shunt or regurgitation are present (excluding isolated atrial septal defect, fully repaired ventricular septal defect or patent ductus arteriosus, and closure devices that are judged to be endothelialized).

genes involved in inflammation (including *TLR2*, *TNF*, *IL1B*, and *IL6*) have also been associated with increased IE risk.^{29,30} Genetic screening and sequencing hold promise as powerful tools to quantify IE risk and target interventional strategies.

Bacteremia Bacteremia is a requisite factor for the initiation of IE. However, bacteremic load may vary from a low grade (eg, during toothbrushing) to higher grades (eg, during invasive dental procedures, bacterial sepsis, or contaminated hemodialysis). The degree of risk associated with each bacteremia-inducing event is important when determining the potential role of prophylactic measures.³¹

Only in the past few years, the risk of IE from bacteremia-inducing events has been effectively quantified. In a cohort of 138 876 adults with prosthetic heart valves in France, Tubiana et al³² compared the rate of dental procedures in the 3 months preceding oral streptococcal IE with 3 earlier 3-month follow-up periods. In the cohort analysis, there was no significant increase in the rate of IE after invasive dental procedures (relative rate, 1.25; 95% CI, 0.82-1.82) whether antibiotic prophylaxis was used (relative rate, 1.57; 95% CI, 0.9-2.53) or not (relative rate, 0.83; 95% CI, 0.33-1.69). However, when a case-crossover design was used (such that subjects served as their own controls), exposure to invasive dental procedures was more frequent during case periods than matched control periods (5.1% vs 3.2%; odds ratio [OR], 1.66; 95% CI, 1.05-2.63).32 An analogous study design using health insurance data for the Taiwanese population demonstrated similar conclusions.33

The existing data suggest that the contribution of invasive dental procedures to IE risk over baseline low-grade everyday bacteremia is relatively small—and, while statistically significant, the increase in risk is of unclear clinical relevance.34 Risk ratios (RRs) were established for a range of interventions in a Swedish retrospective case-crossover study comparing the incidence of invasive nondental medical procedures in the 12 weeks before the diagnosis of IE in 7013 patients between 1998 and 2011 against a corresponding 12-week period a year earlier. Outpatient procedures had an RR of 1.98 (95% CI, 1.66-2.37), ranging from transfusion (RR, 5.5; 95% CI, 1.22-24.8) to phacoemulsification (RR, 0.71; 95% CI, 0.41-1.22). Inpatient procedures were associated with an RR of 3.86 (95% CI, 3.31-4.5), bronchoscopy having an RR of 16 (95% CI, 2.12-120.65), and coronary artery bypass grafting an RR of 13.8 (95% CI, 5.57-34.21). The study lacked information concerning the use of antibiotic prophylaxis and may have been subject to confounding, since the indication for invasive procedures and the effect of those procedures were inseparable.

Lifestyle interventions A number of lifestyle interventions recommended by international guidelines are intuitive but supported by relatively weak evidence. The ESC recommends strict cutaneous hygiene and disinfection of wounds, eradication or decrease of chronic bacterial carriage of skin and urine, curative antibiotics for any focus of bacterial infection, strict infection control measures for any at-risk procedures, and avoidance of tattooing and piercing. Intravenous drug use remains an important cause of preventable IE in the United States, and the opioid epidemic has driven an increase in IE mortality.³⁶ Patient education in groups at risk is an essential step that clinicians and patients should take to permit early identification and treatment and reduce the risk of IE complications. Patients should know that persistent flu--like symptoms (>1 week), night sweats, general malaise, and weight loss should prompt urgent medical attention. At-risk patients should carry information cards (FIGURE 2) emphasizing the need for symptom vigilance and prompt assessment at the time of suspected illness.

Dental care The gingivae are a portal of bacterial entry into the bloodstream and poor dental hygiene is unequivocally linked to increased risk of bacteremia, ³⁷ although the correlation with IE is less certain. Paradoxically, overuse of dental hygiene (particularly interdental manipulation without toothbrushing after meals) was associated with IE of oral streptococcal origin in a single study. ³⁸ Nonetheless, regular dental scaling is associated with reduced risk of IE³⁹ and should be particularly encouraged in at-risk patients (TABLE 1). ¹⁹ The ESC guidelines specifically recommend strict dental hygiene (including dental check-ups twice yearly) in high-risk patients (and yearly in others).

Recommendations to dentists regarding the measures that should be taken to reduce the risk of bacteremia before and during an invasive procedure vary from country to country. In 2015, the United Kingdom NICE guidance discouraged the use of chlorhexidine mouthwash as prophylaxis against IE in at-risk patients undergoing dental procedures.²⁶ However, emerging evidence suggests that mouthwash with 0.2% chlorhexidine prior to tooth extraction leads to fewer patients with measurable bacteremia compared with control patients (4% vs 23%; P = 0.005). Combined with prior evidence (8 studies in total), the RR for the effect of treatment with chlorhexidine on the incidence of bacteremia is 0.88 (95% CI, 0.8-0.97) compared with control groups (number needed to treat, 16).41 The AHA, ESC, and Japanese guidelines recommend dental examination prior to heart valve surgery, but there are no specific recommendations for dental care prior to TAVI. This omission is illogical, since the risk of prosthetic

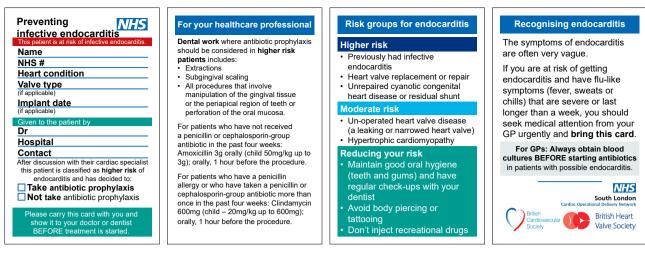


FIGURE 2 Infective endocarditis warning card for patients (reprinted with permission of the authors: John Chambers and Kate Jones, South London Cardiac Operational Delivery Network)

valve IE is similar after TAVI and surgical valve implantation,⁴² and both groups have equivalent levels of oral health.⁴³

Central venous catheters and intracardiac devices

Various attempts have been made to modify and improve intravascular devices in order to minimize the risk of IE. Central venous catheters (CVCs) are an important source of bacteremia and their widespread use is likely to contribute to IE. Coated CVCs and care bundles (hand hygiene, maximal barrier precautions, chlorhexidine skin washes, optimal catheter site selection, and daily review of central line requirement) are promising approaches to reduce CVC-related bloodstream infections (CRBSIs).

When chlorhexidine/silver sulfadiazineand antibiotic-coated catheters were compared with standard catheters in a meta-analysis of 10464 patients, coating was associated with lower numbers of CRBSIs per 1000 catheter-days (OR [95% CI], 0.64 [0.4-0.96] and OR [95% CI], 0.53 [0.25-0.95], respectively) and lower incidence of catheter colonization (OR [95% CI], 0.44 [0.34-0.56] and OR [95% CI], 0.3 [0.2-0.46], respectively). Newer polyhexanide- and biguanide--coated catheters have shown similar benefits. 44,45 The additional value of care bundles in reducing CRBSIs has also been clearly demonstrated in intensive care unit settings, 46 but not elsewhere.⁴⁷ Importantly, however, while reduction in bacteremia is a relevant surrogate endpoint, its impact on the incidence of IE remains unconfirmed.

A range of surgical valve options (namely, biological or mechanical) is available to clinicians and patients. While durability and need for anticoagulation are key considerations, the associated risk of IE should also be addressed. In a single study, biological prostheses were associated with a higher incidence of prosthetic valve IE after age and sex matching than mechanical

prostheses (hazard ratio [HR], 1.54; 95% CI, 1.29–1.83), with no significant difference between early and late presentation (although residual confounding limited the interpretation of these data). ⁴⁸ Several strategies have been proposed to limit the potential risk of prosthetic valve IE, including impregnation of the sewing ring with minocycline and rifampin, ⁴⁹ gentamicin salt, gentamicin sulfate, and clindamycin palmitate. ⁵⁰ However, progress in this field was set back dramatically by the failure of the silver-coated sewing ring of the Silzone valve, which led to increased risk of thrombosis and paravalvular leak. ⁵¹

The ideal prosthetic valve would be absorbed over time, allowing native tissue to replace the scaffold and eliminate the nidus of prosthetic material for biofilm formation. Prostheses based on poly-4-hydroxybutyrate, polyglycolic acid, and gelatin have demonstrated preclinical success. 52 Supramolecular elastomers have also been proposed as effective materials for this purpose: the Xeltis valves target the pulmonary and aortic valves and first human trials in the pulmonary position are scheduled to be completed in 2022 (ClinicalTrials.gov identifier, NCT02700100). 53 Reduction in the risk of IE remains hypothetical.

Pacemakers and implantable cardioverter-defibrillators are inserted increasingly frequently and carry a 10-fold increased risk of developing IE associated with significant morbidity and mortality. Reducing pacemaker pocket infections should theoretically confer reduced risk of bacteremia and IE. Specific procedure-based interventions, including optimization of preprocedural clinical status, antiseptic skin preparation, minimized hematoma formation, and preprocedural antibiotic prophylaxis reduce infection rates. These procedural interventions combined with antibiotic and novel nonantibiotic device coatings may reduce the risk of device-related IE.

Indeed, the WRAP-IT study (World-wide Randomized Antibiotic Envelope Infection Prevention Trial) on the TYRX absorbable antibacterial envelope (rifampicin and minocycline) showed reduction in device-associated infections over a 2-year follow-up.⁵⁵

Preventative interventions Antibiotic prophylaxis Antibiotic prophylaxis prior to invasive medical and dental procedures has been the historical cornerstone for the prevention of IE. Treatment prevents or reduces bacteremia after dental extraction, 56 but there are no randomized controlled trial data to demonstrate its efficacy in preventing IE. In the absence of firm evidence, its use has become increasingly controversial. Furthermore, antibiotic prophylaxis carries potential risks, including anaphylaxis and promotion of antibiotic resistance. While there were no fatal reactions to amoxicillin among 3 million prescriptions in the United Kingdom between 2004 and 2014, there were 13 fatal reactions per 1 million prescriptions of clindamycin over the same period. Nonfatal reactions occurred in 22.6 and 149 cases per 1 million prescriptions, respectively,⁵⁷ and overall conclusions concerning cost-effectiveness are uncertain.⁵⁸

In the United Kingdom in 2008, the NICE provided guidance advising against the use of antibiotic prophylaxis. Over subsequent years, the incidence of IE in England increased significantly beyond the projected historical trend (by 0.11 cases per 10 million people per month [95% CI, 0.05-0.16])—an estimated 419 extra IE cases per year (including 66 deaths)—although the true cause-effect relationship could not be determined in the absence of microbiological data. 59,60 Similarly, restriction of antibiotic prophylaxis to high-risk groups only in the AHA 2007 and ESC 2009 guidelines was associated with an increase in IE incidence in the United States in the years 2003 to 2015 (high risk: +177% [95% CI, 66–361], moderate risk: +75% [95% CI, 3-200], and unknown or low risk: no change).61 While the amendment of the NICE guidelines in 2016 provided United Kingdom clinicians with greater freedom to interpret the guidelines, they still fall short of a mandate to reintroduce antibiotic prophylaxis. A further guidance update produced by the Scottish Dental Clinical Effectiveness Programme in 2018 emphasized a patient-centered approach to determine whether antibiotic prophylaxis should be prescribed, considering the uncertain benefits and potential harms.²⁵

Vaccination Vaccination is a potentially attractive means to eliminate infection by the most common organisms. Vaccination against *S. aureus* would have a significant impact but, although preclinical studies have shown promise, ^{60,62,63} phase II and III trials have been negative to

date. ⁶⁴ Results of an ongoing clinical trial (Clinical Trials.gov identifier, NCT00584454) evaluating the safety and efficacy of a novel vaccine against *Coxiella burnetii* (the organism responsible for chronic Q fever) are awaited.

Novel pharmacological strategies Biofilm formation has been identified as a critical step in the pathophysiology of IE.65 Once established, a combination of penetrative antimicrobial therapy and mechanical removal (ie, surgery) is required for its elimination. Several approaches have been proposed with targeting of 'quorum sensing' offering the biggest potential. Following initial bacterial attachment, cells secrete quorum-sensing molecules that alter microbial gene expression from the planktonic to sessile form, allowing generation of a biofilm.66 Blockade of this pathway (also known as "quorum quenching") may also reduce the risk of multidrug resistance. Inhibitors of S. aureus accessory gene regulators can also be targeted⁶⁷ using small drug fragments,68 membrane-embedded peptidases, 69 or apicidin (a fungal metabolite). 70 While these approaches have far-reaching potential benefits, they remain a long way from clinical application.

Platelets are also critical in biofilm pathogenesis, although inhibition of platelet function with aspirin has generally been deemed harmful in the treatment of IE. Despite evidence from animal models demonstrating rapid resolution of vegetations and a lower rate of embolism, the Multicenter Aspirin Study in Infective Endocarditis showed an increased risk of bleeding and no influence on the risk of embolic events. 71 Used in a different manner, however, aspirin may prove beneficial. While the acetylsalicylic acid component acts mainly on platelets, the predominant metabolite related to salicylic acid influences the genetic regulation of S. aureus virulence factors. Given that fibrin and microthrombi facilitate the interaction of bacterial surface adhesins with the extracellular proteins of an abnormal or damaged endothelium, there may be merit in platelet inhibition to prevent IE.⁷² Indeed, in vitro studies suggest particular effectiveness against S. aureus and Enterococcus faecalis. 73 Similar effects are also observed with ticagrelor, whose antiplatelet activity interferes with platelet-leukocyte activity and whose major metabolite may have bactericidal activity.74 The post hoc analysis of the PLATO (Platelet Inhibition and Patient Outcomes) study comparing ticagrelor and clopidogrel in patients with acute coronary syndromes showed that ticagrelor was associated with a lower risk of infection-related death.75 However, the concentrations of ticagrelor required to achieve bactericidal activity far exceed those found in vivo, suggesting that further investigation is required.

Conclusions Although our understanding of the pathophysiology of IE has undoubtedly improved, challenges remain in quantifying how bacteremia-inducing events increase risk and how the interplay of host and pathogen factors determines the development of the disease in individual patients. Importantly, while there are many preventative strategies, clinical trials only show evidence for reduction in bacteremia but not in IE. Controversy surrounding the efficacy of antibiotic prophylaxis persists, though quantification of the risks of certain procedures should enable clinicians to target those patients who are most likely to benefit from treatment. Novel approaches to inhibit biofilm formation are particularly promising and avoid the hazards of antimicrobial resistance, but remain in preclinical development. Infective endocarditis is still a significant challenge for cardiology and allied specialties in 2020 and looks set to remain so for years to come.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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