Challenges in Infective Endocarditis: A State-of-the-Art Review

Brief title: Challenges in Infective Endocarditis

<AU>Thomas J. Cahill, MBBS,[a] Larry M. Baddou, MD,[b] Gilbert Habib, MD,[c,d] Bruno Hoen, MD, PHD,[e] Erwan Salaun, MD,[d] Gosta B. Pettersson, MD, PHD,[f] Hans Joachim Schäfers, MD,[g] Bernard D. Prendergast, DM[h]

From the [a]Department of Cardiology, Oxford University Hospitals, Oxford, United Kingdom; [b]Division of Infectious Diseases, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, Minnesota; [c]Aix-Marseille Universite, URMITE, Marseille, France; [d]APHM, La Timone Hospital, Cardiology Department, Marseille, France; [e]Université des Antilles et de la Guyane, Faculté de Médecine Hyacinthe Bastaraud; Inserm, Service de Maladies Infectieuses et Tropicales, Dermatologie, Médecine Interne, Centre Hospitalier Universitaire de Pointe-à-Pitre/Abymes, Pointe-à-Pitre, France; [f]Department of Thoracic and Cardiovascular Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio; [g]Department of Thoracic and Cardiovascular Surgery, Saarland University Medical Center, Homburg/Saar, Germany; [h]Department of Cardiology, St Thomas' Hospital, London, United Kingdom

<COR>REPRINT REQUESTS AND CORRESPONDENCE: Dr. Bernard D. Prendergast, Department of Cardiology, St Thomas' Hospital, London, United Kingdom. E-mail: bernard.prendergast@gstt.nhs.uk

Disclosures: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

<BEGIN ABSTRACT> ABSTRACT
Infective endocarditis (IE) is defined by a focus of infection within the heart, and is a feared disease across the breadth of cardiology. It is frequently acquired in the health care setting, and over one-half of cases now occur in patients without known heart disease. Despite optimal care, mortality approaches 30% at 1 year. The challenges posed by IE are significant. It is heterogeneous in etiology, clinical manifestations, and course. *Staphylococcus aureus*, which has become the predominant causative organism in the developed world, leads to an aggressive form of the disease, often in vulnerable or elderly patient populations. There is a lack of research infrastructure and funding, with few randomized clinical trials to guide practice. Longstanding controversies, such the timing of surgery or the role of antibiotic prophylaxis, have not been resolved. Herein we review the challenges posed by IE, and outline current and future strategies to limit its impact.
<END ABSTRACT>

<KW>KEY WORDS: antibiotic prophylaxis, bacteremia, biofilms, echocardiography, *Staphylococcus aureus*, stroke

ABBREVIATIONS AND ACRONYMS
^{18}FDG-PET = 18-fluorodeoxyglucose positron emission tomography
CDI = cardiac device infection
CHD = congenital heart disease
CI = confidence interval
CIED = cardiac implantable electronic device
CoNS = coagulase-negative staphylococci
IE = infective endocarditis
NVE = native valve infective endocarditis
PVE = prosthetic valve infective endocarditis
TAVR = transcatheter aortic valve replacement

Infective endocarditis (IE) is a rare disease, but its impact is significant (1). It affects 3 to 10 per 100,000 per year in the population at large, and epidemiological studies suggest that the incidence is rising (2-5). In the United States, there are 40,000 to 50,000 new cases each year, with average hospital charges in excess of $120,000 per patient (3). Despite trends toward earlier diagnosis and surgical intervention, the 1-year mortality from IE has not improved in over 2 decades.

Infective endocarditis is an old problem in a new guise (6). In the pre- and early antibiotic era, it typically affected young or middle-aged adults with underlying rheumatic heart disease (RHD) or congenital heart disease (CHD) (7). The development of antibiotics, decline of RHD, and advances in medicine through the 20th century heralded a change in the risk factor profile, patient demographic, and microbiology of IE. Prosthetic valve replacement, hemodialysis, venous catheters, immunosuppression, and intravenous (IV) drug use became the principal risk factors (8). The average patient was older and frailer, with increasing comorbidities. Concurrently, staphylococci overtook oral streptococci as the most frequent causative organism (9,10).

In the 21st century, IE has continued to evolve such that it is now health care-acquired in over 25% of cases (9), while advances in cardiology have driven further changes in the patient demographic and manifestations of the disease. Alongside the emergence of cardiac implantable electronic devices (CIEDs), IE affecting complex devices has burgeoned (11). Similarly, transcatheter valve replacement is revolutionizing the management of valvular heart disease, but may be associated with higher rates of IE than surgically implanted prosthetic valves (12-14).

In this review, we outline the challenges posed by contemporary IE in developed countries, and the reasons why diagnostic and treatment advances have failed to have an impact on the disease. We highlight recent data on the effect of changing antibiotic prophylaxis guidelines, the current status of molecular and imaging diagnostics, and review strategies for improving service delivery and surgical outcomes. Reflecting the constant evolution of the disease, we also examine the data on IE in 3 patient groups that encapsulate some of the key challenges: those with transcatheter aortic valve replacement (TAVR)-endocarditis, those presenting with stroke, and those with CIED infection. Finally, we look ahead and emphasize the future need for enhanced clinical care pathways, interdisciplinary collaboration, and research, which will be required for effective disease prevention, diagnosis, and cure.

<H1>PREVENTION

Prevention of IE is better than cure, and requires insight into the mechanisms of disease, the patient populations at risk, and an effective preventive intervention. The disease develops in 3 stages. The initiating step is *bacteremia,* with bacteria commonly entering the bloodstream via the mouth, gastrointestinal and urinary tracts, or the skin, through venous catheters or following an invasive medical or surgical procedure. The second step is *adhesion*: whereas the normal endothelial lining of the heart is resistant to bacterial adhesion, bacteria (particularly Gram-positive species) are able to adhere to abnormal or damaged endothelium via surface adhesions that mediate attachment to extracellular host matrix proteins, which in turn are facilitated by fibrin and platelet microthrombi (15). Gram-positive bacteria also lack an outer membrane and have a thick surrounding peptidoglycan, and are therefore less sensitive to serum-induced killing.

Bacterial adhesion gives rise to *colonization*, where cycles of bacterial proliferation occur alongside thrombosis, monocyte recruitment, and inflammation, leading to formation of a mature vegetation (16). Many of the microorganisms associated with IE (including staphylococci, streptococci, and enterococci, but also less common pathogens, such as *Candida* species and *Pseudomonas aeruginosa*) produce biofilms, which allow bacterial populations to embed within an extracellular polysaccharide slime-like matrix, with quorum sensing (chemical cell-to-cell communication) and synchronized gene expression promoting assembly and maturation. Once established, the biofilm protects bacteria from host immune defenses, impedes antimicrobial efficacy, and hides resistant persister organisms (17). Biofilm-forming capacity is now recognized as an important determinant of virulence in the development of staphylococcal device-related infections (18).

<H2>ANTIBIOTIC PROPHYLAXIS. Preventive strategies have historically focused on bacteremia. In 1909, Thomas Horder recognized that the mouth was a major portal for bacterial entry, and, in 1935, streptococcal bacteremia was detected after dental extraction (19,20). The first trials of penicillin prophylaxis were conducted in the 1940s, and showed that antibiotics reduced the incidence of bacteremia following dental extraction (21,22). Consequently, in 1955, the American Heart Association (AHA) published guidelines recommending antibiotic prophylaxis for patients with RHD and CHD (23). Maintenance of good oral hygiene and antibiotic prophylaxis for at-risk groups undergoing dental extraction became the standard of care for 50 years.

Between 2007 and 2009, guidelines in the United States and Europe were substantially revised to restrict the use of antibiotic prophylaxis. The reasons were

several: first, in the era of evidence-based practice, there was (and remains) no randomized controlled trial (RCT) of antibiotic prophylaxis in the context of dental extraction. Second, the efficacy of prophylaxis was questioned on the basis of an apparent failure rate of up to 50% (24). Third, the importance of widespread antibiotic use as a contributor to emerging resistance was gaining recognition, while the indications for prophylaxis had expanded significantly to encompass groups at moderate risk. Finally, the significance of dental procedures as a cause of IE was questioned due to population studies that did not show dental intervention as a major risk factor (25,26). In contrast, "everyday" bacteremia, due to tooth brushing, chewing, and inadequate dental hygiene, was recognized as a possible cause of IE. In a cohort awaiting dental extraction (i.e., with dental disease), tooth brushing alone was sufficient to cause bacteremia in 23% (27). The relative importance of rare and high-magnitude bacteremia (for example, caused by dental extraction) compared with common, low-level bacteremia in the pathogenesis of IE remained poorly defined. Therefore, in the United States and Europe, antibiotic prophylaxis was restricted to those at highest risk (28,29). Meanwhile, in the United Kingdom, antibiotic prophylaxis was abandoned entirely in a highly controversial decision by the U.K. National Institute for Health and Care Excellence (NICE) (30,31).

<H2>EFFECTS OF CHANGING GUIDELINES ON THE INCIDENCE OF IE. Several studies have now examined the effect of restricting oral antibiotic prophylaxis on the incidence of IE (**Table 1**). In France, where antibiotic prophylaxis was limited to high-risk groups as early as 2002, a survey approach was used to gather data on all cases of IE across several different regions (32,33). The incidence of IE in 3 survey years (1991, 1999, and 2008) was found to be stable at 35, 33, and 32 cases per million,

suggesting no significant change following restriction of oral antibiotic prophylaxis. Importantly, the number of cases caused by oral streptococci was also stable.

In 2007, the American College of Cardiology (ACC)/AHA restricted antibiotic prophylaxis in the United States to patients with prosthetic valves, congenital heart disease, previous IE, and cardiac transplant recipients with valvulopathy (29). Using data from the Rochester Epidemiology Project, DeSimone et al. (34,35) analyzed the incidence of IE due to viridans group streptococci (VGS) before and after this change. No increased incidence was identified and, conversely, there was a fall in incidence from 3.6 per 100,000 person-years from 1999 to 2002 to 1.5 per 100,000 person-years from 2011 to 2013. Similarly, 2 population studies from Canada and the United States found no evidence for a change point in the incidence of IE coinciding with the ACC/AHA guideline amendment (36,37).

In contrast, 2 nationwide epidemiological studies from the United States and the United Kingdom have given cause for concern. Using the Nationwide Inpatient Sample, Pant et al. (2) identified a statistically significant increase in the incidence of IE caused by streptococci, although there was no significant change in the (upward) trend in total hospitalizations, or in staphylococcal endocarditis. This study included both non-VGS and *Enterococci* in the incidence calculations, however, and did not perform change point analysis to confirm that the change in rate coincided with the ACC/AHA guideline amendment. Furthermore, the investigators had no access to antibiotic prophylaxis prescribing data to confirm that this had declined.

In the United Kingdom, where national guidance advised against use of antibiotic prophylaxis in March 2008, early analyses signaled no rise in the incidence of IE (38). In

2015, however, Dayer et al. (5) published an extended analysis looking at NHS hospital discharge diagnoses up to 2013. Antibiotic prophylaxis dropped from 10,900 prescriptions per month to 2,236 prescriptions per month after the NICE guidelines were introduced. In parallel, there was a significant rise (above the projected trend) in the number of IE cases, by 0.11 cases per 10 million persons (or an additional 35 cases in England) per month. Statistical analysis identified June 2008 (3 months after implementation of the new guidelines for the use of antibiotic prophylaxis) as the point of change, but it was not possible to confirm that these cases were due to oral *Streptococci* because microbiological data were unavailable.

These data are observational, and cannot establish a causal link between restriction of antibiotic prophylaxis and incidence of IE. They are subject to confounding, for example by increasing numbers of device implants, although this has been adjusted for in some studies. Despite the longstanding controversy and difficulty with observational data, a randomized trial is highly unlikely due to cost, logistics, and ethical debate as to whether true equipoise exists to allow conduct of a placebo-controlled trial. The current pragmatic approach (endorsed by the ACC/AHA and the ESC) (**Table 2)** is to limit prophylaxis to individuals at highest risk on the basis of the underlying cardiac condition. In our view, this approach correctly balances the risks and benefits of individual and population antibiotic use. Importantly, this classification omits patients who have noncardiac risk factors (e.g., those who are immunocompromised), and may be at increased risk of both IE and poor outcome if the disease develops. There are few data to guide specific practice in these groups, and a tailored approach for individual patients remains appropriate, according to clinical circumstances (39,40).

<H2>PREVENTION OF HEALTH CARE-ASSOCIATED IE. Health care-associated infective endocarditis (HCAIE) accounts for an increasing proportion of cases and requires specific strategies for prevention. The affected patient demographic is older, and most have either degenerative valve disease or no intrinsic cardiac risk factors. Instead, the most frequent risk factors are hemodialysis, cancer, diabetes mellitus, and the presence of a CIED (9,41). *Staphylococcus aureus* is the causative organism in approximately one-third of cases, and the overall proportion of IE due to *S. aureus* in the United States rose from 24% to 32% between 1998 and 2009 (3). *S. aureus* is consistently an independent risk factor for in-hospital death (42). In keeping with the affected patient population and underlying microbiology, the in-hospital mortality for patients with HCAIE is significantly higher than for community-acquired infection (31.1% vs. 20.3%, $p < 0.01$) (9).

Reduction of health care-acquired bacteremia is therefore a logical target. Longitudinal studies from Denmark show that an increase in *S. aureus* bacteremia (SAB) occurred from 3 to 20 per 100,000 person-years between 1957 and 1990, mirroring increasing rates of hospital admission and invasive medical procedures (although rates have now plateaued in the developed world) (43,44) In the United States, 10% to 20% of the population are persistent carriers of *S. aureus* (45). For central line-associated blood stream infection, practice-changing interventions to improve adherence to sterile practice (hand hygiene, barrier precautions and antisepsis) have already significantly reduced rates of bacteremia (46,47). Bundled interventions to reduce catheter-related blood stream infection in high-risk groups, such as those on hemodialysis, could translate to a major impact on the incidence of IE (48,49).

Novel approaches to prevention of bacteremia and strategies to target adherence are desperately required (50). Innovative material technologies, which prevent interaction of bacteria with prosthetic surfaces (so-called low fouling coats), or contain long-lasting bactericidal coatings, hold promise, but have so far failed to translate into clinical practice. Indeed, enthusiasm for antibacterial coatings has been tempered by experience with the St. Jude Silzone valve with a silver-coated sewing ring, which had to be recalled within 3 years of its release in 1997 due to an increased risk of thrombosis and paravalvular leak (51,52). Furthermore, this was seen as a failure of regulatory approval processes for modification of existing valves. A vaccine targeted at bacterial components has long been seen as attractive for patients at high risk of bacteremia. However, 2 candidate *S. aureus* vaccines failed to demonstrate efficacy in phase 3 clinical studies, with 1 failing to reach an efficacy endpoint (prevention of SAB in patients undergoing hemodialysis), and another leading to increased mortality in median sternotomy patients who developed staphylococcal infection (53,54). More positively, a new composite vaccine targeting 5 components of *S. aureus* has recently been shown to be highly protective in mouse models (55).

<H1>DIAGNOSIS

Reaching a rapid and accurate diagnosis in cases of suspected IE is a central challenge of the disease. Delayed diagnosis and initiation of therapy lead to complications and worse clinical outcomes (56-58). Clinical presentation is notoriously diverse, ranging from acute sepsis to an indolent low-grade febrile illness, a heart failure syndrome, or stroke. Furthermore, the modified Duke criteria, originally designed for research purposes and advocated by AHA guidelines for evaluation of patients with

suspected IE, have a lower sensitivity for patients with prosthetic valve endocarditis (PVE) or cardiac device infection (CDI) (59,60). Up to 30% of patients with subsequently proven IE are labeled as "possible" due to equivocal or negative findings on echocardiography or blood cultures (61,62). Definitive cardiac imaging and microbiology are therefore of integral importance in making the diagnosis, and also inform risk stratification, direct management, identify complications, and assist with monitoring therapy. Key advances have been made in recent years in reaching a definitive diagnosis in patients who fall into the Duke "possible" group.

<H2>IMAGING. Echocardiography remains the cornerstone of imaging and is rapid, straightforward, and in many cases, diagnostic (63). Transthoracic echocardiography (TTE) is the recommended initial modality of choice for both native valve infective endocarditis (NVE) and PVE. For suspected NVE, TTE has a sensitivity of 50% to 90% and a specificity of 90%. For suspected PVE, the sensitivity of TTE is lower, at 40% to 70%, yet it provides value in assessment of ventricular size and function, hemodynamic severity of valve lesions, and in the diagnosis of anterior prosthetic aortic valve abscesses, which may be difficult to visualize on transesophageal echocardiography (TEE). TEE is indicated when TTE is positive or nondiagnostic, when complications are suspected, or when intracardiac device leads are present. For suspected NVE, TEE has a sensitivity of 90% to 100% and a specificity of 90% for detection of vegetations, and is superior to TTE for detection of complications, such as perforation, abscess, and fistulae (63). In PVE, a recent meta-analysis reported a pooled sensitivity of only 86% (95% CI: 77% to 92%) for TEE in making the diagnosis (64), and other imaging modalities are emerging to help make or exclude the diagnosis in cases where TEE is nondiagnostic.

Even when abnormalities are detected, it can be difficult to differentiate nodules from small vegetations, or distinguish signs of infection from post-operative changes.

Cardiac computed tomography (CT) is the key adjunctive modality for use when the anatomy is not clearly delineated by echocardiography, and now has a Class II, Level of Evidence B recommendation for use in IE in the 2014 ACC/AHA valvular heart disease guidelines (**Figure 1**) (59). CT is equivalent (and possibly superior) to TEE for demonstrating paravalvular anatomy and complications (for example, paravalvular abscesses or mycotic aneurysms), and is subject to fewer prosthetic valve artifacts than echocardiography (65-67). This may help with planning surgical strategy, and concurrent CT angiography allows exclusion of significant coronary disease in younger patients. Detection of paravalvular lesions by CT imaging is now a major diagnostic criterion in the 2015 European Society of Cardiology (ESC) guidelines on IE (68).

Combining CT with metabolic imaging by 18-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) or leucocyte scintigraphy (radiolabeled leucocyte single-photon emission computed tomography [SPECT]) to show regions of metabolic activity or inflammation, respectively, is a hugely promising approach in patients with Duke "possible" IE or suspected CDI (**Figure 2**). Several studies have now investigated the sensitivity and specificity of PET/CT or SPECT/CT in this setting. In a cohort of 72 patients with suspected PVE, ^{18}FDG PET/CT had an overall sensitivity of 73% and specificity of 80% (69). Addition of "abnormal prosthetic valve ^{18}FDG-PET signal" as a diagnostic criterion increased the sensitivity of the modified Duke criteria from 70% to 95%, reducing the number of patients with "possible IE" from 56% to 32%. In a Spanish cohort of patients with suspected PVE or CDI, ^{18}FDG-PET/CT(angiography [A])

demonstrated an overall sensitivity and specificity of 87% and 90%, respectively, and increased the sensitivity of the modified Duke criteria from 51% to 91% (70). Use of PET/CT imaging allowed reclassification of 90% of cases (35 of 39) with "possible" IE and provided a conclusive diagnosis in 95% of cases overall. For leucocyte scintigraphy with SPECT/CT, a sensitivity of 90% and specificity of 100% have also been reported (71). When directly compared in a cohort with suspected PVE and inconclusive echocardiography, ^{18}FDG-PET/CT had higher sensitivity than SPECT/CT but SPECT demonstrated higher specificity (72). The significance of abnormal ^{18}FDG-PET/SPECT imaging has been recognized in the 2015 ESC guidelines; a positive signal at the site of a prosthetic valve (if implanted > 3 months previously) is now regarded as a major diagnostic criterion for PVE.

Routine cross-sectional imaging of the brain, chest, spine, and viscera can be diagnostic and change management. Imaging cohort studies suggest that patients with IE have a high incidence of subclinical complications, such as embolism, hemorrhage, or abscess. Routine cerebral magnetic resonance imaging (MRI) identifies abnormalities in 80% of patients, and, in 1 prospective study, upgraded 14 of 53 patients (26%) from "possible" to "definite" IE (73). In another series, CT cerebral angiography identified intracranial mycotic aneurysms in 32% of left-sided endocarditis patients, of whom 50% subsequently underwent endovascular or neurosurgical intervention (74). Similarly, MRI imaging of the abdomen identified abnormalities in the spleen, liver, or kidneys in 34% of patients (75). Evidence of embolism by cross-sectional imaging is a novel minor diagnostic criterion in the ESC 2015 guidelines.

Multimodality assessment by cross-sectional imaging, cardiac CT and ^{18}FDG-PET or SPECT has the potential to improve diagnosis and the detection of complications in patients with suspected IE (**Figure 2**). We see CT and ^{18}FDG-PET/CT becoming widely used for diagnosis in the "Duke possible" subgroup of patients, and for CDI (see later discussion). There are drawbacks, however. Metabolic imaging cannot accurately discriminate between sterile inflammation and infection, and is therefore of limited use in the early post-operative period. False positives for PET/CT have been reported following cardiac surgery due to post-pericardiotomy syndrome, prosthetic valve thrombosis, and at the site of an aortic graft. Access to advanced imaging is often limited, and there is a risk that logistical hurdles may delay definitive surgical intervention. Finally, identifying which patient groups derive the most clinical benefit from advanced imaging (and through precisely which modalities) remains to be established.

<H2>MICROBIOLOGY. Health care-associated organisms have increasingly defined the microbiology of contemporary IE. *S. aureus* is now the most common causative organism and accounts for approximately 30% of cases (9,10). *S. aureus* endocarditis is characterized by aggressive disease with increased risk of embolism, stroke, persistent bacteremia, and death (76). *S. aureus* is also the most common cause of PVE, often requiring redo surgery, and is associated with mortality rates approaching 50% in some centers (77,78). Coagulase-negative staphylococci (CoNS) have a rising incidence of ~10% and play a major role in PVE occurring in the first year after the initial procedure (79,80). Importantly, CoNS have emerged as a cause of NVE, as well as PVE (81). They are often methicillin-resistant and, in the case of *S. lugdunensis*, associated with highly destructive valvular and perivalvular lesions. Oral streptococci make up ~20% of cases,

other streptococci ~10%, and enterococci a further 10%. HACEK organisms (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species), zoonoses, and fungi collectively account for <5% of cases.

Approximately 10% to 20% of patients have negative blood cultures at presentation, leading to diagnostic uncertainty. Negative blood cultures may occur due to prior antibiotic use, infection with fastidious intracellular organisms or fungi, or an alternative diagnosis. The incidence of blood culture-negative infective endocarditis (BCNIE) may fall with increasing use of newer blood culture techniques, which allow direct identification of bacterial species by mass spectroscopy and are significantly faster than standard culture (82).

A rigorous diagnostic approach to patients with BCNIE allows a causative organism to be identified in two-thirds (83). The first stage is serological testing for zoonotic agents, specifically *Coxiella burnetti* (causing Q fever), *Bartonella quintana* and *Bartonella henselae*, *Brucella* sp., as well as *Myocoplasma* sp. and *Legionella* sp. If serology is positive, blood polymerase chain reaction (PCR) targeting the causative bacteria should be undertaken. If serology is negative, molecular testing of blood or excised valve material is valuable, including broad PCR for bacterial 16S ribosomal RNA) genes and targeted PCR for *Tropheryma whipplei*, *Bartonella* sp., and fungi. If microbiological investigation remains negative, consideration should be given to autoimmune disease, and testing for antinuclear antibodies and rheumatoid factor. In a French cohort of 759 patients with BCNIE, 476 patients ultimately had an identified etiologic agent, most commonly zoonoses (229 Q fever, 86 *Bartonella*). Twelve patients

were diagnosed with *T. whipplei*, 8 with fungi, and 70 with common bacteria, whereas 19 (2.5%) were found to have noninfectious endocarditis caused by autoimmune disease or marantic endocarditis (83).

<H1>MANAGEMENT

Management of patients with IE is both a clinical and logistical challenge. Delivery of optimal care requires an administrative infrastructure and the involvement of multiple hospital specialists, including cardiologists, surgeons, infectious disease physicians, microbiologists, nephrologists, neurologists, and radiologists. Optimizing service delivery and early decision-making have the potential to improve clinical outcomes, leading to calls for formation of "IE teams," modeled on the heart team approach to coronary and heart valve disease (84).

Introduction of a formalized multidisciplinary team (MDT) approach in Italy, defined by initial evaluation within 12 h, early surgery (within 48 h) if indicated, and weekly review, led to a reduction in in hospital (28% vs. 13%, $p = 0.02$) and 3-year mortality (34% vs. 16%, $p = 0.0007$), despite patients being older and having more comorbidities (85). Similarly, a French MDT approach to standardizing care, including antibiotic protocols and indications for surgery, reduced 1-year mortality from 18.5% to 8.2% (86).

Centralized care concentrated in tertiary centers with advanced diagnostic imaging, surgical expertise, and higher throughput clearly has a role in complex cases and may also be universally beneficial. There are arguments against this model, however, such as delays during transfer and loss of local expertise. Reconfiguration towards a system of centralized IE care (or a hub and spoke model, with central multidisciplinary

review) should therefore be on the basis of evidence. The efficacy of centralized care to improve decision-making, time to surgery, cure rates, and short- and long-term outcomes could be readily tested in a before and after study.

<H2>ANTIBIOTIC THERAPY. Prior to the discovery of penicillin, IE was an untreatable disease (87,88). Effective microbial clearance requires bactericidal antibiotic regimens, usually in combination. Detailed empirical and organism-specific antibiotic protocols are beyond the scope of this review, but are provided in the latest AHA and ESC guidelines (68,89).

The importance of balancing efficacy of treatment with the overall risk and toxicity of prolonged inpatient therapy is increasingly recognized. Emerging evidence supports short-course or stepped-down antibiotic treatment in selected groups. In patients with uncomplicated IE caused by oral streptococci and normal renal function, a combination of a penicillin or ceftriaxone with an aminoglycoside for a total of 14 days is safe and effective (90). Similarly, a 2-week course of penicillin monotherapy or penicillin-aminoglycoside in combination is effective for uncomplicated methicillin-sensitive *S. aureus* right-sided IE (91).

There are increasing data to suggest that the use of aminoglycosides may be causing harm without clear clinical benefit. In a 2006 RCT of daptomycin compared with conventional therapy (penicillin or vancomycin with initial gentamicin) for SAB or right-sided endocarditis, daptomyin was shown to be noninferior. Importantly, renal dysfunction occurred in 11% of those treated with daptomycin in comparison with 26% of the conventional therapy arm (92,93) Aminoglycosides have now been removed from the ESC and AHA guidelines for treatment of methicillin-sensitive *S. aureus* (MSSA) or

methicillin-resistant *S. aureus* (MRSA) NVE. Although aminoglycosides have historically been widely used for enterococcal IE, the increasing frequency of resistance (25% to 50% of isolates in recent studies), along with the recognition of potential harm, has led the ESC 2015 guideline committee to identify ampicillin and ceftriaxone (Class IB recommendation) as the treatment of choice for aminoglycoside-resistant *Enterococcus faecalis*. This is supported by large observational studies showing that ampicillin/ceftriaxone is as effective as ampicillin/gentamicin, with reduced levels of nephrotoxicity (94,95).

Further research is needed to determine whether additional patient groups may be suitable for shortened courses of antibiotic therapy. For example, in patients who have undergone successful surgery and have negative valve cultures suggesting successful microbial elimination (following initially positive blood cultures), it may be safe to stop antibiotics after 2 weeks (96,97). However, current AHA guidelines suggest that the remaining duration of antibiotics is given (including administration before surgery), but this is on the basis of level C evidence (89).

Reduction of in-hospital stay may also be achieved through an early switch to regimes of oral antibiotics with good bioavailability. In IV drug users, there are RCT data supporting the safety and efficacy of oral ciprofloxacin and rifampicin for uncomplicated MSSA NVE, although increasing rates of fluoroquinolone resistance limit applicability (98). The POET trial is an ongoing Danish multicenter study designed to address whether step-down to oral treatment is safe following the first 10 days of IV antibiotics in staphylococcal, streptococcal, or enterococcal NVE. Four hundred patients will be randomized to 4 to 6 weeks of IV treatment, compared with step down to oral therapy

after a minimum of 10 days, with a primary endpoint of all-cause mortality, unplanned cardiac surgery, embolism, or relapse of positive blood cultures (99).

Early hospital discharge is frequently facilitated by the use of outpatient parenteral antibiotic therapy (OPAT). OPAT can be initiated in specific patients following completion of the first 2 weeks of treatment, after which the risk of complications is reduced. OPAT is contraindicated in patients with heart failure, complex infection, high risk of embolism, neurological complications, or renal impairment (100-102). Facilitated readmission pathways, and close nursing and medical monitoring are necessary.

The major challenges to successful antibiotic therapy are bacterial tolerance and antibiotic resistance. Tolerance occurs when phenotypic variants of bacteria persist despite antibiotic therapy, and resume growth and infection once antibiotic concentrations fall. There are multiple underlying mechanisms, including the very high bacterial density and poor antibiotic penetration within vegetations, low bacterial metabolic activity, and production of protective biofilms on prosthetic material (103). The risk of tolerance, combined with relatively slow bactericidal antibiotic effects, underlies the historical requirement for 4 to 6 weeks of parenteral antibiotic therapy.

Novel strategies are required to prevent and treat IE caused by biofilm-forming strains of multidrug-resistant *S. aureus*. These may include initial inhibition of bacterial adhesion to both living and inert surfaces (thus reducing further biofilm development), disruption of biofilm architecture, and antipathogenic or signal interference approaches involving inhibition of quorum-sensing (18). Prevention of bacterial adhesion at the time of intracardiac device insertion is key, and may be achieved using implants coated with

various adhesion inhibitors. However, despite inhibiting biofilm formation in vitro, antibiotic-, silver ion-, and silver nanoparticle-coated implants have proved to be ineffective and poorly tolerated in humans. Disruption of biofilm architecture may be a more promising approach, and several compounds, including human monoclonal antibodies such as TRL1068, are under current assessment. Treatment of established biofilm using a combination of TRL1068 with daptomycin in an in vivo murine model (where biofilm was formed by infection with MRSA) significantly reduced adherent bacterial count compared with daptomycin alone (104).

<H2>SURGERY. Surgery is undertaken for the specific indications of progressive valve and tissue damage, uncontrolled infection, and high risk of embolism. The objectives are to remove infected tissue, foreign material, and hardware, clear and debride paravalvular infection and cavities, restore cardiac integrity and valve function, and remove threatening sources of embolism. Although different surgical techniques have been used (e.g., mitral valve repair or aortic homograft implantation), a clear long-term advantage of one technique has yet to be proven. Regardless of approach, the long-term results are inferior to elective valve surgery: 10-year survival is in the range of 40% to 60% (105,106). It remains unclear whether this late mortality relates to late prosthetic valve complications, extracardiac manifestations of the disease, or persistence of the biofilm complex.

Surgery is currently performed in 50% to 60% of patients, and 6-month survival rates are over 80% (107,108). The indications for surgery have been predominantly derived from historical observational studies that demonstrate benefit in patients with valve dysfunction causing heart failure, uncontrolled infection (defined as paravalvular

extension, abscess, or persistent bacteremia), or recurrent embolism. For a specific patient, there is often debate, for example, in cases of mild heart failure or regarding the definition of persistent bacteremia (109). Current indications for surgery, as defined in the AHA and ESC guidelines, are shown in **Table 3**.

In the real world, a significant number of patients with a guideline indication for intervention still do not undergo surgery: 24% (202 of 863) of patients with left-sided IE and a guideline indication for intervention in the ICE-PCS registry (108). Predictors of nonsurgical treatment were liver disease (OR for surgery: 0.16, 95% CI: 0.04 to 0.64), stroke prior to surgical decision (OR: 0.54, 95% CI: 0.32 to 0.90), and *S. aureus* infection (OR: 0.50, 95% CI: 0.30 to 0.85). In contrast, severe aortic regurgitation, abscess, and embolization were associated with surgery. Reasons for avoiding surgery in 181 patients included an anticipated poor prognosis regardless of treatment (34%), hemodynamic instability (20%), death before surgery (23%), stroke (23%), sepsis (21%), and surgeon declined to operate (26%). Ultimately, the perceived risk of the operation determines the threshold for surgery; operations for active IE present high risk, with an overall in-hospital mortality of 20% (and higher still in many centers).

Improved risk scoring models for IE would help to clarify the decision-making process. Gaca et al. (110) used the Society of Thoracic Surgeons database to derive an IE surgical risk score, identifying 13 risk factors for mortality, including emergency status, cardiogenic shock, hemodialysis, and "active endocarditis." Other, smaller cohorts have incorporated more detailed parameters of infection, including valve type and organism (111,112). The PALSUSE score includes age ≥ 70 years, substantial intracardiac destruction, staphylococcal infection, urgent surgery, female sex, and EuroSCORE ≥ 10

as predictors of in-hospital mortality, with in-hospital mortality ranging from 0% in patients with a score of 0% to 45% in patients with a score > 3 (112).

The optimal timing of surgical intervention is also contentious. Delaying surgery may allow a longer duration of antibiotic therapy and hemodynamic stabilization, but incurs a risk of disease progression with valve destruction, abscess formation, heart block, embolic complications, and even death. Indeed, for some outcomes (e.g., embolism) the potential gains from surgery reduce with time (56). In 2012, the first RCT of surgery for IE compared early surgery (undertaken within 48 h of randomization) with conventional care in patients with NVE, severe valve regurgitation, and large vegetations. The South Korean study cohort was young (mean age 47 years), with little comorbidity and predominantly streptococcal infection. Early surgery was associated with a significant reduction in the composite endpoint of in-hospital death or embolism (entirely driven by a reduction in embolism). Furthermore, >90% of patients in the conventional group eventually required surgery, thereby validating present indications for intervention. The Kang study is a landmark achievement for research in IE and has encouraged a trend toward early surgery, but its findings are of uncertain applicability in older populations with multiple comorbidities and staphylococcal infection. Studies from the ICE-PCS registry, which define early surgery as that undertaken "within the course of the initial hospitalization for IE," have shown conflicting results. Although early surgery for NVE is associated with reduced mortality, this does not hold true for PVE after adjustment for confounding variables, including survivor bias (the increased likelihood of patients who survive to undergo surgery) (113-115).

The emphasis on "early surgery" differs significantly between European and American guidelines. The ESC guidelines distinguish emergency surgery (performed within 24 h), urgent surgery (within a few days), and elective surgery (after 1 to 2 weeks of antibiotic therapy), with surgery advised on an urgent basis for the majority of cases (68). In contrast, the AHA guidelines define early surgery as "during initial hospitalization and before completion of a full course of antibiotics." Our conclusion at this time is that there is no proven benefit in delaying surgery once an indication for intervention has been established. Whether this is undertaken the same day or within 48 h depends on the individual clinical circumstances and availability of appropriate surgical expertise. Current series demonstrate that very low mortality can be achieved in centers of excellence with high-level experience of the management of complex patients, and concentrated cardiological, microbiological, and surgical expertise (106,116).

Resolving the controversy of early surgery requires robust evidence to move the field forward. RCT-level data are required to drive practice change, which is harder to progress on the basis of observational data alone. In the last 20 years, only 7 RCTs involving patients with IE have been published, the majority of which have focused on antibiotic therapy (**Table 4**). The first stage is to carefully define the priorities for new RCTs that are reasonable and acceptable to the medical community. Multicenter studies are challenging, as experience and outcomes are so variable between centers, whereas few have the volume to perform such studies in isolation. Furthermore, unresolved issues, such as early surgery, may be left behind as competing research priorities emerge. For example, should PVE be considered as a uniformly surgical disease? Should all patients with IE and severe valve dysfunction have surgery, even if they are not in heart failure?

San Roman et al. (109) have proposed a trial of patients with left-sided IE and high-risk features (but not classical surgical indications) randomized to surgery within 48 h or conventional care, with mortality as the primary endpoint. Although logistically challenging, this study would be extremely valuable, and may herald a long-awaited shift from observational studies to RCT-level research.

<H1>CONTEMPORARY MANAGEMENT CHALLENGES IN IE

<H2>1. IE AFTER TAVR.

1. IE AFTER TAVR. TAVR has transformed the outlook for patients with aortic stenosis who were previously deemed inoperable or at high risk for surgery. Although the technology looks set to expand to intermediate-risk populations over time, current TAVR patients are frequently frail, undergoing multiple health care interventions, and may therefore be at high risk of bacteremia and IE. The TAVR-endocarditis population represents a common challenge to cardiologists and surgeons managing contemporary IE, namely, how should we manage PVE in patients who are elderly and at high risk of surgery, but with expected poor outcome if managed medically?

Small numbers of cases of TAVR-endocarditis were reported in the seminal PARTNER trials (117,118), and real-world cohorts are now starting to shed light on incidence and outcomes (**Table 5**). Amat-Santos et al. (12) described 53 patients with TAVR-endocarditis in a multicenter U.S. registry, representing an overall incidence of 0.67% at a mean follow-up of 1.1 years. The incidence of TAVR-endocarditis was 0.5% in the first year post-procedure, occurring at a median time point of 6 months. Over 70% of patients presented with fever, and 77% had an identifiable vegetation on echocardiography. An antecedent procedure was identified as the likely cause of bacteremia in approximately one-half, and antibiotic prophylaxis had been used in 59%

of cases. Infection was most commonly due to staphylococci (CoNS 25%, *S. aureus* 21%, enterococci 21%). Although the self-expanding Medtronic CoreValve system was an independent risk factor for IE (HR: 3.1, 95% CI: 1.37 to 7.14), this requires validation in other series.

Mangner et al. (13) described 55 patients with TAVR-endocarditis from a single center in Germany, representing a cumulative incidence of 3.02% (1.82% per patient-year); 42% of cases (23 of 55) were health care-acquired. On multivariate analysis, chronic hemodialysis and peripheral arterial disease were significant risk factors for development of subsequent TAVR-endocarditis (HR: 8.37, 95% CI: 2.54 to 27.63, $p < 0.001$; HR: 3.77, 95% CI: 1.88 to 7.58, $p < 0.001$, respectively). Infection was caused by *S. aureus* in 38% of cases, enterococci in 31%, CoNS in 9%, and streptococci in 9.1% of cases. In 7 patients, a valve other than the TAVR prosthesis was infected.

Most recently, 250 cases from the Infective Endocarditis after TAVR International Registry were reported from 47 centers worldwide (119). The overall incidence was 1.1% per person-year, presenting at a median time of 5.3 months post-procedure. On multivariate analysis, predictive factors were younger age (HR: 0.97 per year, 95% CI: 0.94 to 0.99), male sex (HR: 1.69, 95% CI: 1.13 to 2.52), diabetes mellitus (HR: 1.52, 95% CI: 1.02 to 2.29), and moderate-severe aortic regurgitation (HR: 2.05, 95% CI: 1.28 to 3.28). Infective organisms were enterococci in 24.6% and *S. aureus* in 23.3%. The in-hospital mortality rate was 36%, and 2-year mortality 67%. Additional patient- and device-related factors contributing to increased risk of endocarditis are likely to be identified, and may also teach us more about the nature of endocarditis. The apparently high incidence may also be due to front-loaded risk in the early months after

the procedure, and longer follow-up will be required to compare outcomes with surgical valve replacement.

Management of TAVR-endocarditis is highly challenging. It remains to be shown whether transcatheter techniques can be used successfully in its management without removal of the infected implant. Many of these patients were considered high or very high risk for surgery before undergoing TAVR. Indeed, < 20% of patients underwent either open-heart surgery or a transcatheter valve-in-valve procedure in the studies to date. Meanwhile, outcomes with antibiotic therapy alone are extremely poor, with in-hospital and 1-year mortality ranging from 47% to 64% and 66% to 75%, respectively. These data underscore the importance of developing better preventive strategies in terms of valve design and prevention of bacteremia.

<H2>2. STROKE AND IE. Infective endocarditis is complicated by stroke in 20% to 40% of cases (120,121). In addition to causing variable neurological disability, stroke is an independent adverse prognostic factor for survival (120,122). The risk of stroke is highest at diagnosis and decreases rapidly after the initiation of antibiotic therapy (incidence falls from 4.82 per 1,000 patient-days in the first week of therapy to 1.71 per 1,000 patient-days in the second week) (56). Identified risk factors for embolism are vegetation size (> 10 to 15 mm), mitral valve involvement, vegetation mobility, and *S. aureus* infection (123-125.)

A key unresolved challenge in the contemporary management of IE is the role of surgery in prevention of stroke/embolism and selection of patients for such surgical intervention. The 2015 update to the AHA/ACC guidelines provided a Class IIa indication for surgery to prevent *recurrent* embolism in patients with 1 or more previous

emboli and ongoing high risk of further embolism (defined as persistent or enlarging vegetations) (89). Similarly, the ESC guidelines provide a Class I recommendation for surgery to prevent recurrent emboli in patients with a persisting vegetation > 10 mm in size (68). On the basis of RCT evidence, both guidelines make a Class IIa recommendation for surgery in patients at risk of first embolism (vegetation > 10 mm in size) when associated with severe valvular regurgitation or stenosis (126). Surgery for prevention of embolism (in the absence of valve dysfunction) may be considered in patients at highest risk (e.g., vegetations > 15 mm), but is rarely undertaken in most institutions for this indication alone.

The optimal timing of surgical intervention in patients who have already had a stroke is contentious, with a number of older studies suggesting poor outcomes from early surgery. There is a risk of hemorrhagic transformation caused by anticoagulation for cardiopulmonary bypass, and hypotension during surgery might theoretically worsen cerebral ischemia. Observational studies have typically been small and inadequately controlled for confounding variables (120,121). In the largest study from the ICE-PCS collaboration, the outcome from 58 patients with an ischemic stroke undergoing early surgery (< 7 days) was compared with late surgery. After risk adjustment, surgery was associated with a nonsignificant increase in the risk of in-hospital mortality (OR: 2.3, 95% CI: 0.94 to 5.65) (121). This finding has been interpreted by both the AHA and ESC to suggest that surgery can be undertaken safely if required, although stroke remains a common reason for lack of surgical intervention in everyday practice (108). In contrast, transient ischemic attack or silent embolism should not delay surgery that is indicated for other reasons (120). Conversely, patients with cerebral hemorrhage or complex stroke

(causing coma) have significantly higher surgical mortality, and surgery should be deferred for at least 4 weeks if indicated in these patients (125,127). What to do with patients with minor bleeding or minor hemorrhagic conversion of an ischemic stroke remains open to clinical judgment. Clinical scenarios are often complex, and the risk and benefit equation often challenges any rigid recommendation.

<H2>3. CARDIAC DEVICE INFECTION. CIEDs include permanent pacemakers, implantable cardioverter-defibrillators, and cardiac resynchronization therapy devices. The number of CDIs in the United States has increased out of proportion to the increase in implantation rates (128). Overall, the incidence of CDI following first implantation is 1 to 10 per 1,000 device-years (approximately 1 per 1,000 device years for pacemakers and 8 to 9 per 1000 device-years for complex devices) (129-131). Patients with CDI have increased short- and long-term morbidity and mortality, and the incremental cost of management is estimated at > $15,000 per patient (132,133).

CDI may involve the generator pocket, device leads, or endocardial (valve or nonvalve) surfaces (or any combination of these locations). Pocket infections are characterized by cellulitis, erythema, wound discharge, and pain, and there may be incipient or overt erosion of the skin overlying the pocket. Infection involving CIED leads or the endocardial surface (CIED IE) is characterized by systemic features (such as fevers and rigors), and frequently coexists with pocket infection. Infective endocarditis may originate from a pocket infection or occur by seeding of infection to the leads via the bloodstream. Staphylococci (particularly CoNS) account for 60% to 80% of cases (134).

Risk factors for CDI may be patient-, procedure-, or device-related (135). Patient-specific risk factors include corticosteroid use, diabetes mellitus, end-stage kidney

disease, previous device infection, chronic obstructive pulmonary disease, malignancy, and heart failure. Procedural risk factors are the development of a post-operative hematoma (OR: 8.46, 95% CI: 4.01 to 17.86), reintervention for lead displacement, long procedure times, and implantation of 2 or more leads. Need for a revision procedure is associated with a 2- to 5-fold higher risk of infection than initial implantation. Use of antibiotic prophylaxis has been shown to protect against CDI in both RCTs and observational studies (136).

Diagnosis of CIED IE is on the basis of echocardiography and blood cultures, with TEE having better sensitivity and specificity than TTE for detection of lead vegetations (137). Importantly, sterile clots are seen in a high percentage of CIED patients without infection, and these lesions are indistinguishable from infected vegetations (138). Where echocardiography is negative or equivocal, radiolabeled leucocyte scintigraphy or ^{18}FDG-PET/CT are highly valuable, and may become the definitive investigation on the basis of a number of studies demonstrating high sensitivity and specificity for infection (**Figure 3**) (139-141). However, there is evidence that ^{18}FDG-PET/CT may give a false negative result for CIED-IE (i.e., lead involvement), if patients have received prior antibiotic therapy. In 1 study, 9 of 13 patients had a false negative scan for CIED-IE,(sensitivity 30.8%) (141). Further studies are required to assess the time course over which the diagnostic value of ^{18}FDG-PET/CT is preserved.

Strategies for the prevention and management of CDI are beyond the scope of this review, but covered in detail by recent guidelines (142). If CIED-IE is confirmed, complete removal of the infected system is indicated because medical therapy alone is associated with increased risk of recurrence and mortality (142,143). Percutaneous

extraction is usually feasible, but associated with a major complication rate of 1.9% (144). Prolonged antibiotic therapy is advised, and blood cultures should be negative for at least 72 h prior to reimplantation if a new device is essential.

<H1>CONCLUSIONS

The challenges of IE are diverse, but many are tractable. Prevention is undoubtedly better than cure. Translating advances in materials science into prosthetic devices with reduced susceptibility to bacterial adhesion would be revolutionary. Understanding the relative importance of dental procedures for patients with known cardiac risk factors would help direct use of antibiotic prophylaxis. The value of integrated diagnostic strategies using multimodality imaging is emerging, and needs refinement on the basis of real-world patient cohorts. Surgical treatment plays an increasing role, but the current wide variation in outcomes suggests that management should be concentrated in larger valve centers of excellence. Further improving the quality and breadth of the evidence base through new RCTs is essential. At the time of writing, only 6 RCTs in IE are shown as currently recruiting on ClinicalTrials.gov. Trials may be difficult to design, but are eminently achievable and could be used to assess novel antibiotic strategies, and indications for and optimal timing of surgery. The ESC and AHA, in collaboration with the surgical societies, are well placed to host and coordinate such studies, which will need to be multicenter and multinational in design, and rely on noncomposite, hard endpoints, such as mortality. Now is the time to transform current challenges in IE into answers.

REFERENCES

1. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet 2016;387:882-93.
2. Pant S, Patel NJ, Deshmukh A, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. J Am Coll Cardiol 2015;65:2070-6.
3. Bor DH, Woolhandler S, Nardin R, et al. Infective endocarditis in the U.S., 1998–2009: a nationwide study. PLoS One 2013;8:e60033.
4. Federspiel JJ, Stearns SC, Peppercorn AF, et al. Increasing US rates of endocarditis with *Staphylococcus aureus*: 1999-2008. Arch Intern Med 2012;172:363-5.
5. Dayer MJ, Jones S, Prendergast B, et al. Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis. Lancet 2015;385:1219-28.
6. Prendergast BD. The changing face of infective endocarditis. Heart 2006;92:879-85.
7. Seckeler MD, Hoke TR. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. Clin Epidemiol 2011;3:67-84.
8. Slipczuk L, Codolosa JN, Davila CD, et al. Infective endocarditis epidemiology over five decades: a systematic review. PLoS One 2013;8:e82665.
9. Selton-Suty C, Célard M, Le Moing V, et al.; AEPEI Study Group. Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based survey. Clin Infect Dis 2012;54:1230-9.

10. Murdoch DR, Corey G, Hoen B, et al.; International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS) Investigators. 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.

11. Voigt A, Shalaby A, Saba S. Rising rates of cardiac rhythm management device infections in the United States: 1996 through 2003. J Am Coll Cardiol. 2006;48:590-1.

12. Amat-Santos IJ, Messika-Zeitoun D, Eltchaninoff H, et al. Infective endocarditis After transcatheter aortic valve implantation: results from a large multicenter registry. Circulation 2015;131:1566-74.

13. Mangner N, Woitek F, Haussig S, et al. Incidence, predictors, and outcome of patients developing infective endocarditis following transfemoral transcatheter aortic valve replacement. J Am Coll Cardiol 2016;67:2907-8.

14. Van Dijck I, Budts W, Cools B, et al. Infective endocarditis of a transcatheter pulmonary valve in comparison with surgical implants. Heart 2015;101:788-93.

15. Patti JM, Allen BL, McGavin MJ, et al. MSCRAMM-mediated adherence of microorganisms to host tissues. Ann Rev Microbiol 1994;48:585-617.

16. Werdan K, Dietz S, Löffler B et al. Mechanisms of infective endocarditis: pathogen-host interaction and risk states. Nat Rev Cardiol 2014;11:35-50.

17. Elgharably H, Hussain ST, Shrestha NK, et al. Current hypotheses in cardiac surgery: biofilm in infective endocarditis. Semin Thorac Cardiovasc Surg 2016;28:56-9.

18. Chung PY, Toh YS. Anti-biofilm agents: recent breakthrough against multi-drug resistant *Staphylococcus aureus*. Pathog Dis 2014;70:231-9.

19. Horder TJ. Infective endocarditis: with an analysis of 150 cases and with special reference to the chronic form of the disease. Q J Med 1909;os2:289-324.

20. Okell CC, Elliott S. Bacteraemia and oral sepsis with special reference to the aetiology of subacute endocarditis. Lancet 1935;2:869-72.

21. Glaser RJ, Dankner A, Mathes SB, et al. Effect of penicillin on the bacteremia following dental extraction. Am J Med 1948;4:55-65.

22. Hirsh HL, Vivino JJ, Merril A, et al. Effect of prophylactically administered penicillin on incidence of bacteremia following extraction of teeth; results in patients with healed rheumatic and bacterial endocarditis. Arch Intern Med (Chic) 1948;81:868-78.

23. Jones TD, Baumgartner L, Bellows MT, et al. Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections. Circulation 1955;11:317-20.

24. van der Meer JTM, Michel MF, Valkenburg HA, et al. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet 1992;339:135-9.

25. van der Meer JM, Thompson J, Valkenburg HA, et al. Epidemiology of bacterial endocarditis in the Netherlands. II. antecedent procedures and use of prophylaxis. Arch Intern Med 1992;152:1869-73.

26. Strom BL, Abrutyn E, Berlin JA, et al. Dental and cardiac risk factors for infective endocarditis: a population-based, case-control study. Ann Intern Med 1998;129:761-9.

27. Lockhart PB, Brennan MT, Sasser HC, et al. Bacteremia associated with toothbrushing and dental extraction. Circulation 2008;117:3118-25.

28. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 2009;30:2369-413.

29. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: guidelines 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.

30. Chambers JB, Shanson D, Hall R, et al. Antibiotic prophylaxis of endocarditis: the rest of the world and NICE. J R Soc Med 2011;104:138-40.

31. Richey R, Wray D, Stokes T. Prophylaxis against infective endocarditis: summary of NICE guidance. BMJ 2008;336:770-1.

32. Danchin N, Duval X, Leport C. Prophylaxis of infective endocarditis: French recommendations 2002. Heart 2005;91:715-8.

33. Duval X, Delahaye F, Alla F, et al.; AEPEI Study Group. Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: three successive population-based surveys. J Am Coll Cardiol 2012;59:1968-76.

34. DeSimone DC, Tleyjeh IM, Correa de Sa DD, et al. Incidence of infective endocarditis caused by viridans group streptococci before and after publication of the 2007 American Heart Association's endocarditis prevention guidelines. Circulation 2012;126:60-4.

35. DeSimone DC, Tleyjeh IM, Correa de Sa DD, et al.; Mayo Cardiovascular Infections Study Group. Incidence of infective endocarditis due to Viridans group Streptococci before and after the 2007 American Heart Association's prevention guidelines: an extended evaluation of the Olmsted County, Minnesota, population and Nationwide Inpatient Sample. Mayo Clin Proc 2015;90:874-81.

36. Mackie AS, Liu W, Savu A, et al. Infective endocarditis hospitalizations before and after the 2007 American Heart Association prophylaxis guidelines. Can J Cardiol 2016;32:942-8.

37. Bikdeli B, Wang Y, Kim N, et al. Trends in hospitalization rates and outcomes of endocarditis among Medicare beneficiaries. J Am Coll Cardiol 2013;62:2217-26.

38. Thornhill MH, Dayer MJ, Forde JM, et al. Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. BMJ 2011;342:d2392.

39. Ruttmann E, Bonatti H, Legit C, et al. Severe endocarditis in transplant recipients--an epidemiologic study. Transplant Int 2005;18:690-6.

40. Pulvirenti JJ, Kerns E, Benson C, et al. Infective endocarditis in injection drug users: importance of human immunodeficiency virus serostatus and degree of immunosuppression. Clin Infect Dis 1996;22:40-5.

41. Fernández-Hidalgo N, Almirante B, Tornos P, et al. Contemporary epidemiology and prognosis of health care–associated infective endocarditis. Clin Infect Dis 2008;47:1287-97.

42. Chu VH, Cabell CH, Benjamin DK Jr., et al. Early predictors of in-hospital death in infective endocarditis. Circulation 2004;109:1745-9.

43. Frimodt-Møller N, Espersen F, Skinhøj P, et al. Epidemiology of *Staphylococcus aureus* bacteremia in Denmark from 1957 to 1990. Clin Microbiol Infect 1997;3:297-305.

44. Landrum ML, Neumann C, Cook C, et al. Epidemiology of *Staphylococcus aureus* blood and skin and soft tissue infections in the US military health system, 2005-2010. JAMA 2012;308:50-9.

45. Tong SYC, Davis JS, Eichenberger E, et al. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev 2015;28:603-61.

46. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 2006;355:2725-32.

47. Blot K, Bergs J, Vogelaers D, et al. Prevention of central line–associated bloodstream infections through quality improvement interventions: a systematic review and meta-analysis. Clin Infect Dis 2014;59:96-105.

48. CDC. CDC Approach to BSI Prevention in Dialysis Facilities. 2013. Available at: http://www.cdc.gov/dialysis/PDFs/Dialysis-Core-Interventions-5_10_13.pdf. Accessed November 17, 2016.

49. Rhodes D, Cheng AC, McLellan S, et al. Reducing *Staphylococcus aureus* bloodstream infections associated with peripheral intravenous cannulae: successful implementation of a care bundle at a large Australian health service. J Hosp Infect 2016;94:86-91.

50. Campoccia D, Montanaro L, Arciola CR. A review of the biomaterials technologies for infection-resistant surfaces. Biomaterials 2013;34:8533-54.

51. Ionescu A, Payne N, Fraser AG, et al. Incidence of embolism and paravalvar leak after St Jude Silzone valve implantation: experience from the Cardiff Embolic Risk Factor Study. Heart 2003;89:1055-61.

52. Schaff HV, Carrel TP, Jamieson WRE, et al. Paravalvular leak and other events in silzone-coated mechanical heart valves: a report from AVERT. Ann Thorac Surg 2002;73:785-92.

53. Shinefield H, Black S, Fattom A, et al. Use of a *Staphylococcus aureus* conjugate vaccine in patients receiving hemodialysis. N Engl J Med 2002;346:491-6.

54. Fowler VG, Jr, Allen KB, Moreira ED, et al. Effect of an investigational vaccine for preventing *Staphylococcus aureus* infections after cardiothoracic surgery: a randomized trial. JAMA 2013;309:1368-78.

55. Bagnoli F, Fontana MR, Soldaini E, et al. Vaccine composition formulated with a novel TLR7-dependent adjuvant induces high and broad protection against *Staphylococcus aureus*. Proc Natl Acad Sci 2015;112:3680-5.

56. Dickerman SA, Abrutyn E, Barsic B, et al.; ICE Investigators. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). Am Heart J 2007;154:1086-94.

57. Nihoyannopoulos P, Oakley CM, Exadactylos N, et al. Duration of symptoms and the effects of a more aggressive surgical policy: two factors affecting prognosis of infective endocarditis. Eur Heart J 1985;6:380-90.

58. Lodise TP, McKinnon PS, Swiderski L, et al. Outcomes analysis of delayed antibiotic treatment for hospital-acquired *Staphylococcus aureus* bacteremia. Clin Infect Dis 2003;36:1418-23.

59. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57-185.

60. Pérez-Vázquez A, Fariñas MC, García-Palomo JD, et al. Evaluation of the Duke criteria in 93 episodes of prosthetic valve endocarditis: could sensitivity be improved? Arch Intern Med 2000;160:1185-91.

61. Habib G, Derumeaux G, Avierinos JF, et al. Value and limitations of the Duke criteria for the diagnosis of infective endocarditis. J Am Coll Cardiol 1999;33:2023-9.

62. Vieira MLC, Grinberg M, Pomerantzeff PMA, et al. Repeated echocardiographic examinations of patients with suspected infective endocarditis. Heart 2004;90:1020-4.

63. Habib G, Badano L, Tribouilloy C, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and by the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 2009;30:2369-413.

64. Habets J, Tanis W, Reitsma JB, et al. Are novel non-invasive imaging techniques needed in patients with suspected prosthetic heart valve endocarditis? A systematic review and meta-analysis. Eur Radiol 2015;25:2125-33.

65. Fagman E, Perrotta S, Bech-Hanssen O, et al. ECG-gated computed tomography: a new role for patients with suspected aortic prosthetic valve endocarditis. Eur Radiol 2012;22:2407-14.

66. Habets J, Tanis W, van Herwerden LA, et al. Cardiac computed tomography angiography results in diagnostic and therapeutic change in prosthetic heart valve endocarditis. Int J Cardiovasc Imaging 2014;30:377-87.

67. Feuchtner GM, Stolzmann P, Dichtl W, et al. Multislice computed tomography in infective endocarditis: comparison with transesophageal echocardiography and intraoperative findings. J Am Coll Cardiol 2009;53:436-44.

68. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis. Eur Heart J 2015;36:3075-128.

69. Saby L, Laas O, Habib G, et al. Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis: increased valvular 18F-fluorodeoxyglucose uptake as a novel major criterion. J Am Coll Cardiol 2013;61:2374-82.

70. Pizzi MN, Roque A, Fernández-Hidalgo N, et al. Improving the diagnosis of infective endocarditis in prosthetic valves and intracardiac devices with ^{18}F-fluordeoxyglucose positron emission tomography/computed tomography: initial results at an infective endocarditis referral center. Circulation 2015;132:1113-26.

71. Erba PA, Conti U, Lazzeri E, et al. Added value of ^{99m}Tc-HMPAO–labeled leukocyte SPECT/CT in the characterization and management of patients with infectious endocarditis. J Nucl Med 2012;53:1235-43.

72. Rouzet F, Chequer R, Benali K, et al. Respective performance of ^{18}F-FDG PET and radiolabeled leukocyte scintigraphy for the diagnosis of prosthetic valve endocarditis. J Nucl Med 2014;55:1980-5.

73. Duval X, Iung B, Klein I, et al.; Acute Phase of Endocarditis) Study Group. Effect of early cerebral magnetic resonance imaging on clinical decisions in infective endocarditis: a prospective study. Ann Intern Med 2010;152:497-504.

74. Meshaal MS, Kassem HH, Samir A, et al. Impact of routine cerebral CT angiography on treatment decisions in infective endocarditis. PLoS One 2015;10:e0118616.

75. Iung B, Klein I, Mourvillier B, et al. Respective effects of early cerebral and abdominal magnetic resonance imaging on clinical decisions in infective endocarditis. Eur Heart J Cardiovasc Imaging 2012;13:703-10.

76. Fowler VG Jr., Miro JM, Hoen B, et al.; ICE Investigators. *Staphylococcus aureus* endocarditis: a consequence of medical progress. JAMA 2005;293:3012-21.

77. Chirouze C, Cabell CH, Fowler VG Jr., et al.; International Collaboration on Endocarditis Study Goup. Prognostic factors in 61 cases of *Staphylococcus aureus* prosthetic valve infective endocarditis from the International Collaboration on Endocarditis Merged Database. Clin Infect Dis 2004;38:1323-7.

78. Wang A, Athan E, Pappas PA, et al.; International Collaboration on Endocarditis-Prospective Cohort Study Investigators. Contemporary clinical profile and outcome of prosthetic valve endocarditis. JAMA 2007;297:1354-61.

79. López J, Revilla A, Vilacosta I, et al. Definition, clinical profile, microbiological spectrum, and prognostic factors of early-onset prosthetic valve endocarditis. Eur Heart J 2007;28:760-5.

80. Alonso-Valle H, Fariñas-Álvarez C, García-Palomo JD, et al. Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. J Thorac Cardiovasc Surg 2010;139:887-93.

81. Chu VH, Woods CW, Miro JM, et al.; International Collaboration on Endocarditis-Prospective Cohort Study Group. Emergence of coagulase-negative staphylococci as a cause of native valve endocarditis. Clin Infect Dis 2008;46:232-42.

82. Seng P, Drancourt M, Gouriet F, et al. Ongoing revolution in bacteriology: routine identification of bacteria by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Clin Infect Dis 2009;49:543-51.

83. Fournier PE, Thuny F, Richet H, et al. Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases. Clin Infect Dis 2010;51:131-40.

84. Chambers J, Sandoe J, Ray S, et al. The infective endocarditis team: recommendations from an international working group. Heart 2014;100:524-7.

85. Chirillo F, Scotton P, Rocco F, et al. Impact of a multidisciplinary management strategy on the outcome of patients with native valve infective endocarditis. Am J Cardiol 2013;112:1171-6.

86. Botelho-Nevers E, Thuny F, Casalta JP, et al. Dramatic reduction in infective endocarditis-related mortality with a management-based approach. Arch Intern Med 2009;169:1290-8.

87. Dawson M, Hunter TH. The treatment of subacute bacterial endocarditis with penicillin: results in twenty cases. J Am Med Assoc 1945;127:129-37.

88. Loewe L, Rosenblatt P, Greene HJ, et al. Combined penicillin and heparin therapy of subacute bacterial endocarditis: report of seven consecutive successfully treated patients. JAMA 1944;124:144-9.

89. Baddour LM, Wilson WR, Bayer AS, et al.; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. Circulation 2015;132:1435-86.

90. Francioli P, Ruch W, Stamboulian D. Treatment of streptococcal endocarditis with a single daily dose of ceftriaxone and netilmicin for 14 days: a prospective multicenter study. Clin Infect Dis 1995;21:1406-10.

91. Ribera E, Gómez-Jimenez J, Cortes E, 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.

92. Fowler VG Jr., Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus.* N Engl J Med 2006;355:653-65.

93. Cosgrove SE, Vigliani GA, Campion M, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. Clin Infect Dis 2009;48:713-21.

94. Fernández-Hidalgo N, Almirante B, Gavaldà J, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating *Enterococcus faecalis* infective endocarditis. Clin Infect Dis 2013;56:1261-8.

95. Gavaldà J, Len O, Miró JM, et al. Brief communication: treatment of *Enterococcus faecalis* endocarditis with ampicillin plus ceftriaxone. Ann Intern Med 2007;146:574-9.

96. Morris AJ, Drinković D, Pottumarthy S, et al. Bacteriological outcome after valve surgery for active infective endocarditis: implications for duration of treatment after surgery. Clin Infect Dis 2005;41:187-94.

97. Muñoz P, Giannella M, Scoti F, et al.; Group for the Management of Infective Endocarditis of the Gregorio Marañón Hospital (GAME). Two weeks of postsurgical therapy may be enough for high-risk cases of endocarditis caused by *Streptococcus viridans* or *Streptococcus bovis*. Clin Microbiol Infect 2012;18:293-9.

98. Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med 1996;101:68-76.

99. Iversen K, Høst N, Bruun NE, et al. Partial oral treatment of endocarditis. Am Heart J 2013;165:116-22.

100. Andrews MM, von Reyn CF. Patient selection criteria and management guidelines for outpatient parenteral antibiotic therapy for native valve infective endocarditis. Clin Infect Dis 2001;33:203-9.

101. Cervera C, del Río A, García L, et al.; Hospital Clinic Endocarditis Study Group. Efficacy and safety of outpatient parenteral antibiotic therapy for infective endocarditis: a ten-year prospective study. Enfermedades Infecciosas y Microbiología Clínica 2011;29:587-92.

102. Duncan CJA, Barr DA, Ho A, et al. Risk factors for failure of outpatient parenteral antibiotic therapy (OPAT) in infective endocarditis. J Antimicrob Chemother 2013;68:1650-4.

103. Lewis K. Platforms for antibiotic discovery. Nat Rev Drug Discovery 2013;12:371-87.

104. Estellés A, Woischnig AK, Liu K, et al. A high-affinity native human antibody disrupts biofilm from *Staphylococcus aureus* bacteria and potentiates antibiotic efficacy in a mouse implant infection model. Antimicrob Agents Chemother 2016;60:2292-301.

105. Musci M, Weng Y, Hübler M, et al. Homograft aortic root replacement in native or prosthetic active infective endocarditis: twenty-year single-center experience. Thorac Cardiovasc Surg 2010;139:665-73.

106. Manne MB, Shrestha NK, Lytle BW, et al. Outcomes after surgical treatment of native and prosthetic valve infective endocarditis. Ann Thorac Surg 2012;93:489-93.

107. Prendergast BD, Tornos P. Surgery for infective endocarditis: who and when? Circulation 2010;121:1141-52.

108. Chu VH, Park LP, Athan E, et al.; International Collaboration on Endocarditis Investigators. Association between surgical indications, operative risk and clinical outcome in infective endocarditis: a prospective study from the International Collaboration on Endocarditis. Circulation 2015;131:131-40.

109. San Román JA, Vilacosta I, López J, et al. Critical questions about left-sided infective endocarditis. J Am Coll Cardiol 2015;66:1068-76.

110. Gaca JG, Sheng S, Daneshmand MA, et al. Outcomes for endocarditis surgery in North America: a simplified risk scoring system. J Thorac Cardiovasc Surg 2011;141:98-106.e1-2.

111. De Feo M, Cotrufo M, Carozza A, et al. The need for a specific risk prediction system in native valve infective endocarditis surgery. ScientificWorldJournal 2012;2012:307571.

112. Martínez-Sellés M, Muñoz P, Arnáiz A, et al.; Spanish Collaboration on Endocarditis — Grupo de Apoyo al Manejo de la Endocarditis infecciosa en

ESpaña (GAMES). Valve surgery in active infective endocarditis: a simple score to predict in-hospital prognosis. Int J Cardiol 2014;175:133-7.

113. Lalani T, Chu VH, Park LP, et al.; International Collaboration on Endocarditis–Prospective Cohort Study Investigators. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis. JAMA Intern Med 2013;173:1495-504.

114. Lalani T, Cabell CH, Benjamin DK, et al.; Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis. Circulation 2010;121:1005-13.

115. Chirouze C, Alla F, Fowler VG Jr., et al.; ICE Prospective Investigators. Impact of early valve surgery on outcome of *Staphylococcus aureus* prosthetic valve infective endocarditis: analysis in the International Collaboration of Endocarditis-Prospective Cohort Study. Clin Infect Dis 2015;60:741-9.

116. Hussain ST, Shrestha NK, Gordon SM, et al. Residual patient, anatomic, and surgical obstacles in treating active left-sided infective endocarditis. J Thorac Cardiovasc Surg;148:981-8.e4.

117. Leon MB, Smith CR, Mack M, et al.; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.

118. Smith CR, Leon MB, Mack MJ, et al.; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.

119. Regueiro A, Linke A, Latib A, et al. Association between transcatheter aortic valve replacement and subsequent infective endocarditis and in-hospital death. JAMA 2016;316:1083-92.

120. Thuny F, Avierinos JF, Tribouilloy C, et al. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. Eur Heart J 2007;28:1155-61.

121. Barsic B, Dickerman S, Krajinovic V, et al.; International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS) Investigators. Influence of the timing of cardiac surgery on the outcome of patients with infective endocarditis and stroke. Clin Infect Dis 2013;56:209-17.

122. Hasbun R, Vikram HR, Barakat LA, et al. Complicated left-sided native valve endocarditis in adults: risk classification for mortality. JAMA 2003;289:1933-40.

123. Vilacosta I, Graupner C, San Román JA, et al. Risk of embolization after institution of antibiotic therapy for infective endocarditis. J Am Coll Cardiol 2002;39:1489-95.

124. Thuny F, Di Salvo G, Belliard O, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. Circulation 2005;112:69-75.

125. García-Cabrera E, Fernández-Hidalgo N, Almirante B, et al.; Group for the Study of Cardiovascular Infections of the Andalusian Society of Infectious Diseases (SAEI); Spanish Network for Research in Infectious Diseases (REIPI). Neurological complications of infective endocarditis: risk factors, outcome, and

impact of cardiac surgery: a multicenter observational study. Circulation 2013;127:2272-84.

126. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med 2012;366:2466-73.

127. Ruttmann E, Willeit J, Ulmer H, et al. Neurological outcome of septic cardioembolic stroke after infective endocarditis. Stroke 2006;37:2094-9.

128. Voigt A, Shalaby A, Saba S. Continued rise in rates of cardiovascular implantable electronic device infections in the United States: temporal trends and causative insights. Pacing Clin Electrophysiol 2010;33:414-9.

129. Uslan DZ, Sohail MR, St. Sauver JL, et al. Permanent pacemaker and implantable cardioverter defibrillator infection: a population-based study. Arch Intern Med 2007;167:669-75.

130. Johansen JB, Jørgensen OD, Møller M, et al. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. Eur Heart J 2011;32:991-8.

131. Landolina M, Gasparini M, Lunati M, et al. Long-term complications related to biventricular defibrillator implantation: rate of surgical revisions and impact on survival: insights from the Italian ClinicalService Database. Circulation 2011;123:2526-35.

132. Rizwan Sohail M, Henrikson CA, Braid-Forbes M, et al. Increased long-term mortality in patients with cardiovascular implantable electronic device infections. Pacing Clin Electrophysiol 2015;38:231-9.

133. Sohail MR, Henrikson CA, Braid-Forbes MJ, et al. Mortality and cost associated with cardiovascular implantable electronic device infections. Arch Intern Med 2011;171:1821-8.

134. Bongiorni MG, Tascini C, Tagliaferri E, et al. Microbiology of cardiac implantable electronic device infections. Europace 2012;14:1334-9.

135. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. Europace 2015;17:767-77.

136. Da Costa A, Kirkorian G, Cucherat M, et al. Antibiotic prophylaxis for permanent pacemaker implantation: a meta-analysis. Circulation 1998;97:1796-801.

137. Victor F, De Place C, Camus C, et al. Pacemaker lead infection: echocardiographic features, management, and outcome. Heart 1999;81:82-7.

138. Downey BC, Juselius WE, Pandian NG, et al. Incidence and significance of pacemaker and implantable cardioverter-defibrillator lead masses discovered during transesophageal echocardiography. Pacing Clin Electrophysiol 2011;34:679-83.

139. Sarrazin JF, Philippon F, Tessier M, et al. Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections. J Am Coll Cardiol 2012;59:1616-25.

140. Ahmed FZ, James J, Cunnington C, et al. Early diagnosis of cardiac implantable electronic device generator pocket infection using ^{18}F-FDG-PET/CT. Eur Heart J Cardiovasc Imaging 2015;16:521-30.

141. Cautela J, Alessandrini S, Cammilleri S, et al. Diagnostic yield of FDG positron-emission tomography/computed tomography in patients with CEID infection: a pilot study. Europace 2013;15:252-7.

142. Sandoe JA, Barlow G, Chambers JB, et al. Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. Report of a joint Working Party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE). J Antimicrob Chemother 2015;70:325-59.

143. Baddour LM, Epstein AE, Erickson CC, et al.; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Nursing; Council on Clinical Cardiology; Interdisciplinary Council on Quality of Care and Outcomes Research. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. Circulation 2010;121:458-77.

144. Fu HX, Huang XM, Zhong LI et al. Outcomes and complications of lead removal: can we establish a risk stratification schema for a collaborative and effective approach? Pacing Clin Electrophysiol 2015;38:1439-47.

145. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy. Eur Heart J 2011;32:3147-97.

146. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease) Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e143-e263.

147. Chan KL, Dumesnil JG, Cujec B, et al.; Investigators of the Multicenter Aspirin Study in Infective Endocarditis. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. J Am Coll Cardiol 2003;42:775-80.

148. Fortún J, Navas E, Martínez-Beltrán J, et al. Short-course therapy for right-side endocarditis due to *Staphylococcus aureus* in drug abusers: cloxacillin versus glycopeptides in combination with gentamicin. Clin Infect Dis 2001;33:120-5.

149. Sexton DJ, Tenenbaum MJ, Wilson WR, et al.; Endocarditis Treatment Consortium Group. Ceftriaxone once daily for four weeks compared with ceftriaxone plus gentamicin once daily for two weeks for treatment of endocarditis due to penicillin-susceptible Streptococci. Clin Infect Dis 1998;27:1470-4.

150. Aung T, Poon K, Horvath R, et al. A case series of medically managed infective endocarditis after transcatheter aortic valve replacement. Scand J Infect Dis 2013;45:489-93.

151. Bosmans JM, Kefer J, De Bruyne B, et al.; Belgian TAVI Registry Participants. Procedural, 30-day and one year outcome following CoreValve or Edwards transcatheter aortic valve implantation: results of the Belgian national registry. Interactive CardioVasc Thorac Surg 2011;12:762-7.

152. Latib A, Naim C, De Bonis M, et al. TAVR-associated prosthetic valve infective endocarditis: results of a large, multicenter registry. J Am Coll Cardiol 2014;64:2176-8.

153. Olsen NT, De Backer O, Thyregod HGH, et al. Prosthetic valve endocarditis after transcatheter aortic valve implantation. Circ Cardiovasc Interv 2015;8:e001939.

154. Puls M, Eiffert H, Hünlich M, et al. Prosthetic valve endocarditis after transcatheter aortic valve implantation: the incidence in a single-centre cohort and reflections on clinical, echocardiographic and prognostic features. EuroIntervention 2013;8:1407-18.

155. Thomas M, Schymik G, Walther T, et al. One-year outcomes of Cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry:. Circulation 2011;124:425-33.

FIGURE LEGENDS

FIGURE 1 Cardiac CT in IE

A 78-year-old man was admitted with infective endocarditis on an aortic bioprosthesis. Blood cultures were positive for *Enterococcus faecalis*. Initial TTE imaging demonstrated a suspected anterior and intercoronary pseudoaneurysm on parasternal long-axis **(A)** and short-axis **(B)** views (arrowed). On TEE **(C and D)**, a vegetation **(C, red arrow)** and pseudoaneurysm **(D, white arrow)** were visualized, although the insertion of the vegetation was not apparent due to shadowing from the frame of the bioprosthesis. On cardiac CT, the vegetation was seen in the left ventricular outflow tract view **(E, red arrow),** which also demonstrated the insertion of the vegetation on the anterior leaflet. The short axis cardiac CT view **(F)** confirmed the anterior pseudoaneursym and 3D reconstruction **(G)** allowed delineation of the position of the pseudoaneurysm relative to the coronary arteries. AO = aorta, CT = computed tomography; IE = infective endocarditis; LA = left atrium; LV = left ventricle; RV = right ventricle; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

FIGURE 2: Integrated imaging strategy in patients with suspected IE.

Adjunctive imaging is valuable both for diagnosis of IE and detection of complications. In the challenging subgroup of patients with possible IE after initial evaluation by TTE and TEE, cardiac CT, metabolic imaging, or cross-sectional imaging of the head and viscera by CT or MRI may help to reach an early definite diagnosis. Cross-sectional imaging by CT or MRI (or metabolic imaging) may assist with detection of complications, such as abscess, mycotic aneurysm, infarct, or hemorrhage in patients with definite IE. Figure 2.1: ^{18}FDG-PET/CT for diagnosis. A 54-year old woman with a history of mitral valve replacement 5 years previously was admitted with features of acute left ventricular failure. TTE on admission showed severe

intraprosthetic regurgitation. The TEE bicommissural **(A and B)** and 3-dimensional atrial views **(C)** revealed a leaflet perforation (arrowed) and severe regurgitation, but no evidence of vegetation. Blood cultures on admission were negative, although inflammatory markers were raised. Antibiotics for suspected blood culture-negative IE were started, and ^{18}FDG-PET/CT confirmed the diagnosis with focal signal uptake on the mitral bioprosthesis **(D and E, red arrow)**. Figure 2.2: ^{18}FDG-PET/CT for detection of complications of IE. A 65-year-old woman with a mitral bioprosthesis was diagnosed with *S. aureus* IE. TEE showed a mobile vegetation with leaflet prolapse and severe regurgitation **(A and B)**. On ^{18}FDG-PET/CT there was ^{18}FDG signal from the mitral bioprosthesis **(C and D, white arrow)**, and evidence of a splenic abscess **(C and E, red arrow)**. ^{18}FDG-PET = 18-fluorodeoxyglucose positron emission tomography; MRI = magnetic resonance imaging; SPECT = single-photon emission computed tomography. Other abbreviations as in **Figure 1**.

FIGURE 3 Cardiac CT and ^{18}FDG-PET/CT in the Diagnosis of CDI

Pacemaker lead IE in a young man with congenital atrioventricular block. On TEE, vegetations were seen on the pacemaker leads **(A and B, arrow)**. On CT imaging, vegetations were seen on the pacemaker lead **(C, arrow)** with an accompanying pulmonary embolism **(D, arrow)**. Confirmation of active pacemaker endocarditis was provided by ^{18}FDG-PET/CT, with uptake seen on the pacemaker lead and within the pulmonary vascular tree **(E and F, arrow)**. CDI = cardiac device infection; RA = right atrium; SVC = superior vena cava. Other abbreviations as in **Figures 1 and 2**.

TABLE 1 Time Trend Studies Addressing the Changing Population Incidence of IE After Guideline Change			
Paper	**Study Location**	**Population/Diagnoses Analyzed**	**Incidence Change?**
Bikdeli, 2013 (37)	United States	All diagnoses of IE from Medicare Inpatient Standard Analytic Files	No evidence of an increase in adjusted rates of hospitalization or mortality after 2007 guideline change
Dayer, 2015 (5); Thornhill, 2011 (38)	England, United Kingdom	All diagnoses of IE from NHS Hospital Episode Statistics	In the 2015 analysis, there was an increase detected in the number of cases of IE above the projected historical trend (by 0.11 cases per 10 million people per month). Statistical analysis identified June 2008 as the change point (3 months after NICE guideline change).
De Simone, 2015 (35); DeSimone, 2012 (34)	Olmsted County, Minnesota	Diagnoses of VGS IE from Rochester Epidemiology Project	No evidence of an increase in VGS IE

Duval, 2012 (33)	France: Greater Paris, Lorraine, and Rhône-Alpes	All diagnoses of IE and subgroups by specific organisms	No evidence of an increase in VGS IE
Mackie, 2016 (36)	Canada	Diagnoses of IE from Canadian Institute for Health Information Discharge Abstract Database	No significant change in the rate of increase in IE cases after publication of guideline change. Reducing incidence of VGS IE over time. Change point analysis did not identify guideline change as a significant inflection point.
Pant, 2015 (2)	United States	Diagnosis of IE using Nationwide Inpatient Sample	Significant increase in the rate of rise in streptococcal infective endocarditis after 2007 (change in the slope before and after: 1.37; 95% CI: 0.69–2.05; p = 0.002). No change point analysis.

CI = confidence interval; IE = infective endocarditis; NHS = National Health Service (UK); NICE = National Institute for Health & Care Excellence (UK); VGS = Viridans group streptococci

Table 2 AHA/ESC Guidelines on Use of Antibiotic Prophylaxis for Prevention of IE				
Procedure	**ACC/AHA**	**Class/Evidence**	**ESC**	**Class/Evidence**
Dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa*	1. Patients with prosthetic cardiac valves 2. Patients with previous IE 3. Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve 4. Patients with CHD, including a. Unrepaired cyanotic CHD, including palliative shunts and conduits; b. Completely repaired CHD repaired with prosthetic material or device, whether placed by surgery or catheter intervention, during the first 6 months after the	IIa B	1. Patients with any prosthetic valve, including a transcatheter valve, or those in whom any prosthetic material was used for cardiac valve repair. 2. Patients with previous IE 3. Patients with CHD, including a. Any type of cyanotic CHD b. Any type of CHD repaired with a prosthetic material, whether placed surgically or by	IIa C

	procedure; or c. Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device.		percutaneous techniques, up to 6 months after the procedure, or lifelong if residual shunt or valvular regurgitation remains	
Vaginal delivery†	1. Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair 2. Patients with unrepaired and palliated cyanotic CHD, including surgically constructed palliative shunts and conduits	IIa C	Not recommended. "During delivery the indication for prophylaxis has been controversial and, given the lack of convincing evidence that infective endocarditis is related to either vaginal or caesarean delivery, antibiotic prophylaxis is not recommended" (145).	III C

ESC management of cardiovascular diseases in pregnancy 2011 (145). NB: infective endocarditis prophylaxis at the time of vaginal delivery is controversial and not included as an indication in the ACC/AHA guidelines on valvular heart disease 2014 or the ESC guidelines on infective endocarditis 2015. *ACC/AHA guidelines on valvular heart disease 2014 (59) and ESC guidelines on infective endocarditis 2015 (68). †ACC/AHA management of adults with congenital heart disease 2008 (146); ESC guidelines on infective endocarditis 2015 (68).

CHD = congenital heart disease; IE = infective endocarditis.

Table 3 Indications for Surgery in AHA and ESC Guidelines					
Indication	**AHA Guidelines 2015 (89)**	**Class/Evidence**	**ESC Guidelines 2015 (68)**	**Class/Evidence**	**Timing†**
Heart failure	Early surgery* is indicated in patients with IE who present with valve dysfunction resulting in symptoms or signs of HF Early surgery* is indicated in patients with PVE with symptoms or signs of HF resulting from valve dehiscence, intracardiac fistula, or severe prosthetic valve dysfunction	I B I B	Aortic or mitral NVE, or PVE with severe acute regurgitation, obstruction or fistula causing refractory pulmonary edema or cardiogenic shock	I B	Emergency
			Aortic or mitral NVE, or PVE with severe regurgitation or obstruction causing symptoms of HF, or echocardiographic signs of	I B	Urgent

			poor hemodynamic tolerance		
Uncontrolled infection	Early surgery* is indicated in patients when IE is complicated by heart block, annular or aortic abscess, or destructive penetrating lesions Early surgery* is reasonable for patients with relapsing PVE	I B IIa C	Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	I B	Urgent
	Early surgery* should be considered particularly in patients with IE caused by fungi or highly resistant organisms (e.g., VRE, multidrug-resistant Gram-negative bacilli)	I B	Infection caused by fungi or multiresistant organisms	I C	Urgent/elective
	Early surgery* is indicated for evidence of persistent infection (manifested by persistent bacteremia or fever lasting > 5–7 days, and provided that other sites of	I B	Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic	IIa B	Urgent

	infection and fever have been excluded) after the start of appropriate antimicrobial therapy		metastatic foci		
			PVE caused by staphylococci or non-HACEK gram-negative bacteria	IIa C	Urgent/elective
Prevention of embolism	Early surgery* is reasonable in patients who present with recurrent emboli and persistent or enlarging vegetations despite appropriate antibiotic therapy	IIa B	Aortic or mitral NVE, or PVE with persistent vegetations >10 mm after one or more embolic episode despite appropriate antibiotic therapy	I B	Urgent
	Early surgery* is reasonable in patients with severe valve regurgitation and mobile vegetations >10 mm	IIa B	Aortic or mitral NVE with vegetations >10 mm, associated with severe valve	IIa B	Urgent

			stenosis or regurgitation, and low operative risk		
	Early surgery* may be considered in patients with mobile vegetations >10 mm, particularly when involving the anterior leaflet of the mitral valve and associated with other relative indications for surgery	IIb C	Aortic or mitral NVE, or PVE with isolated very large vegetations (>30 mm)	IIa B	Urgent
			Aortic or mitral NVE, or PVE with isolated large vegetations (>15 mm) and no other indication for surgery	IIb C	Urgent

* Defined as "during initial hospitalization and before completion of a full course of antibiotics."†Defined as: emergency surgery = performed within 24 h; urgent surgery = within a few days; elective surgery = after at least 1–2 weeks of antibiotic therapy.

HACEK = *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; HF = heart failure; IE = infective endocarditis; NVE = native-valve infective endocarditis; PVE = prosthetic-valve infective endocarditis; VRE = vancomycin-resistant *Enterococcus*.

TABLE 4 20 Years of RCTs in IE 1996–2016			
Publication	**Research Question**	**Patient Population**	**Conclusions**
Kang et al. 2012 (126)	What is the role of early surgery (within 48 h of randomization) in NVE?	Adult patients with left-sided NVE, severe valve disease and large vegetations	Early surgery reduced the composite endpoint of in-hospital death and embolic events within 6 weeks from 23% to 3% (driven by a reduction in embolism)
Fowler et al. 2006 (92)	Comparison of daptomycin vs. vancomycin or anti-staphylococcal penicillin with low-dose gentamicin for bacteremia or IE caused by *S. aureus*	Adults with *S. aureus* bacteremia or infective endocarditis. Patients with intravascular material not intended to be removed within 4 days, or high likelihood of valve replacement surgery or death excluded.	Daptomycin was noninferior for the primary endpoint of clinically successful treatment (defined as lack of clinical failure, microbiological failure, death, failure to obtain blood culture at follow-up, receipt of potentially effective nonstudy antibiotics, or premature discontinuation of the study

			medication). Clinically significant renal dysfunction occurred in 11% of patients who received daptomycin and in 26% of patients who received standard therapy (p = 0.004).
Chan et al. 2003 (147)	Does aspirin reduce the incidence of embolism in patients with IE?	Adults with left-sided endocarditis (NVE or PVE). Patients with expected surgical intervention within 7 days excluded	Aspirin did not reduce the risk of embolic events and caused a nonsignificant trend toward increased incidence of bleeding
Fortún et al. 2001 (148)	Is a short course of glycopeptide (vancomycin or teicoplanin) and gentamicin as effective as combination cloxacillin and gentamicin for treatment of right-sided NVE caused by methicillin-	Adult IVDUs with right-sided NVE caused by MSSA	Glycopeptide therapy is inferior to cloxacillin

	sensitive *S. aureus*?		
Sexton et al. 1996 (149)	Is ceftriaxone plus gentamicin (for 2 weeks) superior to ceftriaxone alone (for 4 weeks) for IE due to penicillin-sensitive streptococci?	Adults with penicillin-sensitive NVE	Equivalent clinical cure in both groups
Ribera et al. 1996 (91)	Is cloxacillin alone as effective as cloxacillin plus gentamicin in a 2-week course for treatment of right-sided *S. aureus* endocarditis in IVDUs?	Adult IVDUs with isolated tricuspid valve endocarditis caused by MSSA	No significant benefit from addition of gentamicin to cloxacillin (92% cure in 2-week cloxacillin group, 8% required prolonged treatment)
Heldman et al. 1996 (98)	Is oral ciprofloxacin/rifampicin treatment of right-sided staphylococcal endocarditis in IVDUs as effective as parenteral therapy (oxacillin or vancomycin,	Adult IVDUs with right-sided staphylococcal endocarditis	Oral therapy is as effective as parenteral treatment and associated with reduced drug toxicity

	plus gentamicin for the first 5 days)?		

IVDUs = intravenous drug users; MSSA = methicillin-sensitive *S. aureus.* Other abbreviations as in **Table 3**.

TABLE 5 Studies of IE Following TAVR					
	Number of TAVR-IE Patients	**1-Year Incidence of TAVR-IE**	**Microbiology**	**In-Hospital Mortality**	**1-Year Mortality**
Aung et al. (150)	4 (cohort of 132)	3.0%	Enterococci (75%), oral streptococci (25%)	0%	0%
Amat-Santos et al. (12)	53 (cohort of 7,944)	0.5%	CoNS (24%), *S. aureus* (21%), enterococci (21%), oral streptococci (5.7%)	47%	66%
Bosmans et al. (151)	2 fatal cases (cohort of 328)	0.61%	Not reported	Not reported	100%
Latib et al. (152)	29 (cohort of 2,572)	0.89%*	Enterococci (21%), CoNS (17%), *S.*	45%	Not reported

			aureus (14%), oral streptococci (3.4%)		
Mangner et al. (13)	55 (cohort of 1,820)	2.25%*	*S. aureus* (38%), enterococci (31%), CoNS (9.1%), oral streptococci (3.6%)	64%	75%
Olsen et al. (153)	18 (cohort of 509)	3.1%	Enterococci (33%), *S. aureus* (17%), oral streptococci (17%), CoNS (11%)	11%	Not reported
PARTNER A Smith et al. (118)	3 (cohort of 344)	0.87%*	Not reported	Not reported	33%
PARTNER B Leon et al. (117)	2 (cohort of 179)	1.12%*	Not reported	Not reported	100%
Puls et al. (154)	5 (cohort of 180)	2.78%	Enterococcus (2)	40%	40%

			Oral streptococci (1), *S. aureus* (1)		
Regueiro et al. (119)	250 (cohort of 20,006)	1.1% per person-year	Enterococcus (24.6%), *S. aureus* (23.8%), CoNS (16.8%)	36%	66.7% (2-year mortality)
Thomas et al. (155)	99.0 % free of IE at 1 year (cohort of 1,038)	0.1%	Not reported	Not reported	3 deaths reported

* Calculated/estimated

CoNS = coagulase-negative staphylococci; IE = infective endocarditis; TAVR = transcatheter valve replacement