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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Challenges in Infective Endocarditis

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ABSTRACT

Infective endocarditis is defined by a focus of infection within the heart and is a feared disease across the field of cardiology. It is frequently acquired in the health care setting, and more than 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 infective endocarditis 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 controlled trials to guide practice. Longstanding controversies such as the timing of surgery or the role of antibiotic prophylaxis have not been resolved. The present article reviews the challenges posed by infective endocarditis and outlines current and future strategies to limit its impact. (J Am Coll Cardiol 2017;69:325–44)

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.

IE is an old problem in a new guise (6). In the pre-antibiotic and early antibiotic eras, it typically affected young or middle-aged adults with underlying rheumatic heart disease or congenital heart disease (CHD) (7). The development of antibiotics, the decline of rheumatic heart disease, and advances in medicine through the 20th century heralded a change in the risk factor profile, patient demographic characteristics, and the 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 >25% of cases (9), while advances in cardiology have driven further changes in the patient demographics 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

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ABBREVIATIONS AND ACRONYMS

^{18}FDG-PET = 18 fluorodeoxyglucose positron emission tomography

ACC = American College of Cardiology

AHA = American Heart Association

CDI = cardiac device infection

CHD = congenital heart disease

CI = confidence interval

CIED = cardiac implantable electronic device

CoNS = coagulase-negative staphylococci

CT = computed tomography

ESC = European Society of Cardiology

HR = hazard ratio

IE = infective endocarditis

IV = intravenous

MRI = magnetic resonance imaging

NVE = native valve infective endocarditis

PVE = prosthetic valve infective endocarditis

OPAT = outpatient parenteral antibiotic therapy

OR = odds ratio

RCT = randomized controlled trial

SPECT = single-photon emission computed tomography

TAVR = transcatheter aortic valve replacement

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

revolutionizing the management of valvular heart disease but may be associated with higher rates of IE than surgically implanted prosthetic valves (12–14).

The present review outlines the challenges posed by contemporary IE in developed countries, as well as 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, as well as the current status of molecular and imaging diagnostic strategies, and review policies for improving service delivery and surgical outcomes. Reflecting the constant evolution of the disease, data on IE in 3 patient groups were also examined 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.

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 after 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 adhesins. These specialized proteins mediate attachment to extracellular host matrix proteins, a process which is 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, in which cycles of bacterial proliferation occur in addition to 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).

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 after dental extraction (21,22). Consequently, in 1955, the American Heart Association (AHA) published guidelines recommending antibiotic prophylaxis for patients with rheumatic heart disease 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. There were several reasons for these revisions. First, in the era of evidence-based practice, there was (and remains) no randomized controlled trial (RCT) of antibiotic prophylaxis for prevention of infective endocarditis 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

TABLE 1 Time Trend Studies Addressing the Changing Population Incidence of IE After Guideline Change

First Author, Year (Ref. #)	Study Location	Population/Diagnoses Analyzed	Incidence Change?
Bikdeli et al., 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 et al., 2015 (5); Thornhill et al., 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 case per 10 million people per month). Statistical analysis identified June 2008 as the change point (3 months after the NICE guideline change).
De Simone et al., 2015 (35); DeSimone et al., 2012 (34)	Olmsted County, Minnesota	Diagnoses of VGS IE from the Rochester Epidemiology Project	No evidence of an increase in VGS IE.
Duval et al., 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 et al., 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 et al., 2015 (2)	United States	Diagnosis of IE using Nationwide Inpatient Sample	Significant increase in the rate of increase in streptococcal IE after 2007 (change in the slope before and after: 1.37; 95% CI: 0.69–2.05; $p = 0.002$). No change point analysis.
Keller et al., 2016 (156)	Germany	All patients hospitalized with acute or subacute IE	Yes. Continuous small increase in incidence of IE before guideline change between 2006 and 2010, with an accelerated increase in incidence following guideline change, between 2011 and 2014.
Van den Brink et al., 2016 (157)	Netherlands	All patients with IE identified from the national healthcare insurance database	Yes, significant increase in IE above the projected historical trend, coinciding with change in ESC guidelines in 2009 (rate ratio 1.327, 95% CI: 1.205–1.462; $p<0.001$). Increased proportion of streptococcal IE following guideline change.

CI = confidence interval; IE = infective endocarditis; NHS = National Health Service (United Kingdom); NICE = National Institute for Health & Care Excellence (United Kingdom); VGS = viridans group streptococci.

and high-magnitude bacteremia (e.g., 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 (30,31).

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 after 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, CHD, and previous IE, as well as 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 before and after this change. No increased incidence was identified and, conversely, there was a drop 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-viridans group streptococci 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 rate 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

TABLE 2 ACC/AHA and ESC Guidelines on Use of Antibiotic Prophylaxis for the Prevention of IE

	ACC/AHA	Class, Level of Evidence	ESC	Class, Level of 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 procedure; or c. Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device	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 using percutaneous techniques, up to 6 months after the procedure, or lifelong if residual shunt or valvular regurgitation remains	IIa, C
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

*ACC/AHA guidelines on valvular heart disease 2014 and ESC guidelines on infective endocarditis 2015. †ACC/AHA management of adults with congenital heart disease 2008 (146); and ESC management of cardiovascular diseases in pregnancy 2011 (145). ‡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 main ESC 2015 guidelines.

CHD = congenital heart disease; IE = infective endocarditis.

extended analysis looking at National Health Service hospital discharge diagnoses up to 2013. Antibiotic prophylaxis dropped from 10,900 prescriptions per month to 2,236 prescriptions per month after introduction of the U.K. National Institute for Health and Care Excellence guidelines. In parallel, there was a significant rise (above the projected trend) in the number of IE cases, by 0.11 case 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 factor 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 European Society of Cardiology [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 who 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).

PREVENTION OF HEALTH CARE–ASSOCIATED IE. Health care–associated IE 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 health care-associated IE is significantly higher than for community-acquired infection (31.1% vs. 20.3%; $p < 0.01$) (9).

Reduction of health care-acquired bacteremia is thus a logical target. Longitudinal studies from Denmark found that an increase in *S aureus* bacteremia 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 bloodstream 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 bloodstream infection in high-risk groups, such as those undergoing hemodialysis, could translate into a major impact on the incidence of IE (48,49).

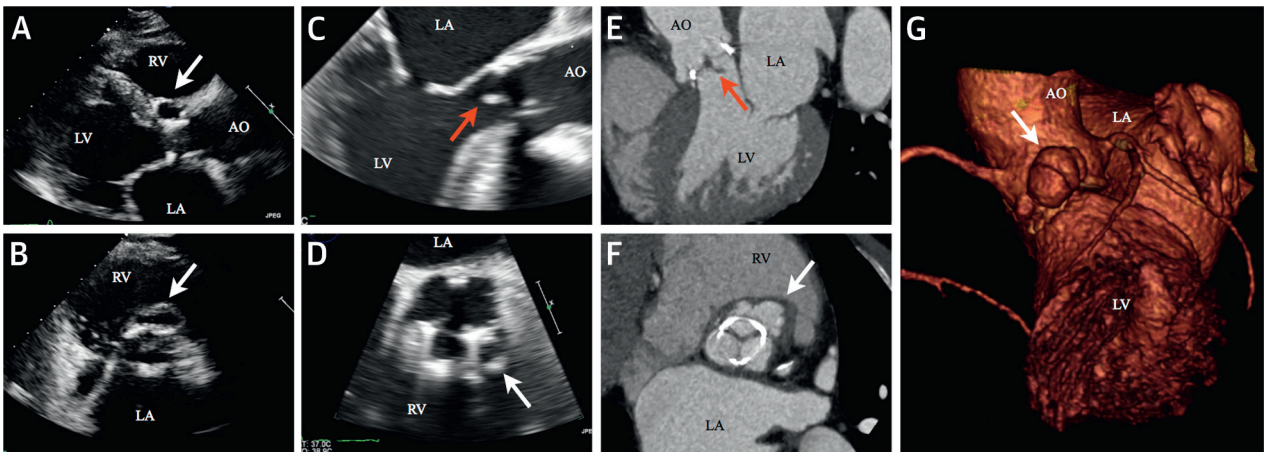
Novel approaches to prevention of bacteremia and strategies to target adherence are urgently required (50). Innovative material technologies, which prevent interaction of bacteria with prosthetic surfaces (so-called low-fouling coats) or contain long-lasting bactericidal coatings, hold promise but have so far failed to translate into clinical practice. Indeed, enthusiasm for antibacterial coatings has been tempered by experience with the Silzone valve (St. Jude Medical, St. Paul, Minnesota), which had a silver-coated sewing ring, but 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 outcome 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 III clinical studies, with 1 failing to reach an efficacy endpoint (prevention of *S aureus* bacteremia in patients undergoing hemodialysis) and another leading to increased mortality in patients undergoing median sternotomy 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).

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 "possible" group according to the Duke criteria.

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 it is superior to TTE for detection of complications, such as perforations, abscesses, and fistulae. In PVE, a recent meta-analysis reported a pooled sensitivity of only 86% (95% confidence interval [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 in which 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.

FIGURE 1 Cardiac CT in IE



A 78-year-old man was admitted with infective endocarditis (IE) on an aortic bioprosthesis. Blood culture specimens were positive for *Enterococcus faecalis*. Initial transthoracic echocardiography imaging demonstrated a suspected anterior and intercoronary pseudoaneurysm on parasternal long-axis **(A)** and short-axis **(B)** views **(arrows)**. On transesophageal echocardiography **(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 computed tomography (CT) scanning, 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 pseudoaneurysm and 3-dimensional reconstruction **(G)** allowed delineation of the position of the pseudoaneurysm relative to the coronary arteries. AO = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle.

Cardiac computed tomography (CT) scanning is the key adjunctive modality for use when the anatomy is not clearly delineated according to echocardiography, and it 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). Cardiac CT is equivalent (and possibly superior) to TEE for demonstrating paravalvular anatomy and complications (e.g., paravalvular abscesses or mycotic aneurysms) and is subject to fewer prosthetic valve artifacts than echocardiography (65-67). This approach may help with planning surgical strategy, and concurrent CT angiography allows exclusion of significant coronary disease in younger patients. Detection of paravalvular lesions by using CT imaging is now a major diagnostic criterion in the 2015 ESC guidelines on IE (68).

Combining CT imaging with metabolic imaging by 18-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) or leukocyte scintigraphy (radiolabeled leukocyte single-photon emission computed tomography [SPECT]) to show regions of metabolic activity or inflammation, respectively, is a hugely promising approach in patients who, according to the Duke criteria, have "possible" IE or suspected CDI (**Figure 2**). Several studies have now investigated the sensitivity and specificity of PET/CT or SPECT/CT imaging in this setting. In a cohort of 72 patients with suspected PVE, ^{18}FDG PET/CT imaging had an overall sensitivity of 73% and a specificity of 80% (69). The 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) 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 leukocyte scintigraphy with SPECT/CT imaging, a sensitivity of 90% and a specificity of 100% have also been reported (71). When directly compared in a cohort with suspected PVE and inconclusive echocardiography findings, ^{18}FDG-PET/CT imaging had higher sensitivity than SPECT/CT imaging, 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 can 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 (26%) of 53 patients from "possible" to "definite" IE (73). In another series, CT cerebral angiography identified intracranial mycotic aneurysms in 32% of patients with left-sided endocarditis, 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 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 it is therefore of limited use in the early postoperative period. False-positive findings for PET/CT imaging have been reported after cardiac surgery due to post-pericardiotomy syndrome and prosthetic valve thrombosis; they have also been reported 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.

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 approximately 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 *Staphylococcus lugdunensis*, associated with highly destructive valvular and perivalvular lesions. Oral streptococci comprise approximately 20% of cases, other streptococci approximately 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.

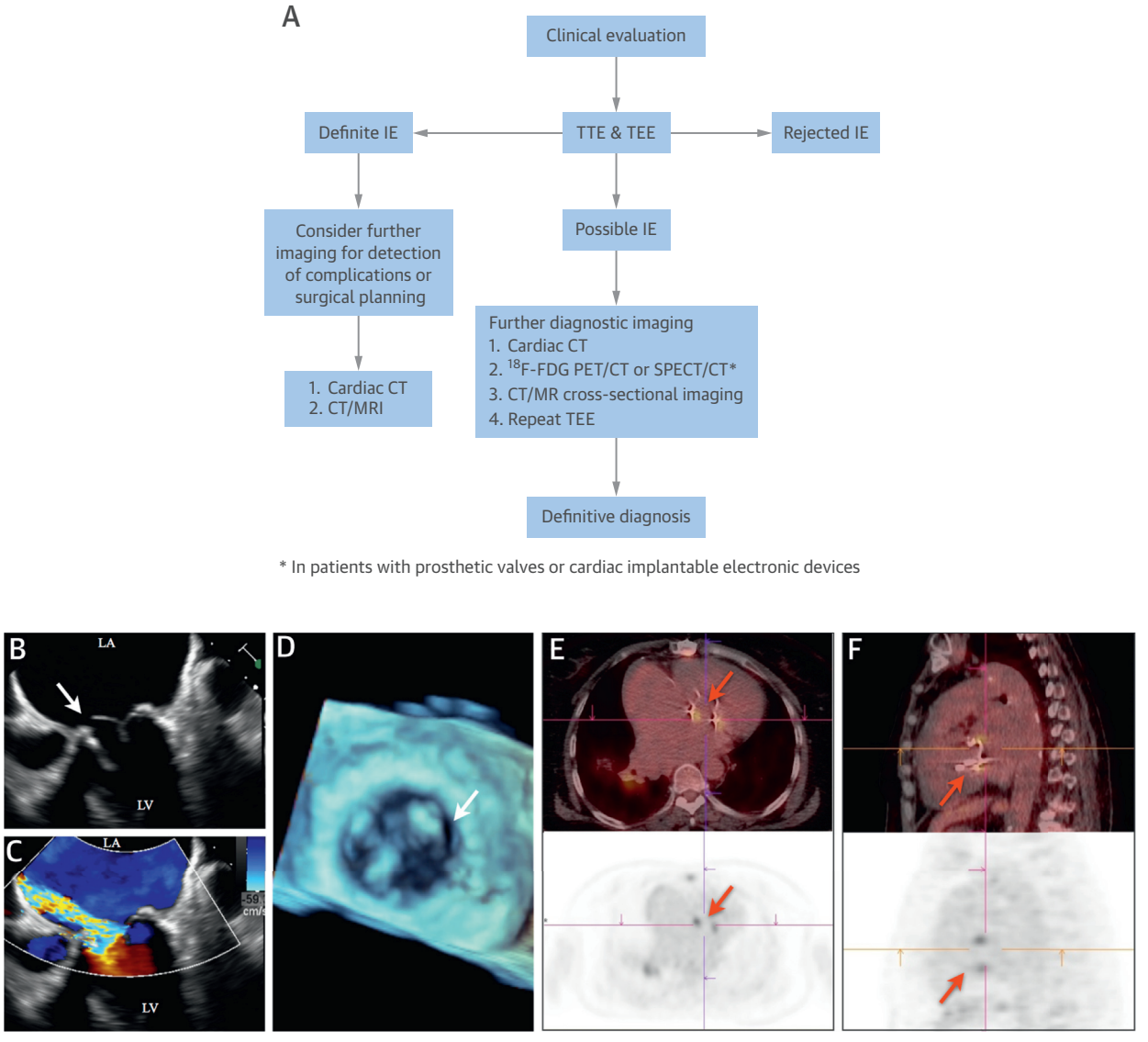
Approximately 10% to 20% of patients have negative blood culture findings at presentation, leading to diagnostic uncertainty. Negative results on blood cultures may occur due to previous antibiotic use, infection with fastidious intracellular organisms or fungi, or an alternative diagnosis. The incidence of blood culture–negative IE may drop 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 methods (82).

A rigorous diagnostic approach to patients with blood culture–negative IE allows a causative organism to be identified in two-thirds of patients (83). The first stage is serological testing for zoonotic agents, specifically *Coxiella burnettii* (causing Q fever), *Bartonella quintana* and *Bartonella henselae*, *Brucella* species, *Myocoplasma* species, and *Legionella* species. If serological findings are positive, blood polymerase chain reaction targeting the causative bacteria should be undertaken. If serological findings are negative, molecular testing of blood or excised valve material is valuable, including broad polymerase chain reaction for bacterial 16S ribosomal ribonucleic acid genes and targeted polymerase chain reaction for *Tropheryma whipplei*, *Bartonella* species, and fungi. If microbiological investigation remains negative, consideration should be given to autoimmune disease, and testing for antinuclear antibodies and rheumatoid factor initiated. In a French cohort of 759 patients with blood culture–negative IE, 476 patients ultimately had an identified etiologic agent, most commonly zoonoses (229 Q fever, 86 *Bartonella* species). Twelve patients were diagnosed with *T whipplei*, 8 with fungi, and 70 with common bacteria; 19 (2.5%) were found to have noninfectious endocarditis caused by autoimmune disease or marantic endocarditis (83).

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

FIGURE 2 Integrated Imaging Strategy in Patients With Suspected IE



(A) Integrated imaging strategy in patients with suspected infective endocarditis (IE). In the challenging subgroup of patients with possible IE after initial evaluation by transthoracic echocardiography and transesophageal echocardiography (TEE), cardiac CT imaging, metabolic imaging, or cross-sectional imaging of the head and viscera by CT scanning or magnetic resonance imaging (MRI) may help to reach an early definite diagnosis. **Panels B to F:** 18-Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET/CT) imaging 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. Transthoracic echocardiography on admission revealed severe intraprosthetic regurgitation. The TEE bicommissural **(B and C)** and 3-dimensional atrial **(D)** views revealed a leaflet perforation **(arrow)** 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 imaging confirmed the diagnosis with focal signal uptake on the mitral bioprosthesis **(E and F, red arrow)**. **Panels G to K:** Cross-sectional imaging by CT or MRI (or metabolic imaging) scans may assist with detection of complications, such as abscess, mycotic aneurysm, infarct, or hemorrhage in patients with definite IE. ^{18}FDG-PET/CT for detection of complications of IE. A 65-year-old woman with a mitral bioprosthesis was diagnosed with *Staphylococcus aureus* IE. TEE revealed a mobile vegetation with leaflet prolapse and severe regurgitation **(G and H)**. On ^{18}FDG-PET/CT imaging, there was ^{18}FDG signal from the mitral bioprosthesis **(I and J, white arrow)** and evidence of a splenic abscess **(I and K, red arrow)**. SPECT = single-photon emission computed tomography; other abbreviations as in Figure 1.

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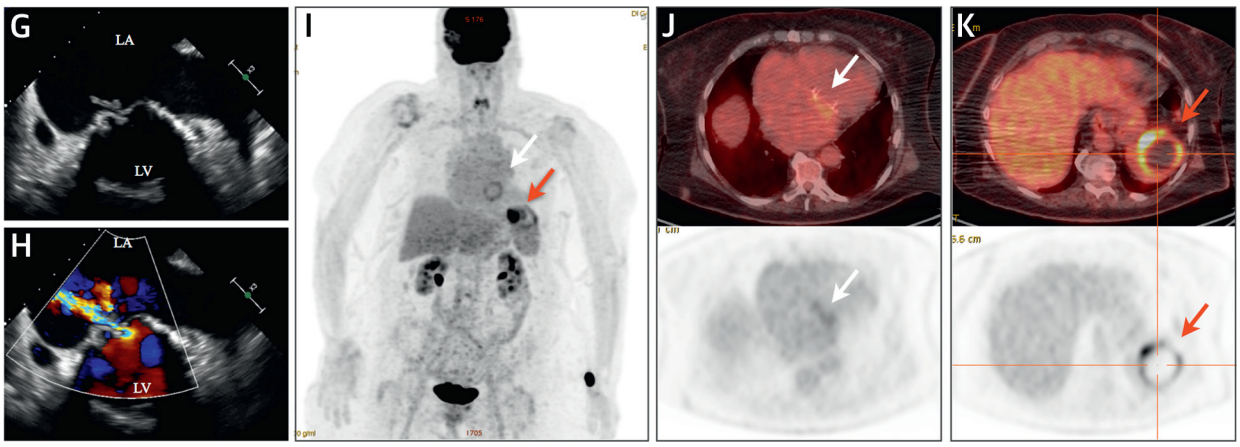
FIGURE 2 Continued



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 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 (34% vs. 16%; $p = 0.0007$) mortality, despite patients being older and having more comorbidities (85). Similarly, a French multidisciplinary team 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 toward a system of centralized IE care (or a hub-and-spoke model, with central multidisciplinary review) should therefore be instituted 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.

ANTIBIOTIC THERAPY. Before 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 the present 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 *S aureus* bacteremia or right-sided endocarditis, daptomycin was shown to be noninferior. Importantly, renal dysfunction occurred in 11% of those treated with daptomycin compared with 26% of the conventional therapy arm (92,93). Aminoglycosides have now been removed from the ESC and AHA guidelines for the treatment of methicillin-sensitive *S aureus* or methicillin-resistant *S aureus* 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, 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 recommendation 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 culture findings suggesting successful microbial elimination (after initially positive blood culture results), it may be safe to stop antibiotics after 2 weeks (96,97). However, current AHA guidelines suggest that the remaining duration of antibiotics be given (including administration before surgery), but this suggestion is indicated on the basis of Level C evidence (89).

Reduction of in-hospital stays may also be achieved through an early switch to regimens 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 methicillin-sensitive *S aureus* NVE, although increasing rates of fluoroquinolone resistance limit applicability (98). The POET (Partial Oral Treatment of Endocarditis) trial is an ongoing Danish multicenter study designed to address whether step-down to oral treatment is safe after the first 10 days of IV antibiotics in staphylococcal, streptococcal, or enterococcal NVE. Four hundred patients will be randomized to receive 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 culture findings (99).

Early hospital discharge is frequently facilitated by the use of outpatient parenteral antibiotic therapy (OPAT). OPAT can be initiated in specific patients after 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, as well as 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 they 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 strategies may include the 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 by 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 currently being assessed. Treatment of established biofilm using a combination of TRL1068 with daptomycin in an in vivo murine model (in which biofilm was formed by infection with methicillin-resistant *S aureus*) significantly reduced the adherent bacterial count compared with daptomycin alone (104).

SURGERY. Surgery is performed for the specific indications of progressive valve and tissue damage, uncontrolled infection, and high risk of embolism. The objectives are as follows: 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 various surgical techniques have been used (e.g., mitral valve repair, 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 ranges from 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 >80% (107,108). The indications for surgery have been predominantly derived from historical observational studies that show 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

TABLE 3 Indications for Surgery in AHA and ESC Guidelines

	AHA Guidelines 2015 (89)	Class, Level of Evidence	ESC Guidelines 2015 (68)	Class, Level of Evidence	Timing†
Heart failure	Early surgery* is indicated in patients with IE who present with valve dysfunction resulting in symptoms or signs of HF	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
	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	Aortic or mitral NVE, or PVE with severe regurgitation or obstruction causing symptoms of HF, or echocardiographic signs of poor hemodynamic tolerance	I, B	Urgent
Uncontrolled infection	Early surgery* is indicated in patients when IE is complicated by heart block, annular or aortic abscess, or destructive penetrating lesions	I, B	Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	I, B	Urgent
	Early surgery* is reasonable for patients with relapsing PVE	IIa, C			
	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 d, and provided that other sites of infection and fever have been excluded) after the start of appropriate antimicrobial therapy	I, B	Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci	IIa, B	Urgent
			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 ≥1 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 stenosis or regurgitation, and low operative risk	IIa, B	Urgent
	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 to 2 weeks of antibiotic therapy.

HACEK = *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; HF = heart failure; NVE = native valve infective endocarditis; PVE = prosthetic valve infective endocarditis; VRE = vancomycin-resistant *Enterococcus*; other abbreviations as in Tables 1 and 2.

indications for surgery, as defined in the AHA and ESC guidelines, are shown in Table 3.

In real-world situations, a significant number of patients with a guideline indication for intervention still do not undergo surgery (i.e., 24% [202 of 863] of patients with left-sided IE and a guideline indication for intervention in the ICE-PCS [International Collaboration on Endocarditis-Prospective Cohort Study] registry) (108). Predictors of nonsurgical treatment were liver disease (odds ratio [OR] for surgery: 0.16; 95% CI: 0.04 to 0.64), stroke before 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 (European System for Cardiac Operative Risk Evaluation) ≥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

TABLE 4 Twenty Years of RCTs in IE, 1996 to 2016

Firs Author, Year (Ref. #)	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 *Staphylococcus aureus*	Adults with *S aureus* bacteremia or IE. Patients with intravascular material not intended to be removed within 4 d 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 specimen 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-sensitive *S aureus*?	Adult IVDUs with right-sided NVE caused by MSSA	Glycopeptide therapy is inferior to cloxacillin
Sexton et al., 1998 (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, plus gentamicin for the first 5 days)?	Adult IVDUs with right-sided staphylococcal endocarditis	Oral therapy is as effective as parenteral treatment and associated with reduced drug toxicity

IVDU = intravenous drug user; MSSA = methicillin-sensitive *Staphylococcus aureus*; RCT = randomized controlled trial; other abbreviations as in Tables 1 and 3.

duration of antibiotic therapy and hemodynamic stabilization but incurs the 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 are reduced 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 (126). 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 care group eventually required surgery, thereby validating present indications for intervention. This 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 scenario does not hold true for PVE after adjustment for confounding variables, including survivor bias (i.e., the increased likelihood of patients who survive to undergo surgery) (113–115).

The emphasis on "early surgery" differs significantly between European and U.S. 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

TABLE 5 Studies of IE After TAVR

First Author, Year (Ref. #)	No. of TAVR-IE Patients	1-Yr Incidence of TAVR-IE	Microbiology	In-Hospital Mortality	1-Yr Mortality
Aung et al., 2013 (150)	4 (cohort of 132)	3.0%	Enterococci (75%), oral streptococci (25%)	0%	0%
Amat-Santos et al., 2015 (12)	53 (cohort of 7,944)	0.5%	CoNS (24%), *Staphylococcus aureus* (21%), enterococci (21%), oral streptococci (5.7%)	47%	66%
Bosmans et al., 2011 (151)	2 fatal cases (cohort of 328)	0.61%	Not reported	Not reported	100%
Latib et al., 2014 (152)	29 (cohort of 2,572)	0.89%*	Enterococci (21%), CoNS (17%), *S aureus* (14%), oral streptococci (3.4%)	45%	Not reported
Mangner et al., 2016 (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., 2015 (153)	18 (cohort of 509)	3.1%	Enterococci (33%), *S aureus* (17%), oral streptococci (17%), CoNS (11%)	11%	Not reported
PARTNER A, 2011 (118)	3 (cohort of 344)	0.87%*	Not reported	Not reported	33%
PARTNER B, 2010 (117)	2 (cohort of 179)	1.12%*	Not reported	Not reported	100%
Puls et al., 2013 (154)	5 (cohort of 180)	2.78%	Enterococcus (40%), oral streptococci (20%), *S aureus* (20%), E. coli (20%)	40%	40%
Regueiro et al., 2016 (119)	250 (cohort of 20,006)	1.1% per person-year	Enterococcus (25%), *S aureus* (24%), CoNS (17%)	36%	66.7% (2-yr mortality)
Thomas et al., 2011 (155)	99.0% free of IE at 1 yr (cohort of 1,038)	0.1%	Not reported	Not reported	3 deaths reported

*Calculated/estimated.

CoNS = coagulase-negative staphylococci; IE = infective endocarditis; PARTNER = Placement of Aortic Transcatheter Valve; TAVR = transcatheter valve replacement.

there is no proven benefit in delaying surgery once an indication for intervention has been established. Whether this surgery is undertaken the same day or within 48 h depends on the individual clinical circumstances and availability of appropriate surgical expertise. Current series show that very low mortality can be achieved in centers of excellence with high-level experience of the management of complex patients and concentrated expertise in cardiology, microbiology, and surgery (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 vary greatly 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 Román et al. (109) have proposed a trial of patients with left-sided IE and high-risk features (but not classical surgical indications) randomized to undergo surgery within 48 h or receive 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.

CONTEMPORARY MANAGEMENT CHALLENGES IN IE.

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 often 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 (Placement of Aortic Transcatheter Valve) 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. More than 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 of patients, and antibiotic prophylaxis had been used in 59% of cases. Infection was most commonly due to staphylococci (CoNS 25%; *S aureus* 21%; and enterococci 21%). Although the self-expanding CoreValve system (Medtronic, Minneapolis, Minnesota) was an independent risk factor for IE (hazard ratio [HR]: 3.1; 95% CI: 1.37 to 7.14), this finding 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 the cases (23 of 55) were health care acquired. On multivariate analysis, chronic hemodialysis and peripheral arterial disease were significant risk factors for the development of subsequent TAVR-endocarditis (chronic hemodialysis—HR: 8.37; 95% CI: 2.54 to 27.63; $p < 0.001$; peripheral arterial disease—HR: 3.77; 95% CI: 1.88 to 7.58; $p < 0.001$). 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-to-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 was 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.

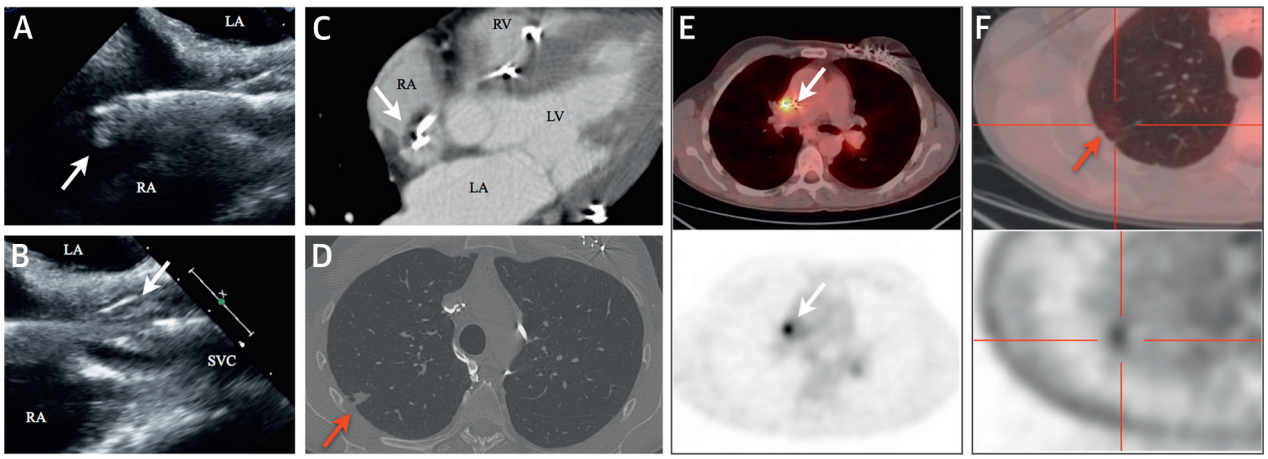
Management of TAVR-endocarditis is highly challenging. It remains to be shown whether transcatheter techniques can be used successfully in its management without removal of the infected implant. Many of these patients were considered high risk or very high risk for surgery before undergoing TAVR. Indeed, <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.

STROKE AND IE. IE 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 drops 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 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 indicate 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 (107). There is a risk of hemorrhagic transformation caused by anticoagulation therapy 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

FIGURE 3 Cardiac CT and ^{18}FDG-PET/CT Imaging 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, white arrow)**. On CT imaging, vegetations were seen on the pacemaker lead **(C, white arrow)** with an accompanying pulmonary embolism **(D, red arrow)**. Confirmation of active pacemaker endocarditis was provided by ^{18}FDG-PET/CT imaging, with uptake seen on the pacemaker lead **(E, white arrow)** and within the pulmonary vascular tree **(F, red arrow)**. CDI = cardiac device infection; RA = right atrium; SVC = superior vena cava; other abbreviations as in Figures 1 and 2.

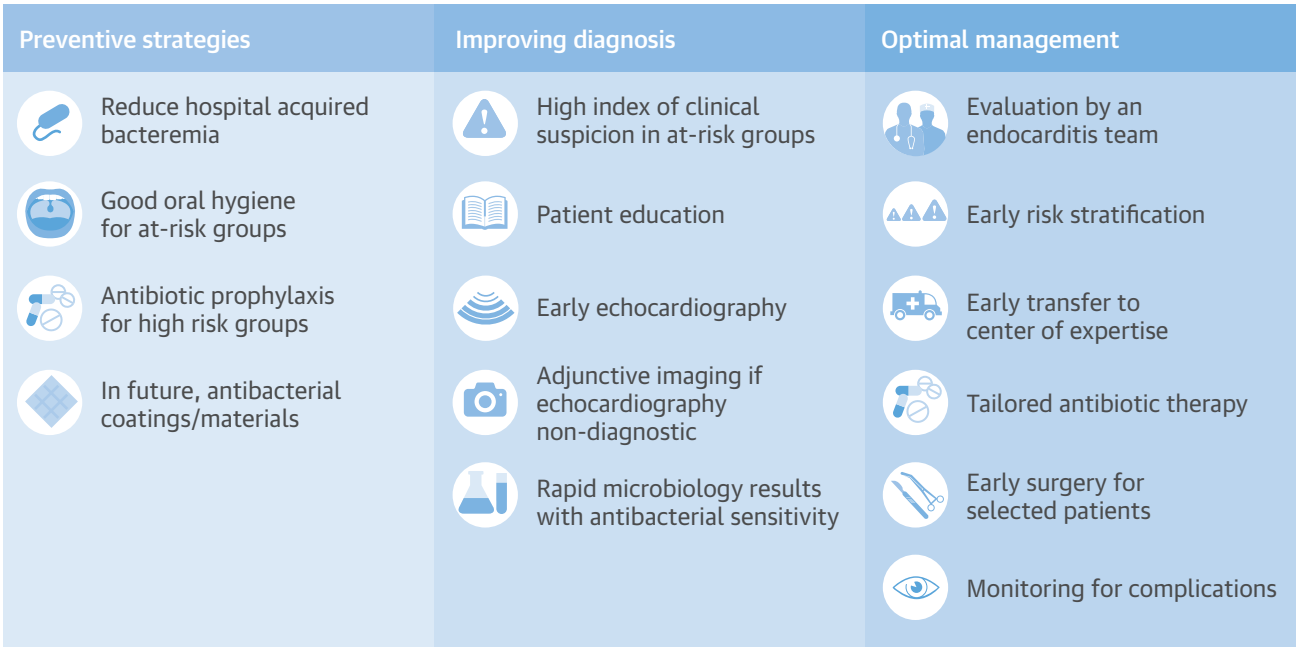
58 patients with an ischemic stroke undergoing early surgery (<7 days) was compared with late surgery. After risk adjustment, surgery was associated with a nonsignificant increase in the risk of in-hospital mortality (OR: 2.3; 95% CI: 0.94 to 5.65) (121). This finding has been interpreted by both the 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). The plan of action for 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.

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 after 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 1,000 device-years for complex devices) (129-131). Patients with CDIs have increased short- and long-term morbidity and mortality, and the incremental cost of management is estimated at more than $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 (e.g., fevers, rigors), and frequently coexists with pocket infection. IE 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 CDIs may be patient-, procedure-, or device-related factors (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 leads. Need for a revision procedure is associated with a 2- to 5-fold higher risk of infection than the initial implantation. Use of antibiotic prophylaxis has

CENTRAL ILLUSTRATION **Infective Endocarditis: Preventive Strategies, Diagnosis, and Management**



Cahill, T.J. et al. J Am Coll Cardiol. 2017;69(3):325–44.

been shown to protect against CDI in both RCTs and observational studies (136).

Diagnosis of CIED-IE is made on the basis of echocardiography and blood culture results, 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). In cases in which echocardiography is negative or equivocal, radiolabeled leukocyte scintigraphy or ^{18}FDG-PET/CT scans are highly valuable, and they 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 imaging may yield a false-negative result for CIED-IE (i.e., lead involvement) if patients have received previous 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 imaging is preserved.

Strategies for the prevention and management of CDI are beyond the scope of the present review but are 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 culture findings should be negative for at least 72 h before reimplantation if a new device is essential.

CONCLUSIONS

The challenges of IE are diverse, but many are tractable (**Central Illustration**). 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. Trials

may be difficult to design but are eminently achievable and could be used to assess novel antibiotic strategies, as well as indications for surgery 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.

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