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Review

Infective Endocarditis: Prevention, Diagnosis, and Management

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ABSTRACT

Infective endocarditis (IE) is among the most severe infectious disease, the prevention of which has not decreased its incidence. The age of patients and the rate of health care-associated IE have increased as a consequence of medical progress. The prevention strategies have been subjected to an important debate and nonspecific hygiene measures are now placed above the use of antibiotic prophylaxis. Indeed, the level of evidence of antibiotic prophylaxis efficiency is low and the indications of its prescription have been restricted in the recent international guidelines. In cases carrying a high suspicion of IE, efforts should be made to rapidly identify patients with a definite or highly probable diagnosis of IE and to find the causative pathogen to ensure that appropriate treatment, including urgent valvular surgery, begins promptly. Although echocardiography remains the main accurate imaging modality to identify endocardial lesions associated with IE, it can be negative or inconclusive especially in cases of prosthetic valve or

RÉSUMÉ

L'endocardite infectieuse (EI) compte parmi les maladies infectieuses les plus graves. Sa prévention n'a pas diminué sa fréquence. L'âge des patients et le taux d'EI liées aux soins ont augmenté à la suite du au progrès médical. Les stratégies de prévention ont fait l'objet d'un important débat et privilégient des mesures d'hygiène non spécifiques plutôt que l'utilisation de l'antibioprophylaxie. D'ailleurs, peu de preuves ont démontré l'efficacité de l'antibioprophylaxie, et ses indications ont été restreintes dans les récentes recommandations internationales. Dans les cas où la suspicion de l'EI est élevée, on devrait s'efforcer à déterminer rapidement les patients ayant un diagnostic certain ou très probable d'EI et à trouver l'agent pathogène responsable afin que le traitement approprié, dont la chirurgie valvulaire urgente, soit offert promptement. Bien que l'échocardiographie reste la principale modalité d'imagerie pour déceler avec précision les lésions endocardiques associées à l'EI, elle peut s'avérer négative ou

Endocarditis is defined as an inflammation of the endocardial surface of the heart. This might include heart valves, mural endocardium, or the endocardium that covers implanted material such as prosthetic valves, pacemaker/defibrillator leads, and catheters. In most cases, the inflammation is related to a bacterial or fungal infection. Streptococci, staphylococci, and enterococci are the most frequent causative pathogens, and rarely endocarditis also can be related to noninfective causes such as immunological or neoplastic.

Infective endocarditis (IE) is a serious disease with an incidence of 30-100 episodes per million patient-years, which did not decreased despite different prevention strategies.[1-5] Its mortality rate remains high despite diagnostic and therapeutic improvements because more than one-third of patients will die within the first year of diagnosis.[6,7] Important changes in the epidemiological profile of this disease that have occurred over the past few decades can explain a part of this situation. Indeed, the age of patients and the rate of health care-associated IE have increased as a consequence of medical progress.[8-10] The decrease in rheumatic heart disease and the increase in degenerative valve heart diseases have led to an increase in patients' age and frequency of comorbidities. Moreover, the use of prosthetic valves and implantable pacemakers/defibrillators among patients has increased steadily and nosocomial IE secondary to intravenous line infections. Thus, the more frequent causative agents now tend to be aggressive pathogens such as staphylococci, resistant-enterococci, or

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other intracardiac devices. Recent studies demonstrated the diagnostic value of other imaging strategies including cardiac computed tomography (CT), positron emission tomography/CT, radiolabelled leukocyte single-photon emission CT/CT, and cerebral magnetic resonance imaging. Novel perspectives on the management of endocarditis are emerging and offer a hope for decreasing the rate of residual deaths by accelerating the processes of diagnosis, risk stratification, and instauration of antimicrobial therapy. Moreover, the rapid transfer of high-risk patients to specialized mediosurgical centres (IE team), the development of new surgical modalities, and close long-term follow-up are of crucial importance.

peu concluante, particulièrement dans les cas de prothèse valvulaire ou d'autres dispositifs intracardiaques. Des études récentes ont démontré la valeur diagnostique d'autres stratégies d'imagerie, dont la tomodensitométrie (TDM) cardiaque, la tomographie par émission de positons/TDM, la scintigraphie aux leucocytes marqués/TDM, et l'imagerie de résonance magnétique cérébrale. De nouvelles perspectives sur la prise en charge de l'endocardite sont apparues et offrent l'espoir de diminuer le taux résiduel de mortalité en accélérant les processus de diagnostic, la stratification du risque et l'instauration de traitements antimicrobiens. De plus, le transfert rapide des patients exposés à un risque élevé vers des centres de spécialités médicochirurgicales, l'élaboration de nouvelles modalités de chirurgie et le suivi étroit à long terme sont d'une importance cruciale.

fungi. Although substantial geographical variations exist, a substantial increase in the rate of staphylococcal IE has been reported, especially in the United States, where chronic hemodialysis, diabetes, and intravascular devices are the 3 main factors associated with IE due to *Staphylococcus aureus.*[9]

Therefore, efforts should be made to develop new strategies at each step of IE management to reduce the residual causes of IE-related deaths. Challenges in IE management include: (1) cost-effective measures of prevention; (2) improvement of diagnostic strategies to reduce the delays for the initiation of the appropriate treatment; and (3) better identification of patients who require close monitoring and urgent surgery.[7]

In this article we review the current knowledge and recommendations in prevention, diagnosis, and management of IE. Perspectives and future directions are also discussed.

Prevention

Existing evidence

The prophylaxis of IE aims at prevention of development of bacteria on endocardial lesions of patients with previously diagnosed cardiac predispositions. It is based on screening and treatment of potential entry sites for organisms, but also sometimes on antibiotic prophylaxis given before health care procedures at risk for bacteremia. In common practice, dental care procedures are the most common situations for which antibiotic prophylaxis has been recommended, but some gastrointestinal and genitourinary tract procedures have also been involved.[11] Those health care procedures carry various rates of induced bacteremia, from 5% for a simple colonoscopy, to 88% for periodontal surgeries.[11] Predisposing cardiac conditions (PCC) have also been stratified depending on the risk of development of endocarditis, but this stratification has changed over time with corresponding recommendations for prophylaxis.[12,13]

Surprisingly, there is no strong evidence supporting the use of antibiotic prophylaxis in patients with PCC. The widely adopted recommendations are mainly based on the results of experimental studies in animals; these works have shown the efficiency of different antibiotic regimens in preventing endocarditis after intravenous inoculation of bacteria in rats, carrying experimentally-induced endocardial lesions.[14,15] Therefore, these experimental models used transient high-grade bacteremia to reproduce the potential effects of a dental care procedure. However, everyday-life actions like chewing or tooth brushing have been shown to cause frequent low-grade bacteremia,[16,17] and might be responsible for a much greater cumulative risk than occasional heath care procedures. Roberts estimated that the cumulative everyday bacteremia over 1 year was 6 million times higher than bacteremia from a dental extraction.[18] Moreover, a recent experimental study confirmed that high-grade bacteremia is not mandatory to induce endocarditis, and supported the hypothesis that everyday exposure to low-grade transient bacteremia represents a greater risk.[19]

As underlined by the recent review from the Cochrane Collaboration concerning antibiotics for the prophylaxis of bacterial endocarditis in dentistry,[20] there are no randomized controlled trials nor cohort studies on this topic. Of the few existing case-control studies, the Cochrane Oral Health Group could include only 1 case-control study in their review, with no significant protective effect of prophylaxis against endocarditis.[21] The few other available case-control studies did not bring contributive results either, and were not included in the Cochrane review because of biases.[22-24] Furthermore, in large observational studies reviewing cases of endocarditis that have developed on known PCC, only a minority of cases are secondary to medical procedures.[25]

Therefore, there is no strong evidence in humans supporting antibiotic prophylaxis against IE, and it is not very likely that some new data will be provided in the near future. Indeed, because of the low incidence of this disease, a randomized controlled trial would need the enrollment of a huge number of patients, and it would probably be fraught with legal and ethical issues.

The eventual benefit of antibiotic prophylaxis must also be balanced with the potential adverse effects of such antibiotics. Indeed, all types of hypersensitivity have been reported with the use of β-lactam, including anaphylaxis. However, in a case-control study, the International Collaborative Study of Severe Anaphylaxis found a low incidence of anaphylaxis after oral amoxicillin, at 6 cases per 10,000.[26] Noteworthy, only 1 case of fatal anaphylaxis related to oral amoxicillin has been reported over 35 years in a recent British survey.[27] Furthermore, the extensive use of such antibiotics is responsible for the development of resistant bacteria. However, the implication of single doses of antibiotics in the selection of resistant micro-organisms is uncertain. Finally, there is a theoretical risk of *Clostridium difficile* colitis after antibiotic prophylaxis.[28]

Table 1. Predisposing cardiac conditions for which prophylaxis with dental procedures is recommended by the ESC[13] and AHA[12] guidelines

Prosthetic valve
Previous IE
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired congenital heart defect with prosthetic material or device, whether placed using surgery or catheter intervention, during the first 6 months after the procedure
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device
Cardiac transplantation recipients who develop cardiac valvulopathy*

AHA, American Heart Association; CHD, congenital heart disease; ESC, European Society of Cardiology; IE, infective endocarditis.

*Only recommended in the AHA guidelines.

Recommendations from learned societies

Antibiotic prophylaxis of IE for patients with PCC has been recommended since 1955, with the first guidelines published by the American Heart Association. Since this seminal paper, recurrent updates have been published by several learned societies from various countries. During the past decade, a dramatic change in antibiotic prophylaxis guidelines has occurred, with a major trend to restrict their indications. This trend started with the 2002 French recommendations,[29] and reached its climax with the publication of the National Institute for Health and Clinical Excellence (NICE) guidance in 2008, which basically did not recommend antibiotic prophylaxis, regardless of the dental, genitourinary, or gastrointestinal procedure, and whatever the PCC.[30] Although the same trend can be noticed in most societies' recommendations, guidelines remain much different between countries. However, the guidelines from the European Society of Cardiology[13] and those from the American Heart Association[12] are similar and still recommend antibiotic prophylaxis only in high-risk patients before a dental procedure (Table 1). American Heart Association guidelines justify this attitude by the fact that patients with a high-risk to develop IE are also those with the highest risk of adverse outcome from IE.

Despite these restrictions, several studies showed that the incidence of IE has not increased since the changing of guidelines for IE prophylaxis.[31-33]

Our recommendations

Despite the low level of evidence supporting the use of antibiotic prophylaxis for IE in patients at risk, malpractice claims are not uncommon from patients who develop endocarditis after dental care for which they did not receive prophylaxis. In a study reviewing 319 cases of legal proceedings from different countries, 83 patients (26%) were successful in legally associating their dental procedure to the onset of IE.[34] However, the most recent guidelines about antibiotic prophylaxis for IE in patients with PCC are disparate between the different learned societies. Therefore, our advice for clinicians would be to follow the current guidelines from the country where they have their practice, mainly to avoid medicolegal issues.

Although data supporting the current recommendations are poor, and the benefits of prophylaxis hypothetic, the education of patients at risk of endocarditis seems to be crucial,[35] and general preventive measures must be highlighted. Indeed, early identification and treatment of potential sources of endocarditis are mandatory: patients with PCC should be urged to consult their physicians in case of fever occurring at 48 hours or later or other lasting symptom, whereas physicians must be aware of the importance of blood cultures before any antibiotic prescription in this setting. Because of the suspected major role of everyday cumulative bacteremia in IE,[16,17,19] the need for good oral hygiene and a frequent dental assessment is critical. Finally, the absolute necessity to limit invasive procedures in patients at risk must be highlighted. Indeed, the use of an intravenous catheter should be dramatically restricted in frequency and duration in patients carrying intracardiac devices, to reduce nosocomial bacteremia and therefore health care-induced IE.[9]

Diagnosis

Evolution of diagnostic strategies

In cases carrying a high suspicion of IE, appropriate antibiotics must be started as soon as possible because delay has negative effects on clinical outcomes. Efforts should be made to rapidly identify patients with a definite or highly probable diagnosis of IE and to find the causative pathogen to ensure that appropriate antibiotic therapy begins promptly.

Diagnosis of IE usually relies on the association between an infectious syndrome and recent endocardial involvement. This is the cornerstone of the various classifications and scores proposed to facilitate the difficult diagnosis of this disease. These classifications have been modified with advances in microbiological testing and cardiac imaging techniques. Thus, von Reyn and colleagues only used results from blood cultures to define the bacterial infection and the presence of a new regurgitant murmur or a predisposing heart disease to define endocardial involvement.[36] The subsequent Duke University criteria included echocardiographic detection of the typical endocardial lesions (vegetation, abscess, new prosthetic dehiscence) as a major diagnostic criterion.[37] In 2002, these criteria were further modified to include *Coxiella burnetii* serology as a new major criterion.[38] The sensitivity of these modified Duke criteria is however limited, especially at an early stage of the disease, in cases of negative blood culture and in the presence of prosthetic valve or pacemaker/defibrillator leads. New diagnostic strategies are thus emerging to improve pathogen identification when blood cultures are negative, and to demonstrate endocardial involvement or vascular complications when echocardiography is negative or doubtful. Polymerase chain reaction (PCR) techniques, immunohistochemistry, systematic serologies, magnetic resonance imaging (MRI), and molecular imaging are promising tools that might be integrated into future diagnostic classifications (Fig. 1).

Clinical presentation

Although the presence of fever in a patient with a cardiac predisposition (heart valve disease, intracardiac materials, congenital heart disease) is the most frequent circumstance leading to diagnosis (almost 50% of cases[39]), clinical histories are highly variable (Table 2). Therefore, a high index of

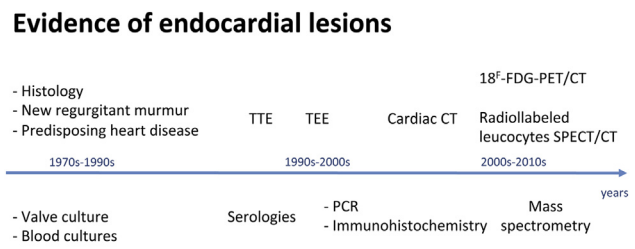

Figure 1. Evolution of the diagnostic methods to diagnose infective endocarditis during the past decades. CT, computed tomography; FDG, fluorodeoxyglucose; PCR, polymerase chain reaction; PET, positron emission tomography; SPECT, single-photon emission computerized tomography; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

suspicion and low threshold for investigation are essential. Blood cultures and echocardiography association still remain the cornerstones for diagnosis.[13]

Microbiological investigations

The challenges are to rapidly identify the causative pathogen and the rare cases of non-IE. In IE, blood cultures are negative in 2.5%-31% of cases.[40,41] This often poses diagnostic and therapeutic issues. Although culture-negative endocarditis is often related to previous antibiotic therapy, a substantial number of cases result from infection with obligate intracellular bacteria, fungi, and fastidious pathogens.[41] Isolation of these organisms requires culture on specialized media, and their growth is often slow. Second, appropriate antibiotic treatment is often delayed in cases in which endocarditis is caused by one of these pathogens, potentially affecting outcomes.

To resolve these issues, some authors proposed to standardise the timing and type of laboratory tests. This improves yields by systematically screening for all potential causes of IE.[40] The "diagnostic kit," composed of 3 units, can be done within 2 hours for every patient with suspected IE. The first, performed immediately, includes a set of 2 blood culture bottles for aerobic and anaerobic cultures, and a tube to collect a serum sample which is used for detection of rheumatoid factor and estimation of specific antibodies directed against *Coxiella burnetii*, *Legionella pneumophila*, *Bartonella*, *Brucella*, *Mycoplasma*, and *Aspergillus* spp. The second and third units each contain a set of 2 blood culture bottles, both to be used 2 hours after the first. The results of these diagnostic tests can be obtained soon after admission, thus shortening the time to institution of a specific therapy. Using this approach, clinicians would not have to defer serological testing until blood cultures are shown to be negative. However, the interest in immediate serological performance in low-prevalence areas must be identified, and we do not know whether this strategy is cost-effective. The diagnostic yield of repeated sampling thereafter is low.[40]

Causative pathogens can also be identified by other means, such as cultures from valve tissue. However, pathogen detection often poses a challenge for pathologists. It can be done using nonspecific histochemical stains or immunohistochemical analyses. Because specific antibodies are often not available, another method, termed autoimmunohistochemistry, which uses the patient's own serum, has been described for detection of microorganisms in valve specimens.[42] This procedure uses a peroxidase-based method with the patient's own serum as the source of antibodies directed against the etiologic microorganism of IE such as *C. burnetti* or *Bartonella* spp.

The rapid and reliable detection of pathogens using PCR has been validated in valve tissue from patients undergoing surgery for IE. Molecular pathogen detection in blood using pathogen-specific or broad-range PCR assays for bacteria and fungi is also promising. However, cautious interpretation of this molecular method is crucial, because of the risk of interfering contamination (false positive results). The clinical context must also be considered. These advanced methods can be integrated into a standardized multimodal strategy that allows better identification of the causes of blood culture-negative endocarditis.[41]

Table 2. Clinical presentation of IE

IE must be suspected in the following situations
1. New regurgitant heart murmur
2. Embolic events of unknown origin
3. Sepsis of unknown origin (especially if associated with IE-causative organism)
4. Fever: the most frequent sign of IE
IE should be suspected if fever is associated with:
a. Intracardiac prosthetic material (eg, prosthetic valve, pacemaker, implantable defibrillator, surgical baffle/conduit)
b. Previous history of IE
c. Previous valvular or congenital heart disease
d. Other predisposition for IE (eg, immunocompromised state, IVDA)
e. Predisposition and recent intervention with associated bacteremia
f. Evidence of congestive heart failure
g. New conduction disturbance
h. Positive blood cultures with typical IE-causative organism or positive serology for chronic Q fever
i. Vascular or immunologic phenomena: embolic event, Roth spots, splinter hemorrhages, Janway lesions, Osler nodes
j. Focal or nonspecific neurological symptoms and signs
k. Evidence of pulmonary embolism/infiltration (right-sided IE)
l. Peripheral abscesses (renal, splenic, cerebral vertebral) of unknown cause

IE, infective endocarditis; IVDA, intravenous drug abuse.
Modified from Habib et al.[13] with permission from Oxford University Press.

Imaging investigations

Echocardiography. This remains an accurate method to detect endocardial involvement in IE and must be done rapidly and repeated weekly as soon as the condition is suspected. Data do not substantiate more than 3 echocardiography examinations as an efficient strategy to increase the diagnostic yield for all but selected patients with suspected IE.[43] Transthoracic echocardiography (TTE) should be used initially as a normal scan in low-risk patients and provides a rapid, noninvasive confirmation that the diagnosis is unlikely. TTE is superior to transesophageal echocardiography (TEE) for hemodynamic assessment of valvular dysfunction and probably for detecting anterior cardiac abscesses. Because of its greater sensitivity and specificity, TEE is recommended in all cases of: (1i) a negative TTE associated with high clinical suspicion; (2) poor TTE quality; (3) the presence of prosthetic valves or intracardiac device; and (4) a positive TTE.[13] As recommended in the European guidelines,[44] we believe that

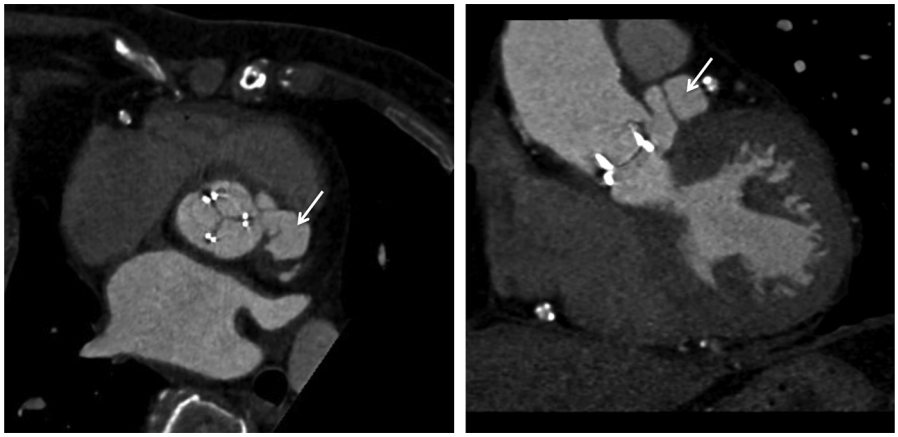

Figure 2. Cardiac computed tomography scan of patient with infective endocarditis on an aortic bioprosthetic valve. The imaging shows a pseudoaneurysm with a prosthetic dehiscence (**white arrows**) at the level of the anterior part of the annulus.

TEE should be performed even in patients with positive TTE because it offers a better evaluation of the lesions; especially TEE could detect a small abscess when a TTE had only diagnosed vegetation. So, in these cases, performing TEE could have an effect on therapeutic management.

Although some guidelines state that TEE is not mandatory in isolated right-sided native valve IE with good quality TTE examination and unequivocal echocardiographic findings, we believe that TEE should be performed at least once to rule out an association with a complicated left-sided IE (perforation, fistula, pseudoaneurysm, or abscess).

Follow-up echocardiography to monitor complications and response to treatment is mandatory. According to the European guidelines, repeat TTE and TEE should be considered during follow-up of uncomplicated IE to detect new silent complications and monitor vegetation size. However, the timing and mode (TTE or TEE) of repeat examination depend on the initial findings, type of micro-organism, and initial response to therapy. We believe that systematic use of TEE in this monitoring should be performed in the first 2 weeks of treatment because most complications occur during this period although it is not based on strong evidence.

The identification of vegetation, abscess, valvular perforation, or new prosthetic-valve dehiscence will enable confirmation of the diagnosis in most, though not all, cases. Diagnosis might be particularly challenging in patients with intracardiac devices, a valvular prosthesis, pre-existing severe lesions, or with very small or no vegetation.

The systematic use of TTE alone vs TTE with TEE in all cases with *S. aureus* bacteremia remains an area of controversy. Although some experts recommend TEE in all patients presenting with *S. aureus* bacteremia, it is believed that the use of TEE could be guided by individual patient risk factors, mode of acquisition of *S. aureus* bacteremia, and clinical presentation. It should be limited to subsets with clinical findings of endocarditis, persistence, intracardiac devices, secondary foci, and relapse. The cost-effectiveness of TTE before TEE among these patients is unknown.[45,46]

The sensitivity of TTE for the diagnosis of vegetation is approximately 75%, but it might be reduced in cases of low echogenicity, very small vegetation, and in IE affecting intracardiac devices or prostheses. TEE enhances the sensitivity to approximately 85%-90% for the diagnosis of vegetation, and > 90% specificity has been reported for TTE with TEE. The sensitivity of TTE for the diagnosis of abscesses is approximately 50%, compared with 90% for TEE. Specificity > 90% has been reported, for both TTE and for TEE.[30,44]

An erroneous diagnosis of IE might occur in several situations; for example, differentiating between vegetation and thrombi, prolapsed cusp, cardiac tumours (myxoma or fibroelastoma), myxomatous changes, Lambl excrescences, or strands. Innovations in imaging techniques are emerging to resolve these issues, (eg, multislice computed tomography [CT], molecular imaging, and MRI).[7] All of these techniques are complementary to echocardiography and do not replace it.

Multislice CT. Recent advances in the temporal and spatial resolution of multislice CT scanners allow high-resolution cardiac imaging. Currently, the major application of multislice CT is in the evaluation of coronary artery disease but it has been used also for heart valve disease, such as aortic stenosis and, more recently, in IE (Fig. 2).[47-49]

In a small study of 37 consecutive patients with clinically suspected IE, Feuchtner et al. found good results in detecting IE valvular and perivalvular damage using electrocardiogram (ECG)-gated 64-slice CT or dual-source CT. The diagnostic performance of CT for the detection of evident abnormalities for IE compared with TEE was: sensitivity 97%, specificity 88%, positive predictive value (PPV) 97% and negative predictive value (NPV) 88% on a per-patient basis. In a per valve-based analysis, the diagnostic accuracy for the detection of vegetation and abscess/pseudoaneurysm compared with surgery was: sensitivity 96%, specificity 97%, PPV 96%, NPV 97%, and sensitivity 100%, specificity 100%, PPV 100%, NPV 100%, respectively, without significant differences compared with TEE. Although the small leaflet perforations were missed, CT provided more accurate anatomical information regarding the perivalvular extent of abscess/pseudoaneurysm than TEE.[48] Gahide et al. found similar results in patients with aortic valve IE.[49] Because prosthetic valve IE represents one of the most difficult situations for echocardiographic studies, Fagman et al. recently investigated

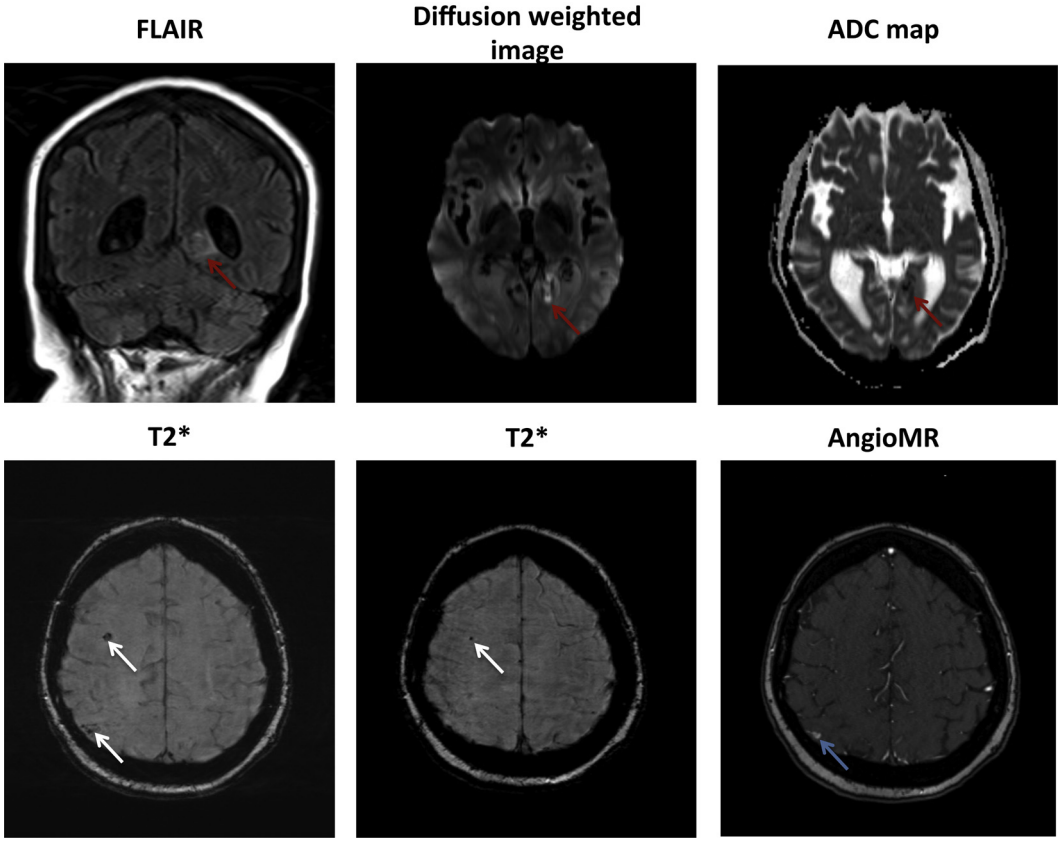

Figure 3. Cerebral magnetic resonance imaging in a patient with infective endocarditis. The FLAIR, diffusion weighted, and ADC map images show a recent ischemic cerebral event (**red arrows**). The T2* sequences show intracerebral microhemorrhages (microbleeds, **white arrows**). Angiography magnetic resonance (AngioMR) shows a right occipital infectious (mycotic) aneurysm (**blue arrow**). ADC, apparent diffusion coefficient; FLAIR, fluid attenuated inversion recovery.

the role of ECG-gated 64-slice CT in the diagnosis of aortic prosthetic valve IE. In 27 patients, the authors showed that the strength of agreement between ECG-gated CT and TEE was good for abscess and dehiscence, and moderate for vegetation. Compared with intraoperative findings, CT detected 3 additional pseudoaneurysms that were unnoticed by TEE. In 2 of these cases, the pseudoaneurysm was located close to the right coronary cusp, a location that is difficult to investigate using TEE.[47]

Thus, this imaging modality offers the possibility to rapidly image the heart and other organs and thus to identify cardiac lesions and extracardiac complications, such as embolic events, infectious aneurysms, hemorrhages, and septic metastases, which can modify the therapeutic strategy. Moreover, it provides an anatomical assessment of the coronary bed, which is important in the preoperative evaluation. However, contrast products should be used with caution in patients with renal failure or hemodynamic instability because of the risk of worsening renal impairment in combination with antibiotic nephrotoxicity. In some cases, the indications for a CT scan might be limited to the brain and its arteries. Specific recommendations are needed to clearly define the appropriate situations in which this modality should be used.

MRI. Although multiple case reports demonstrate how MRI can identify valvular and perivalvular damage in patients with IE, the identification of silent cerebral complications appear to be its main utility. Systematic MRI detected subclinical cerebrovascular complications in approximately 50% of patients, and this might modify disease management (Fig. 3).[50,51] In a single-centre study, Duval et al. described how the identification of brain damage using cerebral MRI modified their classification and management of 130 patients with suspected or definite endocarditis. In this work, MRI identified cerebral lesions in 82% of patients. Solely on the basis of these MRI results, and excluding microhemorrhages, the diagnostic classification of 32% of the cases of nondefinite endocarditis was upgraded to either definite or possible. Moreover, the therapeutic plans were modified for 18% of patients, including surgical plan modifications for 14%.[50] The same investigators analyzed the benefit of the addition of abdominal MRI in these patients; they demonstrated that cerebral and abdominal MRI findings affected diagnosis, but only cerebral MRI affected clinical management plans.[52]

Molecular imaging. Preliminary results have shown much promise for 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT scans in the setting of pacemaker/defibrillator leads and prosthetic valve IE.[53,54] This imaging modality enables measurement of metabolic activity within an organ obtained from the emission of positrons after disintegration of the injected radioactive product. It has been used to

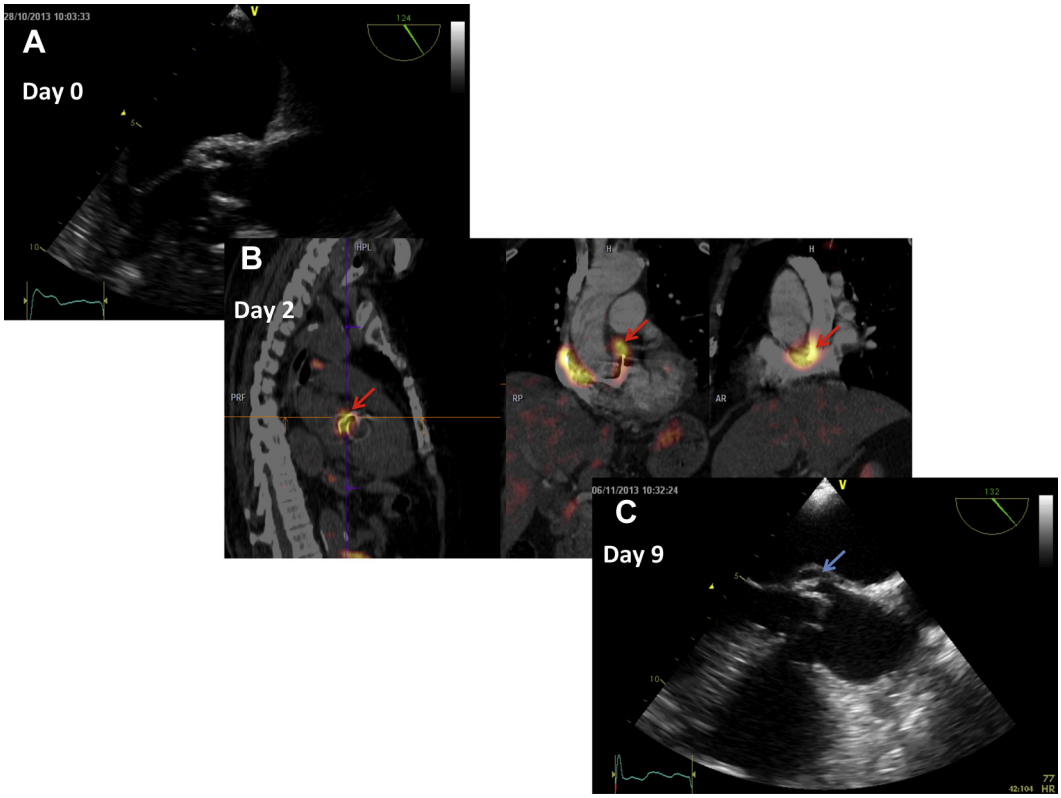

Figure 4. Results of transesophageal echocardiography (TEE) studies and ^{18}F-FDG PET/CT in a case of suspicion of aortic bioprosthetic valve infective endocarditis. (**A**) The first TEE showed minimal thickening of the aortic root wall in a patient with fever and blood cultures positive for *Pseudomonas aeruginosa*. (**B**) The ^{18}F-FDG PET/CT performed 2 days after the first TEE showed an early hyperfixation around the aortic prosthesis (**red arrow**). (**C**) The second TEE, performed 9 days later, showed the development of a periprosthetic abscess (**blue arrow**). CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.

identify inflammatory and infectious processes because the inflammatory cells have significant FDG uptake. Recently, we determined the value of PET/CT for diagnosing prosthetic valve endocarditis. In a sample of 71 patients, the sensitivity and a specificity of PET/CT were respectively 73% and 80%. Interestingly, adding abnormal FDG uptake around the prosthetic valve as a new major criterion significantly increased the sensitivity of the modified Duke criteria at admission from 70% to 97% (Fig. 4). This result was due to a significant reduction in the number of possible diagnoses.[55] This work supports the use of PET/CT in the difficult diagnostic situations of prosthetic valve endocarditis and thus the addition of an abnormal FDG uptake as a novel major criterion in the modified Duke classification.[55] Although the preliminary results of ^{18}F-FDG PET/CT in the diagnosis and the management of IE are encouraging, several limitations remain. Especially, false positive results of PET/CT might occur when this technique is performed too early after the implantation of the prosthetic valve. These false positive results might be related to the early postoperative inflammation around the sewing ring. In addition, its value in native valve IE is unknown.

The role of PET/CT also has been investigated in the diagnosis of cardiovascular implantable electronic device (CIED) infections. Bensimhon et al. investigated the diagnostic value of PET/CT. The authors analyzed 21 patients with suspected CIED infection and 14 control subjects free of infection. The final diagnosis was obtained either from bacteriological data after device culture or a 6-month follow-up according to modified Duke criteria. Sensitivity, specificity, PPV, and NPV were, respectively, 80%, 100%, 100%, and 84.6% in the patient-based analysis; they were 100%, 100%, 100%, and 100% for boxes but only 60%, 100%, 100%, and 73% for leads. None of the control patients were positive for CIED uptake.[56]

In another study, Ploux et al. tested the role of ^{18}F-FDG PET/CT in the management of suspected CIED infections. By including 10 patients with a suspected CIED infection with negative TEE signs, the authors showed that 6 patients had an increased FDG uptake. As a result of this finding, these patients subsequently underwent complete removal of the implanted material. Cultures of the leads were positive in all 6 patients, confirming involvement of the leads in the infectious process. In the other 4 patients, the pacing system was left in place without objective signs of active lead endocarditis during follow-up.[57]

Sarrazin et al. have made additional important contributions regarding the utility of PET/CT for suspected CIED infection. In a study including 66 patients, they confirmed the relative good sensitivity (89%) and specificity (86%) of PET/CT interpreted using a qualitative visual score. Moreover, they provided evidence that inflammation accompanying acute pocket surgery does not result in false positive imaging, thus

extending the applicability of this technique to suspected early device infection. The authors also demonstrated the ability to distinguish deep pocket infection, which implies device infection and the necessity for device extraction, from superficial infection, which can be treated with antibiotics alone.[53] Finally, PET/CT might reveal the source of infection (eg, a neoplasm such as bowel cancer).

Although the preliminary results of PET/CT in the diagnosis and the management of IE are encouraging, several questions remain. What is its value in native and prosthetic valve IE? Is it cost-effective? What is the effect of prolonged previous antibiotic therapy? What is the effect of hyperglycemia? More experience, especially with use of the new ECG-gated PET/CT, is necessary before strong recommendations can be made regarding the use of this technique.

Gallium-67, indium-111 or technetium-99m-hexamethylpropyleneamine oxime labelled-leukocyte scintigraphy is another option for imaging of infection, with or without incorporation with CT images. Unlike PET/CT, this method is more specific for infection, but is more time-consuming (24 hours).[58] A recent study showed that the sensitivity and the specificity of ^{99m}technetium radiolabelled leukocyte scintigraphy in patients with a suspicion of prosthetic valve IE and an inconclusive echocardiogram were 57% and 78%, respectively.[59] Because of a better specificity in detection of infection, this modality might be better than PET/CT in the context of an early prosthetic valve IE suspicion.

Better knowledge of the host-pathogen interaction offers new perspectives in functional imaging of IE. Indeed, by labelling other actors involved in this unique interaction, some investigators have developed novel imaging methods from animal models.[60,61]

Management

Evolution of therapeutic strategies

Despite improvements in therapies, IE is associated with poor prognosis and remains a therapeutic challenge. After the introduction of antibiotics, the development of valvular surgery, especially during the active phase of the disease (early surgery), was considered to be considerable progress in the treatment of IE.[62] Although this aggressive therapeutic strategy has become indispensable to save lives and to eradicate infection in many patients, reported rates of surgery remain heterogeneous, and the beneficial effect of surgery on mortality is still difficult to demonstrate.[7] These difficulties result from the scarcity of randomized trials and several confounding factors that hamper the analysis of observational studies. Nevertheless, the results from most investigations are favourable for early surgical management in complicated IE. Thus, appropriate identification of high-risk patients and their quick transfer to specialized medicosurgical centres is crucial to improve the prognosis.[7,63-65] Despite this trend in treatment, most centres report an in-hospital mortality of approximately 20%, possibly because many patients are referred too late to medicosurgical institutions that are experienced in IE. Therefore, one of challenges is to rapidly introduce antibiotic treatment and, at the same time, to use strategies to identify patients who require close monitoring and urgent surgery.

Antibiotic therapy

Delayed and inappropriate antibiotic therapy has an important effect on outcome. Prompt antibiotic therapy can avoid the occurrence of severe sepsis, multiple organ dysfunction syndrome, and sudden death. Moreover, Dickerman and colleagues showed a 65% reduction in risk of stroke related to IE 1 week after the introduction of antibiotics.[66] Therefore, when IE is suspected or confirmed, antibiotic therapy should be quickly introduced after microbiological sampling. This treatment will be empirical at first and then modified according to the microbiological results during the next few days. The molecules and doses are clearly defined in the different international guidelines.[13,67] Although the emergence of resistant strains is growing, present recommendations for antimicrobial treatment are based on old but efficient antibiotic drugs because most pathogens that cause IE are still sensitive to them. The several new antibiotics recently tested in IE have not proved a significant prognostic improvement compared with the traditional ones.

Risk stratification and indications of surgery

At admission, immediate assessment of prognosis should be done to identify high-risk patients who need closer monitoring and more aggressive treatment such as early surgery. Many predictors of death have been identified, including clinical, biological, and echocardiographic variables.[39,68-71] During the past decade, surgical indications have greatly increased, so we have entered into the era of early surgery. Currently, valvular surgery is performed during the active phase of the disease in approximately 40%-60% of patients.[7] Although aggressive therapy has become indispensable to save lives and to eradicate infection in many patients, reported rates of surgery remain heterogeneous, and the beneficial effect of surgery on mortality is still difficult to show. These difficulties result from the scarcity of randomized trials and several confounding factors that hamper the analysis of observational studies. Nevertheless, the results from most investigations are favourable for early surgical management in complicated IE. The 2009 European guidelines provide clear recommendations on the surgical indications during the active phase of the disease (Table 3).[13,72] Heart failure (HF) or high risk of HF, uncontrolled infection, and high embolic risk are the 3 main situations in which cardiac surgery is required. These guidelines have also established an optimal timing for each indication: emergency surgery (within 24 hours) or urgent surgery (within a few days) basis, irrespective of the duration of antibiotic treatment. In other cases, surgery can be postponed to allow 1 or 2 weeks of antibiotic treatment with careful clinical and echocardiographic observation before an elective surgical procedure is performed. Even though most of these recommendations are not supported by strong evidence, recently a randomized trial demonstrated that surgery performed within 48 hours after diagnosis significantly reduced the risk of systemic embolism in patients with $>$ 10 mm vegetation associated with severe valvular dysfunction.[73]

However, the patients with IE usually have comorbidities, which can increase the operative risk. Thus, an optimal management must take into account the benefit/risk ratio of early valve surgery in each patient. The operative mortality in active IE is 6%-25%. Preoperative shock, HF, renal

Table 3. Indications and timing of surgery in NVE and PVE

Indication	Timing*	Class	Level of evidence
Heart failure			
Aortic or mitral IE or PVE with severe acute regurgitation or valve obstruction or fistula causing refractory pulmonary edema or cardiogenic shock	Emergency	I	B
Aortic or mitral IE with severe acute regurgitation or valve obstruction and persisting heart failure or echocardiographic signs of poor hemodynamic tolerance (early mitral closure or pulmonary hypertension)	Urgent	I	B
Aortic or mitral IE or severe prosthetic dehiscence with severe regurgitation and no heart failure	Elective	IIa	B
Right heart failure secondary to severe tricuspid regurgitation with poor response to diuretic therapy	Urgent/elective	IIa	C
Uncontrolled infection			
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent	I	B
Persistent fever and positive blood cultures > 7-10 days not related to an extracardiac cause	Urgent	I	B
Infection caused by fungi or multiresistant organisms	Urgent/elective	I	B
PVE caused by staphylococci or gram-negative bacteria (most cases of early PVE)	Urgent/elective	IIa	C
Prevention of embolism			
Aortic or mitral IE or PVE with large vegetations (> 10 mm) after 1 or more embolic episodes despite appropriate antibiotic therapy	Urgent	I	B
Aortic or mitral IE or PVE with large vegetations (> 10 mm) and other predictors of complicated course (heart failure, persistent infection, abscess)	Urgent	I	C
Aortic or mitral or PVE with isolated very large vegetations (> 15 mm)†	Urgent	IIb	C
Persistent tricuspid valve vegetations > 20 mm after recurrent pulmonary emboli	Urgent/elective	IIa	C

Class I: evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. Class II: conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the given treatment or procedure. Class IIa: weight of evidence/opinion is in favour of usefulness/efficacy. Class IIb: usefulness/efficacy is less well established by evidence/opinion. Class III: evidence of general agreement that the given treatment or procedure is not useful/effective, and in some cases might be harmful. Level of evidence A: data derived from multiple randomized clinical trials or meta-analyses. Level of evidence B: data derived from a single randomized clinical trial or large nonrandomized studies. Level of evidence C: consensus of opinion of the experts or small studies, retrospective studies, registries.

IE, infective endocarditis; NVE, native valve infective endocarditis; PVE, prosthetic valve infective carditis.

* Emergency surgery: surgery performed within 24 hours, urgent surgery: within a few days, elective surgery: after at least 1 or 2 weeks of antibiotic treatment.

† Surgery might be preferred if procedure preserving the native valve is feasible.

Modified from Thuny et al.[7] with permission from *The Lancet*.

insufficiency, impaired left ventricular function, prosthetic valve IE, perivalvular abscess, and high logistic Euroscore have been identified as the strongest predictors of operative mortality.[72,74,75] One perspective is to classify the prognostic severity and the operative mortality on the basis of risk scores, which will make management decisions more standardized and easier. Recent studies have validated such risk models that incorporate clinical variables available at the bedside.[69,76-78]

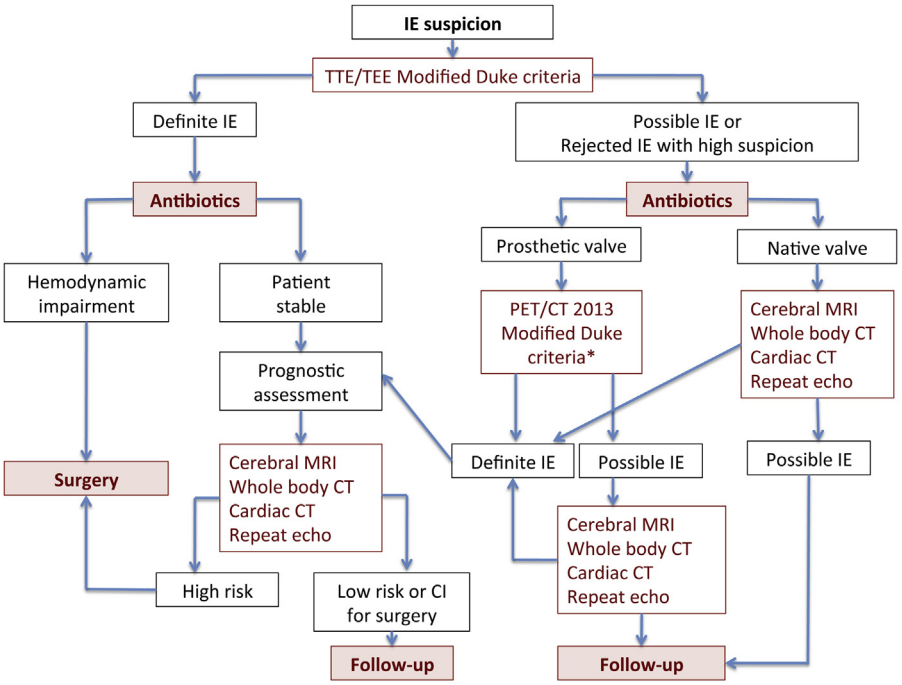

Figure 5. Proposed algorithm of management of IE including the recent imaging modalities. CI, contraindicated; CT, computed tomography; echo, echocardiography; FDG, fluorodeoxyglucose; IE, infective endocarditis; MRI, magnetic resonance imaging; PET, positron emission tomography; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography. * Use ^{99m}technetium radiolabelled leukocyte scintigraphy in patients with an early prosthetic valve IE suspicion rather than ^{18}F-FDG PET/CT.

A calculator of the embolic risk has been recently developed and validated by our team so that clinicians can easily use it.[78]

Indications for surgery and the perioperative approach in intravenous drug users are the same as for nonaddicts but should be more conservative overall because these patients have a much greater incidence of recurrent IE, usually because of continued drug abuse.[13]

Management of neurological complications

Neurological complications occur in 60%-80% of all patients with IE and are usually related to vegetation embolism.[51,79-81] They include ischemic stroke, cerebral hemorrhage, infectious aneurysm, cerebral abscess, and meningitis. They are silent and only detected using cerebral CT scan or MRI in almost 50% of cases.[50,51,80] *Staphylococcus aureus* is the causative microorganism most frequently involved.[51,79] The management of patients developing these complications is difficult and should be multidisciplinary including cardiologists, neurologists, microbiologists, cardiac and neurosurgeons. After the first neurological event, most patients still have at least 1 indication for cardiac surgery, and keep a poor prognosis if this intervention is not performed or cannot be performed.[79] The effect of valvular surgery on outcome in patients with cerebrovascular complications in IE has been largely debated. In the most recent series, the risk of postoperative neurological deterioration was low (0%-6%) even when surgery was performed very early after the first neurological symptoms appeared. In fact, the risk of postoperative neurological deterioration seems to depend more on the severity of cerebrovascular complications than on the timing of surgery.[51,79,81]

Surgery can be performed early after neurological complications if cerebral hemorrhage has been excluded using cranial CT scan and neurological damage is not severe.[58] Conversely, in cases with large intracranial hemorrhage, neurological prognosis is worse and surgery must be postponed for at least 1 month. However, if urgent cardiac surgery is needed, close cooperation with the neurosurgical team is mandatory.[13,81]

The management of intracranial infectious aneurysms in case of indication of cardiac surgery is difficult. They should be sought in any patients with neurological symptoms using CT, MRI, or conventional angiography. Because ruptured aneurysms with severe hemorrhage carry a very poor prognosis, they should be treated using neurosurgery or endovascular therapy before cardiac surgery. In case of unruptured aneurysm, cardiac surgery can be performed first in case of severe hemodynamic impairment, or performed after endovascular or surgical treatment in other cases.[13,82]

Management after the acute phase

Mortality and morbidity associated with IE might extend beyond successful treatment with a risk of death, recurrence, and need of late valvular surgery especially during the first year after the diagnosis. Thus, after discharge, patients should be educated about how to diagnose and prevent a new episode of IE, and should be closely followed using clinical, biological, and echocardiographic evaluations (Fig. 5).[13,83]

Conclusions

IE remains a severe disease, and prevention of which has failed. Its mortality rate remains high because the disease usually involves patients with comorbidities, the causative pathogens are virulent, and the diagnostic/therapy strategies are insufficient. Novel imaging and microbiological test modalities have emerged to improve and accelerate the diagnostic process and subsequently allow a prompt therapeutic strategy to be implemented. Recent data strongly demonstrate the beneficial effect of early surgical management in patients at high risk of complications and thus efforts should be made to rapidly refer IE patients to specialized medicosurgical centres.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. van der Meer JT, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in the netherlands. I. Patient characteristics. Arch Intern Med 1992;152:1863-8.

2. Berlin JA, Abrutyn E, Strom BL, et al. Incidence of infective endocarditis in the Delaware valley, 1988-1990. Am J Cardiol 1995;76:933-6.

3. Hoen B, Alla F, Selton-Suty C, et al. Changing profile of infective endocarditis: Results of a 1-year survey in France. JAMA 2002;288:75-81.

4. Hogevik H, Olaison L, Andersson R, Lindberg J, Alestig K. Epidemiologic aspects of infective endocarditis in an urban population. A 5-year prospective study. Medicine (Baltimore) 1995;74:324-39.

5. Selton-Suty C, Celard M, Le Moing V, et al. Preeminence of Staphylococcus aureus in infective endocarditis: a 1-year population-based survey. Clin Infect Dis 2012;54:1230-9.

6. Cabell CH, Pond KK, Peterson GE, et al. The risk of stroke and death in patients with aortic and mitral valve endocarditis. Am Heart J 2001;142:75-80.

7. Thuny F, Grisoli D, Collart F, Habib G, Raoult D. Management of infective endocarditis: challenges and perspectives. Lancet 2012;379:965-75.

8. Benito N, Miro JM, de Lazzari E, et al. Health care-associated native valve endocarditis: importance of non-nosocomial acquisition. Ann Intern Med 2009;150:586-94.

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

10. Sy RW, Kritharides L. Health care exposure and age in infective endocarditis: results of a contemporary population-based profile of 1536 patients in Australia. Eur Heart J 2010;31:1890-7.

11. Durack DT. Prevention of infective endocarditis. N Engl J Med 1995;332:38-44.

12. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2007;116:1736-54.

13. 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). Eur Heart J 2009;30:2369-413.

14. Glauser MP, Bernard JP, Moreillon P, Francioli P. Successful single-dose amoxicillin prophylaxis against experimental streptococcal endocarditis: evidence for two mechanisms of protection. J Infect Dis 1983;147:568-75.
15. Moreillon P, Wilson WR, Leclercq R, Entenza JM. Single-dose oral amoxicillin or linezolid for prophylaxis of experimental endocarditis due to vancomycin-susceptible and vancomycin-resistant enterococcus faecalis. Antimicrob Agents Chemother 2007;51:1661-5.
16. Forner L, Larsen T, Kilian M, Holmstrup P. Incidence of bacteremia after chewing, tooth brushing and scaling in individuals with periodontal inflammation. J Clin Periodontol 2006;33:401-7.
17. Lockhart PB, Brennan MT, Sasser HC, et al. Bacteremia associated with toothbrushing and dental extraction. Circulation 2008;117:3118-25.
18. Roberts GJ. Dentists are innocent! "Everyday" bacteremia is the real culprit: a review and assessment of the evidence that dental surgical procedures are a principal cause of bacterial endocarditis in children. Pediatr Cardiol 1999;20:317-25.
19. Veloso TR, Amiguet M, Rousson V, et al. Induction of experimental endocarditis by continuous low-grade bacteremia mimicking spontaneous bacteremia in humans. Infect Immun 2011;79:2006-11.
20. Oliver R, Roberts GJ, Hooper L, Worthington HV. Antibiotics for the prophylaxis of bacterial endocarditis in dentistry. Cochrane Database Syst Rev 2008:CD003813.
21. Van der Meer JT, Van Wijk W, Thompson J, et al. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet 1992;339:135-9.
22. Imperiale TF, Horwitz RI. Does prophylaxis prevent postdental infective endocarditis? A controlled evaluation of protective efficacy. Am J Med 1990;88:131-6.
23. Lacassin F, Hoen B, Leport C, et al. Procedures associated with infective endocarditis in adults. A case control study. Eur Heart J 1995;16:1968-74.
24. 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.
25. Duval X, Alla F, Hoen B, et al. Estimated risk of endocarditis in adults with predisposing cardiac conditions undergoing dental procedures with or without antibiotic prophylaxis. Clin Infect Dis 2006;42:e102-7.
26. International Collaborative Study of Severe Anaphylaxis. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. Pharmacoepidemiol Drug Saf 2003;12:195-202.
27. Lee P, Shanson D. Results of a UK survey of fatal anaphylaxis after oral amoxicillin. J Antimicrob Chemother 2007;60:1172-3.
28. Bombassaro AM, Wetmore SJ, John MA. Clostridium difficile colitis following antibiotic prophylaxis for dental procedures. J Can Dent Assoc 2001;67:20-2.
29. Danchin N, Duval X, Leport C. Prophylaxis of infective endocarditis: French recommendations 2002. Heart 2005;91:715-8.
30. Richey R, Wray D, Stokes T. Prophylaxis against infective endocarditis: Summary of NICE guidance. BMJ 2008;336:770-1.
31. 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.
32. Duval X, Delahaye F, Alla F, et al. 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.
33. 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.
34. Martin MV, Longman LP, Forde MP, Butterworth ML. Infective endocarditis and dentistry: the legal basis for an association. Br Dent J 2007;203:E1 [discussion: 38-9].
35. Chen SJ, Liu CJ, Chao TF, et al. Dental scaling and atrial fibrillation: a nationwide cohort study. Int J Cardiol 2013;168:2300-3.
36. von Reyn FC, Arbeit RD, Friedland GH, Crumpacker CS 3rd. Criteria for the diagnosis of infective endocarditis. Clin Infect Dis 1994;19:368-70.
37. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med 1994;96:200-9.
38. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-8.
39. 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.
40. Raoult D, Casalta JP, Richet H, et al. Contribution of systematic serological testing in diagnosis of infective endocarditis. J Clin Microbiol 2005;43:5238-42.
41. 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.
42. Lepidi H, Coulibaly B, Casalta JP, Raoult D. Autoimmunohistochemistry: a new method for the histologic diagnosis of infective endocarditis. J Infect Dis 2006;193:1711-7.
43. Vieira ML, Grinberg M, Pomerantzeff PM, Andrade JL, Mansur AJ. Repeated echocardiographic examinations of patients with suspected infective endocarditis. Heart 2004;90:1020-4.
44. Habib G, Badano L, Tribouilloy C, et al. Recommendations for the practice of echocardiography in infective endocarditis. Eur J Echocardiogr 2010;11:202-19.
45. Khatib R, Sharma M. Echocardiography is dispensable in uncomplicated Staphylococcus aureus bacteremia. Medicine (Baltimore) 2013;92:182-8.
46. Palraj BR, Sohail MR. Appropriate use of echocardiography in managing Staphylococcus aureus bacteremia. Expert Rev Anti Infect Ther 2012;10:501-8.
47. 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.
48. 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.
49. Gahide G, Bommart S, Demaria R, et al. Preoperative evaluation in aortic endocarditis: findings on cardiac CT. AJR Am J Roentgenol 2010;194:574-8.

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

51. Cooper HA, Thompson EC, Laureno R, et al. Subclinical brain embolization in left-sided infective endocarditis: results from the evaluation by MRI of the brains of patients with left-sided intracardiac solid masses (EMBOLISM) pilot study. Circulation 2009;120:585-91.

52. 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.

53. 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.

54. Saby L, Le Dolley Y, Laas O, et al. Early diagnosis of abscess in aortic bioprosthetic valve by 18F-fluorodeoxyglucose positron emission tomography-computed tomography. Circulation 2012;126:e217-20.

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

56. Bensimhon L, Lavergne T, Hugonnet F, et al. Whole body [(18) f]fluorodeoxyglucose positron emission tomography imaging for the diagnosis of pacemaker or implantable cardioverter defibrillator infection: a preliminary prospective study. Clin Microbiol Infect 2010;17:836-44.

57. Ploux S, Riviere A, Amraoui S, et al. Positron emission tomography in patients with suspected pacing system infections may play a critical role in difficult cases. Heart Rhythm 2011;8:1478-81.

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

59. Hyafil F, Rouzet F, Lepage L, et al. Role of radiolabelled leucocyte scintigraphy in patients with a suspicion of prosthetic valve endocarditis and inconclusive echocardiography. Eur Heart J Cardiovasc Imaging 2013;14:586-94.

60. Panizzi P, Nahrendorf M, Figueiredo JL, et al. In vivo detection of Staphylococcus aureus endocarditis by targeting pathogen-specific prothrombin activation. Nat Med 2011;17:1142-6.

61. Thuny F, Gaubert JY, Jacquier A, et al. Imaging investigations in infective endocarditis: current approach and perspectives. Arch Cardiovasc Dis 2013;106:52-62.

62. Thuny F, Beurtheret S, Mancini J, et al. The timing of surgery influences mortality and morbidity in adults with severe complicated infective endocarditis: a propensity analysis. Eur Heart J 2011;32:2027-33.

63. 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.

64. Thuny F, Botelho E, Casalta JP, et al. Can we really achieve a 1-year mortality rate lower than 10% in patients with infective endocarditis? Arch Intern Med 2010;170:211-2.

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

66. Dickerman SA, Abrutyn E, Barsic B, et al. 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.

67. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America [errata in 2005;112:2373, 2007;115:e408, 2007;116:e547, 2008;118:e497]. Circulation 2005;111:e394-434.

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

69. Hasbun R, Vikram HR, Barakat LA, Buenconsejo J, Quagliarello VJ. Complicated left-sided native valve endocarditis in adults: risk classification for mortality. JAMA 2003;289:1933-40.

70. San Roman JA, Lopez J, Vilacosta I, et al. Prognostic stratification of patients with left-sided endocarditis determined at admission. Am J Med 2007;120:369.e1-7.

71. Turak O, Ozcan F, Isleyen A, et al. Usefulness of neutrophil-to-lymphocyte ratio to predict in-hospital outcomes in infective endocarditis. Can J Cardiol 2013;29:1672-8.

72. Thuny F, Habib G. When should we operate on patients with acute infective endocarditis? Heart 2010;96:892-7.

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

74. Alexiou C, Langley SM, Stafford H, et al. Surgery for active culture-positive endocarditis: determinants of early and late outcome. Ann Thorac Surg 2000;69:1448-54.

75. Jault F, Gandjbakhch I, Rama A, et al. Active native valve endocarditis: determinants of operative death and late mortality. Ann Thorac Surg 1997;63:1737-41.

76. Sy RW, Chawantanpipat C, Richmond DR, Kritharides L. Development and validation of a time-dependent risk model for predicting mortality in infective endocarditis. Eur Heart J 2009;32:2016-36.

77. Lopez J, Fernandez-Hidalgo N, Revilla A, et al. Internal and external validation of a model to predict adverse outcomes in patients with left-sided infective endocarditis. Heart 2011;97:1138-42.

78. Hubert S, Thuny F, Resseguier N, et al. Prediction of symptomatic embolism in infective endocarditis: construction and validation of a risk calculator in a multicenter cohort. J Am Coll Cardiol 2013;62:1384-92.

79. 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.

80. Snygg-Martin U, Gustafsson L, Rosengren L, et al. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging and neurochemical brain damage markers. Clin Infect Dis 2008;47:23-30.

81. Garcia-Cabrera E, Fernandez-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. Circulation 2013;127:2272-84.

82. Peters PJ, Harrison T, Lennox JL. A dangerous dilemma: management of infectious intracranial aneurysms complicating endocarditis. Lancet Infect Dis 2006;6:742-8.

83. Thuny F, Giorgi R, Habachi R, et al. Excess mortality and morbidity in patients surviving infective endocarditis. Am Heart J 2012;164:94-101.