Management of infective endocarditis: challenges and perspectives

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Despite improvements in medical and surgical therapies, infective endocarditis is associated with poor prognosis and remains a therapeutic challenge. Many factors affect the outcome of this serious disease, including virulence of the microorganism, characteristics of the patients, presence of underlying disease, delays in diagnosis and treatment, surgical indications, and timing of surgery. We review the strengths and limitations of present therapeutic strategies and propose future directions for better management of endocarditis according to the most recent research. Novel perspectives on the management of endocarditis are emerging and offer hope for decreasing the rate of residual deaths by accelerating the process of diagnosis and risk stratification, reducing delays in starting antimicrobial therapy, rapid transfer of high-risk patients to specialised medico-surgical centres, development of new surgical methods, and close long-term follow-up.

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Introduction

Infective endocarditis is a serious disease with an incidence of 30 to 100 episodes per million patient-years.[1–3] Mortality is high: more than a third of patients will die within the first year of diagnosis.[4,5] Since the first analysis of 209 cases by Sir William Osler in 1885,[6] the epidemiological pattern of infective endocarditis has changed[7,8] and prevention strategies have not lowered the incidence of this life-threatening disease.[1,2,8,9] Mortality has been affected by modifications in therapeutic management. Thus, three distinct periods are evident: (1) before the antibiotic era, infective endocarditis was always fatal; (2) the introduction of penicillin in the 1940s greatly reduced the number of deaths, but the mortality rate did not substantially fall thereafter despite the development of valvular surgery, done during the active phase of infection (early surgery);[10] and (3) during the past decade, surgical indications have greatly increased, so we have entered into the era of early surgery.[11,12] Although aggressive therapy has become indispensable to save lives and to eradicate infection in many patients, reported rates of surgery remain heterogeneous (webappendix), and the beneficial effect of surgery on mortality is still difficult to show. These difficulties result from the scarcity of randomised 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 infective endocarditis. Thus, an appropriate identification of high-risk patients and their quick transfer to specialised medicosurgical centres seem to be crucial to improve the prognosis. Indeed, standardised management by a skilled multidisciplinary team has proven to decrease significantly mortality.[13,14] Despite this trend in treatment, most centres report an in-hospital fatality rate of about 20%, possibly because many patients are referred too late to medicosurgical institutions that are experienced in infective endocarditis. Therefore, challenges in management of this disease include improvement of diagnostic strategies to reduce delays for the start of appropriate treatment, better identification of patients who require close monitoring and urgent surgery, and development of new medical and surgical therapeutic methods.

The aims of this Review are to identify the therapeutic factors that have affected mortality from infective endocarditis throughout the years and to discuss new challenges and perspectives in management to reduce residual causes of death for this severe disease.

Evolution of treatment and mortality

Antimicrobial therapy: benefits and limits

Infective endocarditis was always fatal before the era of antibiotics. The promise of a definitive treatment for this disease appeared with the advent of sulphonamide

See Online for webappendix

Search strategy and selection criteria

We searched PubMed for articles using the search term "endocarditis" in combination with terms relevant for every section of the article, including "epidemiology", "diagnosis", "prognosis", "management", "therapy", "treatment", "antibiotics", "surgery", "outcome", "survival", and "mortality". This search was limited to articles in English and adult patients. We also searched the reference lists of articles identified by this search strategy, and selected those additional references that we judged relevant. Moreover, we added a reference during the peer review process about the use of antibioprophylaxis.[105] To generate the epidemiological data presented in webappendix (p 1) and figure 1, we searched the databases from 1944 to 2010, and included studies with the following quality criteria: (1) inclusion of more than 100 cases of definite, probable, or possible infective endocarditis; (2) inclusion of acute and subacute infective endocarditis; (3) inclusion of native, prosthetic, left-sided and right-sided valve infective endocarditis cases; and (4) availability of information on the rate of in-hospital mortality and early surgery. Because the definition of infective endocarditis has changed over time, we did not deem any specific case definition to be better than another. Early surgery was defined as a valve surgery done at any time during the course of antibiotic treatment. Studies restricted to specific subgroups were excluded. If two or more studies included the same patient population, we included only the report that had the largest sample size and the most complete data. Using these criteria, we included 24 investigations with 8589 cases of infective endocarditis.

For the review of the effect of surgery on mortality, we report on the nine series that used propensity score analyses.[41–49] Because no randomised trials have been published yet, these studies used this statistical method to reduce the selection bias inherent to observational studies.

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therapy in 1938,[15] but the potential to definitively cure patients came with the introduction of penicillin in 1944, which greatly reduced mortality.[16–18] Despite the emergence of resistant staphylococci, this rate of death remained constant thereafter, because of the development of vancomycin in 1956, and of penicillinase-resistant penicillins in the 1960s.[19] In the years after the introduction of these drugs, synergistic antibiotic combinations and new antibiotics have been tested to optimise treatment. In many in-vitro studies, combinations of antibiotics have shown synergistic activities against the pathogens that commonly cause infective endocarditis. These results have been confirmed in most animal models of the disease.[20–23] However, only a few combinations have gained strong interest in clinical practice.[22] The addition of aminoglycosides to an antibiotic with activity against Gram-positive bacteria is the synergistic association most commonly recommended by international guidelines.[24,25] However, no randomised trials have been done for most of the patients and pathogens for which combination therapy is recommended. In the few randomised trials that have addressed this question,[26–29] the addition of an aminoglycoside did not decrease fatality rate,[26–28] clinical failure,[26–29] need for operation,[26–28] or bacteriological failure.[26–29] Moreover, a meta-analysis[30] of these trials showed that the relative risk of nephrotoxic effects in the combination group was 2·22 (95% CI 1·11–4·35). Additionally, no randomised trials have compared vancomycin with a combination of vancomycin and an aminoglycoside. This situation has been quite similar for the more recently developed antibiotics. Although teicoplanin and linezolid have been suggested in rare cases,[25,31] no randomised trial has ever shown their superiority to β-lactam and vancomycin. Finally, results from a randomised trial testing daptomycin versus the standard therapy for bacteraemia and endocarditis caused by *Staphylococcus aureus* only showed non-inferiority for this strategy.[32] Thus, present recommendations for antimicrobial treatment are based on old but efficient antibiotic drugs because most pathogens that cause infective endocarditis are still sensitive to them, even if the emergence of resistant strains is growing.[24,25]

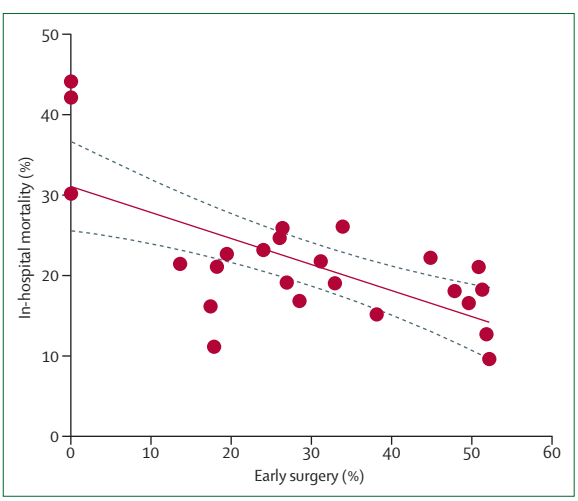

Figure 1: **In-hospital mortality as a function of the rate of early surgery**
This linear regression (R^2=0·45, p=0·0003) was done with the data from the 24 investigations (webappendix). Dotted lines represent the 95% CI. After exclusion of the four studies that differed the most from the line of regression (Anderson al 1948, Morgan et al 1959, Bishara et al 2001, Fefer et al 2002), the correlation remained significant (R^2=0·48, p=0·0008). The references of studies included are presented in the webappendix.

Early valve surgery

Currently, complicated infective endocarditis has become a so-called surgical disease. Although the development of antibiotic drugs had enabled doctors to treat many cases successfully, numerous patients still died, mainly because of severe valvular damage. Thus, at the end of the 1960s, early valvular surgery emerged as an answer to the most serious cases of this disease, especially in cases of heart failure.[10] Then, several encouraging surgical series were reported,[33–40] and the rate of successful operations increased rapidly. In a systematic review[11] of 15 population-based investigations of infective endocarditis from seven countries, the proportion of cases undergoing valve surgery increased 7% per decade between 1969 and 2000. An analysis of published studies shows a significant correlation between the rate of early surgery and in-hospital mortality (figure 1). However, no randomised trials have been published to confirm the role of surgical management. Therefore, present practice guidelines, which recommend surgery in cases of heart failure (or high risk of heart failure), high embolic risk, and uncontrolled infection,[12,24,25] are largely based on the results of observational series and expert opinion. A few works have addressed the issue of the prognostic effect of surgery with statistical methods that reduce the potential biases met with observational series (table 1).[41–49] Indeed, in a non-randomised observational design, investigators choose the type of treatment; therefore, direct comparisons of outcomes might mislead investigators because of selection bias. This selection bias can be reduced with propensity score analyses. The propensity score is the conditional probability of valve surgery given the observed confounders. Matching on or adjusting for this score enables the effect of selection bias to be reduced.[41–49] However, this method cannot replace a randomised trial, especially in infective endocarditis because of the number of potential confounding factors. Survivor treatment bias is another problematic source that was also taken into account by the most recent investigations.[47–49] This bias means that patients who live longer are more likely to undergo surgery because they have more time to be selected for surgery than those who die earlier. It can be reduced by consideration of surgery as a time-dependent covariate, or by a match on the follow-up time, so that the patient in the non-surgical group survives at least as long as the time to surgery in the surgically treated patient.[47–49] Finally, hidden bias (unmeasured patient characteristics

	Period of inclusion	Type of infective endocarditis	Number of patients	Rate of surgery	Outcome	Biases addressed	Mortality (no surgery/surgery)	Conclusion of the authors about the effect of surgery
Vikram et al[41]	1990–2000	NVE	513 (218 in propensity matched cohort)	44·8%	6-month mortality	Treatment selection bias	33·0%/16·0% (28·0%/15·0% in propensity matched cohort)	Benefit
Mourvillier et al[42]	1993–2000	NVE	146 (54 in propensity matched cohort)	49·3%	In-hospital mortality	Treatment selection bias	47·3%/29·7%	No significant benefit
Cabell et al[43]	1985–99	NVE	1516	40·2%	In-hospital mortality	Treatment selection bias	16·4%/13·6%	Benefit in patients with high propensity score
Wang et al[44]	1985–99	PVE	355 (136 in propensity matched cohort)	41·7%	In-hospital mortality	Treatment selection bias	24·7%/23·4% (32·4%/22·1% in propensity matched cohort)	No significant benefit
Aksoy et al[45]	1996–2002	NVE and PVE	333 (102 in propensity matched cohort)	23·0%	5-year mortality	Treatment selection bias	21·6%/11·8% (18·0%/11·5% in propensity matched cohort)	Benefit
Tleyjeh et al[46]	1980–98	NVE and PVE	546 (186 in propensity matched cohort)	23·6%	6-month mortality	Treatment selection and survivor biases	23·7%/27·1% (19·4%/29·0% in propensity matched cohort)	No significant benefit
Sy et al[47]	1996–2006	NVE and PVE	223	27·8%	Median: 5·2 years	Treatment selection and survivor biases	51·0%/32·0%	No significant benefit
Bannay et al[48]	1999	NVE and PVE	449	53·4%	5-year mortality	Treatment selection and survivor biases	50·0%/30·0%	Benefit
Lalani et al[49]	2000–05	NVE	1552 (1238 in propensity matched cohort)	46·4%	In-hospital mortality	Treatment selection survivor, and hidden biases	20·7%/12·1% (17·4%/11·8%)	Benefit

NVE=native valve endocarditis. PVE=prosthetic valve endocarditis.

Table 1: **Propensity analysis studies assessing the effect of surgery in infective endocarditis**

that affect both the decision to treat and the outcome) was also taken into account in one work[49] that used instrumental variable analysis.[49] Although the first propensity analyses assessing treatment strategies in infective endocarditis have led to conflicting results, some investigations[48,49] have confirmed the beneficial effect of surgery in the management of complicated infective endocarditis. Indeed, Bannay and colleagues[48] showed that the discrepancies recorded in the first five propensity score series were due to differences in the methods used, especially the coding of the surgery variable (binary or time-dependent) and the duration of the follow-up. With the appropriate models, these authors showed that valve surgery was associated with significantly reduced long-term mortality in patients with left-sided infective endocarditis.[48] This beneficial effect of surgery was confirmed by a large multicentre study[49] that adjusted the results for most important biases—namely, treatment selection, survivorship, and hidden biases.

Therefore, management of complicated infective endocarditis has moved to the era of early surgery, and the challenge now is to correctly identify high-risk patients and rapidly transfer them to a specialised medicosurgical team. Recent international guidelines[25] confirm this trend as an extension of surgical indications, especially at the early stage of the disease (table 2).

Challenges and perspectives

Despite improvements in the diagnostic and therapeutic strategies, the fatality rate due to infective endocarditis has not significantly decreased since the end of the 1970s. Important changes in the epidemiological profile of this disease that have occurred in the past few decades can explain part of this situation. The age of patients has increased and the incidence of health-care-associated infective endocarditis has increased as a consequence of medical progress.[7,50,51] Thus, the more frequent causative agents now tend to be aggressive pathogens such as staphylococci, resistant-enterococci, or fungi. Although substantial geographical variations exist, a substantial increase in the rate of staphylococcal infective endocarditis has been reported, especially in the USA, where chronic haemodialysis, diabetes, and intravascular devices are the three main factors associated with infective endocarditis due to *Staphylococcus aureus*.[4,7] Nevertheless, patients with infective endocarditis in developing countries differ substantially from those in developed countries in some characteristics, including younger age at presentation, higher incidence of predisposing cardiac conditions such as rheumatic heart disease or uncorrected congenital heart disease, and higher incidence of culture-negative endocarditis.[52–54] Moreover, access to new diagnostic technologies and surgical facilities remains difficult in developing countries,[53] thus affecting prognosis of these patients.

Therefore, efforts should be made to develop new strategies at every step of the management of infective endocarditis to reduce the residual causes of deaths related to the disease. After reviewing the causes of these deaths at our institution during 18 years of follow-up, heart failure, stroke, multiorgan dysfunction syndrome, and sepsis seem to be the most frequent situations leading to death. Interestingly, sudden death represents 10% of all causes of death. Sudden death occurred in more than 1% of all patients with infective endocarditis during the hospital period in our institution (unpublished data).

	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 oedema 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 haemodynamic 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
Persisting 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) following one 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

IE=infective endocarditis. PVE=prosthetic valve endocarditis. Class I=evidence or general agreement, or both, that a given treatment or procedure is beneficial, useful, and effective. Class II=conflicting evidence or divergence of opinion, or both, about the usefulness or efficacy of the given treatment or procedure. Class IIa=weight of evidence or opinion is in favour of usefulness or efficacy. Class IIb=usefulness or efficacy is less well established by evidence or opinion. Class III=evidence of general agreement that the given treatment or procedure is not useful or effective, and in some cases may be harmful. Level of evidence A=data derived from multiple randomised clinical trials or meta-analyses. Level of evidence B=data derived from a single randomised clinical trial or large non-randomised studies. Level of evidence C=consensus of opinion of the experts or small studies, retrospective studies, registries. *Emergency surgery=surgery done within 24 h. Urgent surgery=surgery done within a few days. Elective surgery=surgery done after at least 1 or 2 weeks of antibiotic treatment. †Surgery might be preferred if procedure preserving the native valve is feasible.

Table 2: **Indications and timing of surgery in native valve (NVE) and prosthetic valve (PVE) infective endocarditis. Adapted from Habib and colleagues[25] with permission**

These data accord with the results of a European[55] and an American series[56] in which rates of sudden death were 3·4% and 1·5%, respectively. These results emphasise the need for acceleration of the diagnostic process and improvement of both prognosis-assessment and therapeutic strategies to avoid such fatal complications.

In cases with high suspicion of infective endocarditis, the appropriate antibiotics must be used as soon as possible, because a delay in antibiotic therapy has negative effects on clinical outcomes in acute bacterial infectious diseases.[57] Thus, efforts should be made to rapidly identify patients with a definite or highly probable diagnosis and the causative pathogen to ensure that the appropriate antibiotic therapy begins promptly. A diagnosis of infective endocarditis usually relies on the association of an infectious syndrome and a recent endocardial involvement. However, clinical histories are highly variable. Therefore, a high index of suspicion and low threshold for investigation are essential. With this strategy, blood cultures and echocardiography remain the cornerstone for diagnoses, but their results can be negative or doubtful and then require more advanced investigations.

Challenges in diagnostic strategies: perspectives in microbiological testing

The challenge is to obtain a rapid recognition of the causative pathogen and identify the rare cases of non-infective endocarditis. However, in infective endocarditis, blood cultures are negative in 2·5% to 31% of cases.[58–60] These cases of so-called blood culture-negative endocarditis (BCNE) often pose diagnostic and therapeutic issues. First, although cases of culture-negative endocarditis are often related to a previous antibiotic therapy, a substantial number result from infection with obligate intracellular bacteria, fungi, and fastidious pathogens.[60,61] To isolate these organisms, they need to be cultured on specialised media, and their growth is slow on artificial culture media. Second, appropriate antibiotic treatment is often delayed in cases in which endocarditis is caused by one of these pathogens and might adversely affect the treatment outcome.[62]

To resolve these issues, some authors propose to standardise the timing and type of laboratory tests, as was implemented at our institution in 1994. This protocol has improved yields for this diagnostic strategy by a systematic screening of all potential causes of infective endocarditis.[60] The diagnostic kit can be done within 2 h for every patient with suspected infective endocarditis. It is composed of three units. The first, which is to be used immediately, includes a set of two blood culture vials 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*, *Bartonella* spp, *Brucella* spp, *Chlamydia* spp, *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Aspergillus* spp. The second and third units each contain a set of two vials of blood culture to use 2 h after the first vial. The results of these diagnostic tests can be obtained quickly after admission. Thus, these tests can shorten the delay before a specific treatment is instituted. Using this approach, clinicians would not have to defer serological testing until the blood cultures are shown to be negative. Instead, clinicians can do blood cultures and serological tests at the same time. However, the interest in immediate serological performance in low-prevalence areas must be identified.

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 through the use of

non-specific histochemical stains or by immunohistochemical analyses. Because specific antibodies are often not available, another method termed autoimmunohistochemistry, which uses the patient's own serum, has been described for the detection of microorganisms in valve specimens.[63]

Moreover, the rapid and reliable detection of pathogens by PCR has been validated with valve tissue from patients undergoing surgery for infective endocarditis.[64–68] Molecular detection of pathogens in blood using pathogen-specific or broad-range PCR assays is also promising. However, cautious interpretation of this molecular method is crucial, because of the risk of interfering contamination (false positives), and should account for the clinical context. Presently, because of more widely available data and rapid advances in biotechnology, two important improvements allow for new perspectives in molecular diagnosis. Indeed, complete genome sequences have provided an important source of gene sequences for PCR-based assays. Additionally, the development of real-time PCR offers several advantages over conventional PCR, such as speed, simplicity, quantitative capability, and a low risk of contamination.[69] Although PCR has a crucial role in the identification of pathogens in culture-negative cases, it can also be useful in the classification of cultured pathogens, especially after the isolation of two or more microorganisms in separated cultures (to identify a possible contamination), and for identification of genes of antibiotic resistance.[70] Furthermore, even though PCR is unlikely to supersede blood cultures as the primary diagnostic method for pathogen identification, it offers perspectives for shortening the amount of time needed to identify pathogens.[71] All of these advanced methods can be integrated into a standardised multimodal strategy and can allow us to better identify the causes of blood-culture-negative endocarditis[61] (figure 2). Thus, we showed a high prevalence of fungi in postoperative cases[72] and that culture-negative disease can include a substantial number of cases of non-bacterial thrombotic endocarditis associated with cancers and autoimmune diseases.[61] Additionally, a rare case of relapsing and afebrile culture-negative disease on porcine bioprosthetic valves was reported in a patient allergic to porcine protein.[73]

Finally, the identification of a specific profile of serum proteins for infective endocarditis offers novel perspectives. Using SELDI-TOF mass spectrometry, Fenollar and colleagues[67] identified a serum proteomic signature with the potential for positively diagnosing endocarditis. The serum protein model built in that study[67] perfectly discriminated between endocarditis-positive and endocarditis-negative patients.

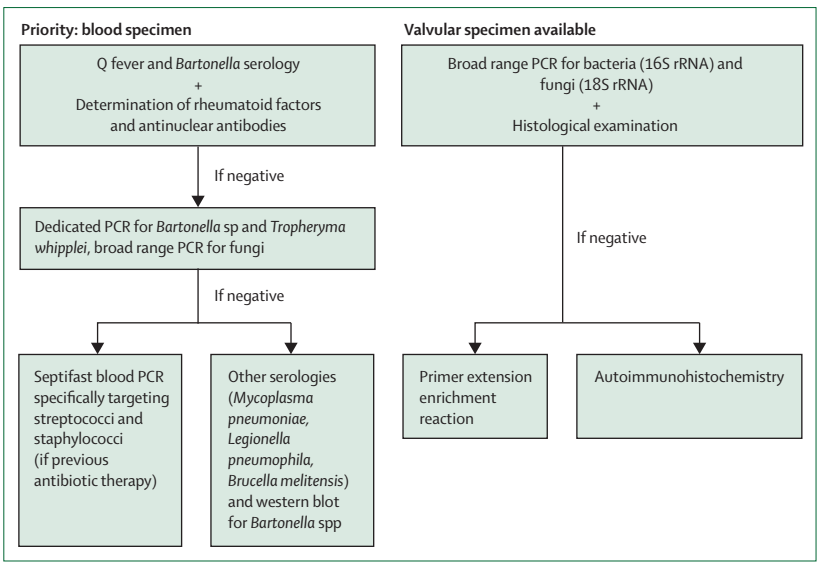

Figure 2: **Diagnostic tests applied to clinical specimens for the identification of the causative agents of blood culture–negative endocarditis**

Septifast=LightCycler SeptiFast (Roche). Serum should be considered a priority specim en, with Q fever and *Bartonella* serological analysis being routinely done. We also suggest that detection of antinuclear antibodies and rheumatoid factor should be routinely done for diagnosis of non-infective endocarditis.

Challenges in diagnostic strategies: perspectives in imaging investigations

Echocardiography remains an accurate method to detect endocardial involvement in infective endocarditis and must be done rapidly and repeated once a week as soon as the condition is suspected. Transthoracic echocardiography (TTE) is the initial technique of choice for investigation. A normal scan in low-risk patients provides a rapid, non-invasive confirmation that the diagnosis is unlikely.[74] Moreover, TTE is better than transoesophageal echocardiography (TEE) for detection of anterior cardiac abscesses and for haemodynamic assessment of valvular dysfunction. Because of its higher sensitivity and specificity, TEE is recommended in cases of (1) negative TTE associated with a high clinical suspicion, (2) poor TTE quality, (3) the presence of prosthetic valves or intracardiac device, and (4) positive TTE.[25] The identification of vegetation, abscess, valvular perforation, or new prosthetic-valve dehiscence will allow for confirmation of diagnoses in most cases; however, sometimes neither technique is sufficient to confirm infective endocarditis. A diagnosis might be particularly challenging in some cases such as in intracardiac devices, valvular prosthesis, the presence of pre-existing severe lesions, very small vegetations, or no vegetation. Innovations in the specialty of diagnostic strategy have emerged to resolve these issues through new imaging techniques such as three-dimensional (3D) echocardiography, multislice CT, PET, molecular imaging, and MRI.

In preliminary studies, 3D-TEE provided incremental value to 2D-TEE in its ability to accurately identify and localise vegetations and to identify complications such as abscesses, perforations, and ruptured chordae (webappendix).[75,76] Cardiac CT scan has also recently been shown to provide information not only about silent embolic events[5] and preoperative coronary assessment but also about

valvular and perivalvular damage, which is useful for diagnosis and therapeutic strategies[77] (webappendix).

Results from some preliminary studies have shown much promise for PET-CT scans in the setting of infective endocarditis (figure 3). These investigations suggest that this technique can be especially useful in the detection of silent peripheral embolic events and infectious metastases. Early detection of peripheral emboli or metastatic infections, or both, without previous clinical suspicion has been noted in 28% of episodes of infective endocarditis.[78] Positive PET-CT findings had a therapeutic effect in almost a third of patients.[78] Moreover, although the PET-CT scans cannot show small vegetations usually seen by TTE-TEE, some works have reported encouraging results in the detection of aortic root infections (small abscesses)[79] and pacing system infections[80] in cases of negative or equivocal echocardiography. However, the best use for this technique in the setting of infective endocarditis has yet to be defined. Additionally, some molecular imaging studies offer perspectives in functional imaging of vegetations and embolic events.[81,82]

Finally, the role of cerebral MRI in the diagnosis and management of this disease has been defined in some studies.[83–85] Results from these studies showed that systematic MRI could detect subclinical cerebrovascular complications in about 50% of patients. In a single-centre study, Duval and colleagues[85] described how the identification of brain damage by 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 cases. Solely on the basis of these MRI results, and excluding microhaemorrhages, the diagnostic classification of 32% of the cases of non-definite endocarditis was upgraded to either definite or possible. Moreover, the therapeutic plans were modified for 18% of patients, including surgical plan modifications for 14%.[85] Obviously, indications for all these imaging methods will have to be clearly defined in the future, and we must keep in mind that contrast products should be used with caution because of the risk of acute renal failure. Moreover, our experience has led us to maintain patients at rest and to avoid moving them during the very acute stage of the disease, if possible, because we noticed cases of sudden death during intrahospital transfers for radiological examinations.[12]

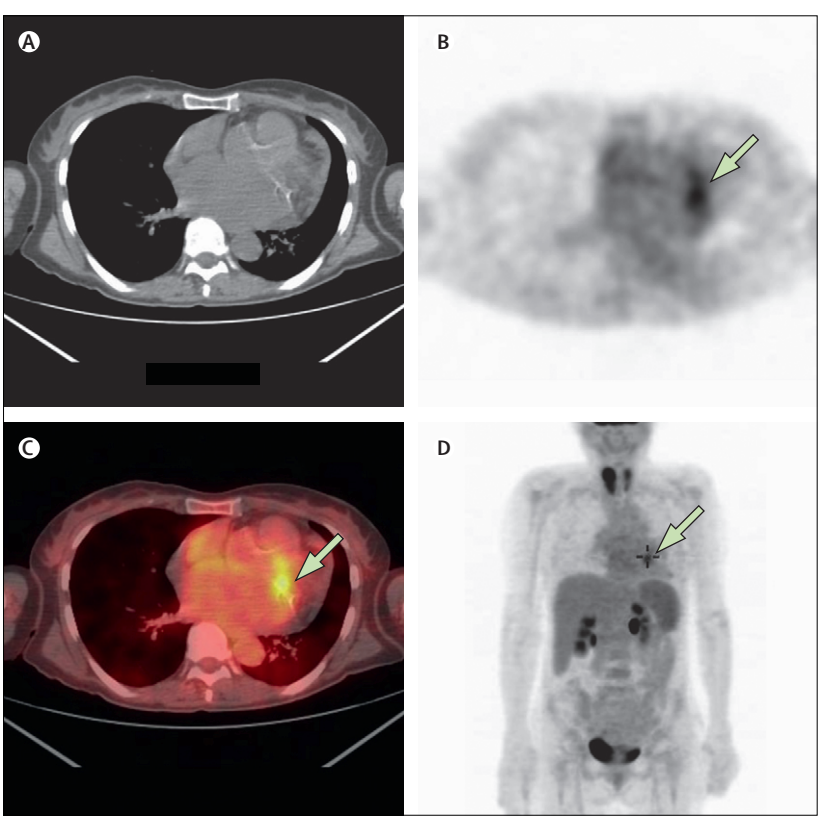

Figure 3: **PET-CT of a 64-year-old woman with a mass on thickened mitral valve but no pathogen identified by blood cultures or serology**
FDG=fluorodeoxyglucose. (A) Transaxial CT scan. (B) Transaxial PET image. (C) Transaxial PET-CT fused image showing an increase FDG uptake in the area of the mitral valve (green arrow). (D) Anterior three-dimensional maximum intensity projection. The endocarditis diagnosis was confirmed by pathological examination after surgery (recurrent emboli) showing vegetation but no pathogen could be identified.

Challenges in prognostic assessment

At admission, immediate assessment of prognosis should be done to identify high-risk patients who need a closer monitoring and more aggressive treatment such as early surgery. Many predictors of death have been identified, including clinical, biological, and echocardiographic variables.[5,56,86–88] However, to exactly assess the prognosis of patients through these numerous factors remains difficult. One perspective is to classify the prognostic severity on the basis of risk scores, which will make management decisions more standardised and easier. Recent studies[86,89–91] have validated such risk models that incorporate clinical variables available at the bedside. In this risk stratification, echocardiography has a crucial role by providing strong predictors for negative outcomes such as large or enlarging vegetations,[5] paravalvular extension of infection,[49] signs of increased left-cavities filling pressures, pulmonary hypertension, and low left-ventricular ejection fraction.[90] Moreover, biomarkers such as brain natriuretic peptide (BNP) and troponin have also been identified as potential predictors of outcome.[92] Additionally, the results of a recent physiopathological study that analysed the transcriptional profile of cardiac valves from patients with infective endocarditis offer a perspective for the identification of new biomarkers that might be used in prognosis assessment.[93]

Improvement of the optimum risk stratification will help with therapeutic decisions (medical *vs* surgical treatments) in some difficult cases and allow for decisions about which patients to refer to intensive care units. Thus, the risk of sudden death in infective endocarditis raises the question of recommendations for a permanent monitoring in intensive-care units. This monitoring would allow for the early detection of rare but life-threatening complications

such as atrioventricular conduction block, which could require transient cardiac pacing and urgent surgery.

Challenges in treatment

Delayed and inappropriate antibiotic therapy has an important effect on outcome.[57,94] A prompt antibiotic therapy can avoid the occurrence of severe sepsis, multiple organ dysfunction syndrome, and sudden death. Moreover, Dickermann and colleagues[95] showed a 65% reduction in risk of stroke related to infective endocarditis 1 week after the introduction of antibiotics.[95] Therefore, when infective endocarditis 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.

Optimisation of a surgical approach offers the best immediate opportunity to reduce mortality. After prognosis assessment, the clinician must decide whether to operate and when. However, such a decision is usually difficult and is dependent not only on the patient's condition but also on clinicians from different specialties and with different experiences. Despite existing guidelines, a study[96] reported that surgery was not done on 42% of patients with a recommended indication.[96] These deviations from the guidelines have been associated with a negative effect on patients' prognosis.[96,97] This phenomenon was also noted in our department before we implemented a standardised strategy based on a local consensus of infective endocarditis among microbiologists, cardiologists, infectious disease specialists, and surgeons (the infective endocarditis team). Such a strategy has been introduced to obtain some degree of reproducibility for treatment. Therefore, all patients will benefit from a treatment suitable for every defined clinical situation, regardless of the attending physician. Our consensual protocol includes the administration of a few antimicrobial drugs and clearly defined surgical indications based on international guidelines. Each case is discussed weekly among a multidisciplinary staff, and a decision is made about surgical priorities. This rationalisation for management of the disease will enable a substantial increase in compliance to surgical indications and decrease mortality.[13,14]

Moreover, the skill and experience of the surgeons in the specialty of infective endocarditis are one of the most important points that affect mortality, but no controlled study will ever provide this evidence because valvular surgery in this context is a very "surgeon-dependent" therapy. The two primary objectives of surgery are total removal of infected tissues and reconstruction of cardiac morphology. The type of prosthetic valve has no influence on prognosis,[98] and valvular repair is always preferable when possible.[33,35] Surgical series have shown that the surgical results are more related to a surgeon's recognition of and ability to remove all infected tissues than to the type of valve used for a replacement.[37,38] However, because infective endocarditis is a rare disease associated with the most severe valvular damage, surgical training is difficult and requires a long time. Hence, the creation of a specialised surgical department, in which all of the severe cases from a specific region would be regrouped, is of crucial importance for the increase of team experience and improvement of patient prognosis.

Future perspectives for surgery in infective endocarditis might involve minimally invasive cardiac operations that have been proven to reduce both the degree of surgical insult and the need for reoperation for bleeding.[99] Although this technique is usually done for degenerative valvular disease, some encouraging results have been reported in patients with infective endocarditis.[100] This technique might represent a good alternative for the standard cardiac surgery in frail patients with the disease.

Finally, a recent description of the intra-annular implantation of a biodegradable annuloplasty ring during mitral and tricuspid valve repair might represent an advantageous technique in the context of infective endocarditis by hindering direct blood contact and the associated risk of microbial colonisation.[101]

Close long-term follow-up

Because the mortality and morbidity associated with infective endocarditis can extend beyond a successful treatment, patient monitoring should not stop after hospital discharge. Long-term complications include infectious recurrences, cardiac surgery because of the valvular sequelae of the disease, and death. Physicians who manage cases of infective endocarditis must closely follow

Panel: **Key points for optimum management of infective endocarditis**

- Quick start of empirical antimicrobial treatment after microbiological sampling
- Secondary adaptation of antimicrobial treatment according to the appropriate laboratory tests
- Rapid identification of high-risk patients
  - Heart failure
  - Stroke, abnormal mental status
  - Recurrent embolic events
  - Septic shock
  - Persisting fever >7–10 days
  - Large or enlarging vegetation
  - Perivalvular extension of infection (abscess, pseudoaneurysm, fistula)
  - New heart block
  - Severe left-sided regurgitation, severe prosthetic dysfunction
  - Signs of increased left-cavities filling pressures, pulmonary hypertension
  - Low left-ventricular ejection fraction
  - Pathogens other than viridans streptococci, especially *Staphylococcus aureus*, fungi, and Gram-negative bacilli
  - Acute renal failure
- Transfer of high-risk patients to specialised medicosurgical centres
- Close monitoring of high-risk patients (transfer to an intensive-care unit should be discussed)
- Reduction of delays for operations when cardiac surgery is indicated
- Long-term follow-up by a multidisciplinary team and education

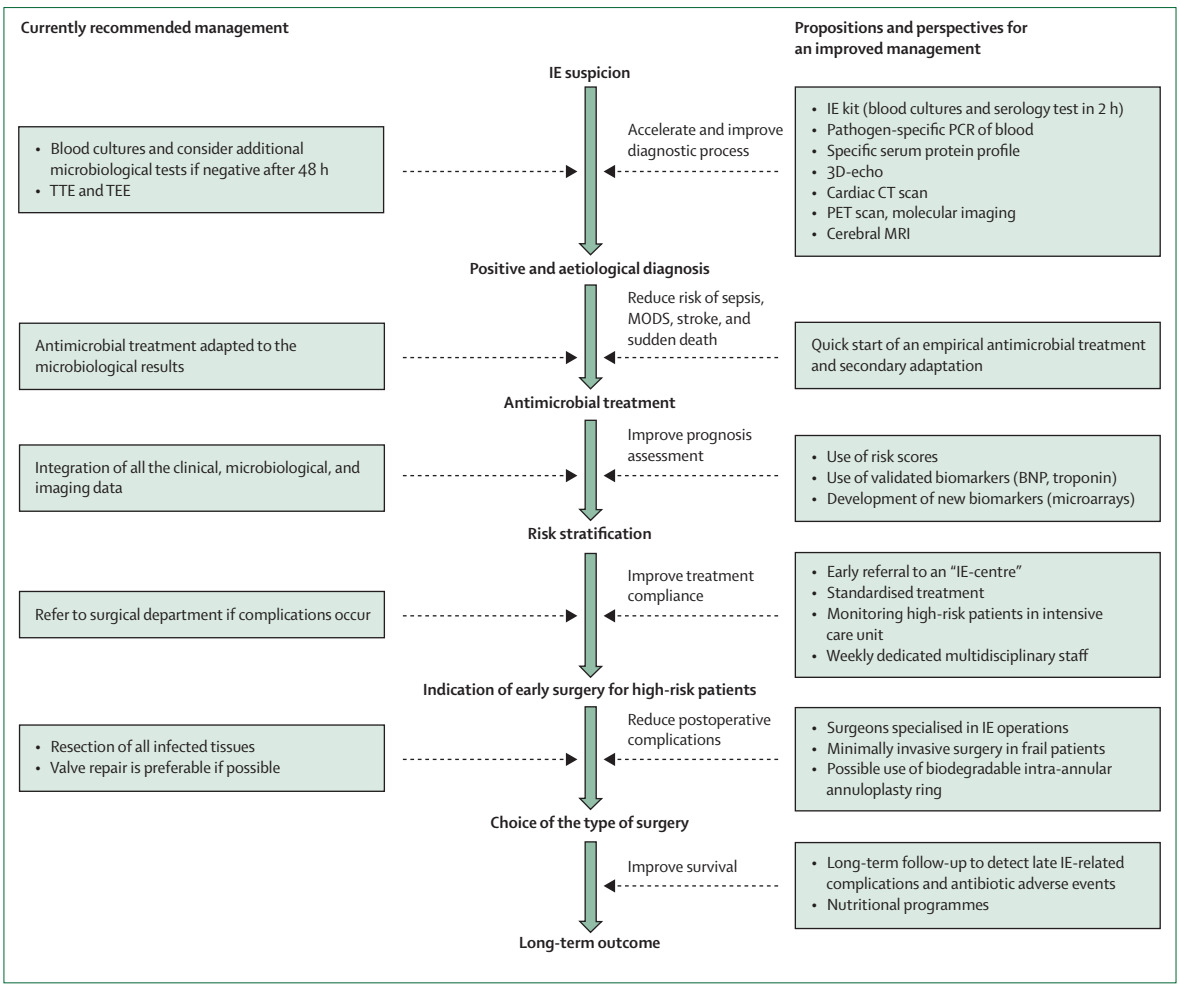

Figure 4: **Perspectives for improvement of management and a subsequent reduction of mortality related to infective endocarditis in specialised centres**
IE=infective endocarditis. TTE=transthoracic echocardiography. TEE=transoesophageal echocardiography. MODS=multi-organ dysfunction syndrome. BNP=brain natriuretic peptide.

their patients for a few months after the end of the acute phase. In our centre, after discharge, patients are educated about the signs and symptoms of the disease, and they are systematically seen for a consultation on the same day by a cardiologist and an infectious disease consultant 1, 3, 6, and 12 months after the end of treatment, as now recommended by European guidelines.[25] Additionally, this medical follow-up is very important to eradicate potential new sources of re-infections (eg, intravenous lines, colorectal tumours, and buccodental infections). Preventive measures should be applied in these patients, especially good oral hygiene and regular dental review. Prevention of infective endocarditis has been subject to important changes during the past decade; the importance of non-specific hygiene is now placed above the prophylactic antibiotic therapy, the use of which is restricted.[25] Almost all present national or international guidelines, including those from USA,[102] Europe,[25] and Australia,[103] have narrowed these recommendations radically, but still recommend prophylaxis for some dental procedures in high-risk cardiac patients. The British guidelines from the National Institute for Health and Clinical Excellence[104] are alone in recommending no antibiotic prophylaxis for any cardiac patients, but they remain controversial.[105] Additionally, patients should be educated about the signs and symptoms of infective endocarditis after discharge. They should be aware that recurrence can occur and that a new onset of fever, chills, or other signs of infection mandate immediate assessment, including the procurement of blood cultures before the empirical use of antibiotics. Moreover, the clinician will be able to detect side-effects of prolonged antibiotic therapy such as hearing loss and renal failure, especially after treatment with vancomycin and gentamicin. Finally, nutritional programmes can also be important for these patients.[106]

Conclusion

Infective endocarditis remains among the deadliest of infectious diseases. Novel methods in management are emerging and offer hope in decreasing the rate of residual

deaths (panel). These methods aim to accelerate the process of diagnosis and risk stratification, reduce delay in starting antimicrobial therapy, and transfer high-risk patients to specialised medicosurgical centres (figure 4). These future management strategies will implicate more physicians from different specialties, which will lead to recommendations for the creation of infective endocarditis teams in expert centres and to the development of research programmes for new diagnostic and prognostic markers.

Contributors

FT participated in literature search, data analysis, and writing of the report. DG participated in interpretation of data and critical revision of the report for important intellectual content. FC participated in critical revision of the report for important intellectual content. GH participated in critical revision of the report for important intellectual content. DR participated in supervision and design of the review, data interpretation, and critical revision of the manuscript for important intellectual content. DR had full access to all the data in the review and had final responsibility for the decision to submit for publication.

Conflicts of interest

We declare that we have no conflicts of interest.

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