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Infective Endocarditis: Therapeutic Options and Indications for Surgery

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Abstract Infective endocarditis is a serious, life-threatening condition with mortality of 30 % at one year. Established treatment is a combination of anti-microbial therapy and close interface between multiple specialist teams of cardiologists, microbiologists and cardiac surgeons to ensure availability of early surgery to those patients who require it. There are evidence-based established indications for surgery and a shifting body of evidence advocating earlier surgical intervention. The development of complications is often the driving cause of referral for surgical intervention. Here we discuss the management of infective endocarditis, considering both anti-microbial therapy and indications for surgery to treat this debilitating disease.

Keywords Infective endocarditis · Surgery · Cardiology · Antibiotics · Valvular disease · Echocardiography · Diagnosis · Treatment · Management · Bacteria · Valve surgery

Introduction

Infective endocarditis (IE) remains an important and serious healthcare problem that continues to have poor outcomes. Mortality remains at around 30 % at one year [1] and this has not improved despite advances in identification and treatment [2]. The long term survival rate from endocarditis irrelevant of treatment options is around 70 % [3]. The lack of improvement in mortality and morbidity is attributed to the changing demographics and causes of IE over the last few decades. Decreases in IE as a result of rheumatic fever, for example, have been outweighed by the increasing incidence of staphylococcal infection related to modern medical practice [4] and the increasing age and comorbidity of the patients that has overall led to stable incidence and outcomes.

Antibiotic therapy remains the mainstay of treatment with surgical treatment supplementing this in 50 % of cases [5]. Decisions concerning the need for surgery and its timing are often complex but the indications for early surgery seem set to increase as more robust evidence becomes available [6]. Helpful international guidelines provided by both the European Society of Cardiology (ESC) and American College of Cardiology (ACC) set down practical indications and advice regarding the timeliness and indications for surgical intervention [5, 7].

The scope of this article will consider the timing and indications for surgery in IE with a focus predominantly on infection affecting native heart valves. The indications as stipulated in international guidelines are considered along with special cases and discussions on appropriate timing of surgery for each indication.

Antibiotic Therapy

Antimicrobial therapy remains the mainstay of IE treatment and the goal is eradication of the causative organism [5]. The key to successful antibiotic treatment is identification of the causative organism and this is emphasized in published guidance [5, 7] and by recently updated British Society for Antimicrobial Chemotherapy (BSAC) guidelines [8]. Most cases of native valve endocarditis (NVE) are due to streptococci and staphylococci but a wide variety of organisms can be causative in early (<2 months) prosthetic valve infection. The

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HACEK group of organisms has shown increasing prevalence along with rarer fungal infections [7].

If possible, empirical treatment should wait in stable patients until blood culture results are known to try and minimize incidences of negative blood cultures leading to difficulties with precise antibiotic therapy [8]. When necessary, current recommendations for empirical therapy involve a combined approach using a β-lactam antibiotic (penicillin, amoxicillin, ampicillin) in conjunction with gentamicin. Where there is a high suspicion of staphylococcal infection (for example with severe sepsis, intravenous drug use or diabetes mellitus) or in cases of prosthetic valve infection, the use of vancomycin instead of penicillin is suggested [8]. The combination of antibiotics with bactericidal properties is important to eradicate these organisms.

Antibiotic treatment should continue for 2–6 weeks in cases of native valve endocarditis but often longer for prosthetic valves [5, 7–9]. Timing of treatment starts from the first incidence of a negative blood culture or specimen taken at surgery [5, 7]. There is little evidence for oral antibiotic treatment and intravenous administration remains the only viable option. There has been an increasing trend towards treatment with intravenous antibiotics in the outpatient setting in recent years, but this should remain limited to patients in whom serious complications have been excluded [5].

A causative organism is sometimes not found and is deemed "culture negative endocarditis." The most common cause is culture sampling after empirical antibiotic treatment [7] but this scenario is also commonly due to infection with more indolent and unusual pathogens, such as those in the HACEK group [9]. There are published and well established guidelines for antibiotic choice once an organism is identified.

Indications for Surgical Intervention

In total, approximately half of all patients with IE will undergo surgical treatment [5]. International guidelines stipulate that common indications for surgical intervention are the development of congestive cardiac failure, uncontrolled infection and systemic embolism [5, 7] although other indications also exist [6]. The optimal timing of surgery, where appropriate, is debated and it is not yet clear when the optimum time for surgery is [9], due mainly to the lack of randomized controlled trials in this area.

Congestive Cardiac Failure

Congestive cardiac failure (CCF) often develops in IE due to valvular insufficiency that can either develop insidiously or acutely; less commonly, valve destruction and fistula formation may also lead to cardiac failure [6]. Around 60 % of patients undergoing surgical treatment will do so due to CCF, making it the most common reason for surgical intervention [10]. These patients may present with pulmonary edema, dyspnea and, occasionally, cardiogenic shock. Best medical therapy should be employed to optimize cardiac function in these patients but many go on to require surgery. Transthoracic echocardiography (TTE) is used to evaluate cardiac function in cases of IE and this should be complemented by the use of transesophageal echocardiography (TOE) in most cases [11].

Where cardiac failure develops as a result of IE, surgery has been shown to improve outcomes [12–14]. It is important to time surgery such that it occurs before serious hemodynamic compromise occurs in order to achieve improved outcomes [3, 13, 15]. Caution should be used to identify patients with insidious progression of CCF. Progressive CCF is associated with higher operative mortality and the identification of such patients should prompt assessment for surgical intervention [16].

Some patients tolerate mild-moderate valvular disease and thus medical treatment of IE even in the context of CCF may suffice, the main benefit being to protect those at high risk of surgical complications (e.g. the frail elderly) from the risks of operative treatment. These rare patients, however, should be closely followed and monitored so that later valve surgery can be considered if significant problems develop [17]. CCF is the most important predictor of in-hospital and 6 month mortality [5].

Uncontrolled Infection

Uncontrolled infection in IE includes the main scenarios of persistent bacteremia despite adequate antimicrobial therapy, perivalvular extension of infection and the presence of resistant organisms. This group of complications is the second most common indication for surgical treatment and is present in around 40 % of those patients undergoing surgery for IE [10].

Persistent Sepsis

According to international guidelines, surgery is indicated if fever and positive blood cultures persist after more than 7–10 days of appropriate antimicrobial therapy [5, 7]. In this scenario, however, it is imperative to exclude extra-cardiac abscesses which may account for persistent sepsis. Endocarditis as a result of *Staphylococcus aureus* infection may lead to large vegetations and persistent bacteremia and there is clear evidence that surgery should be earlier in this setting [18]. The differentiation should be made between those patients who have ongoing fevers for separate reasons (such as line infections) and those who have a persistent bacteremia as a result of poorly controlled IE. Surgery should only be performed when this distinction is clear.

Perivalvular Extension

Perivalvular extension of infection (i.e. infection beyond the valve leaflets) is the most common reason for failure of antimicrobials to control infection. Perivalvular complications are known to carry a poorer prognosis and increase the likelihood of surgical intervention being undertaken [19, 20]. These complications are more frequent in aortic valve endocarditis, infections of prosthetic valves, in the presence of atrioventricular (AV) conduction block and when coagulase-negative staphylococci are the causative organisms [21]. It is suggested that 10–40 % of patients with native valve endocarditis (NVE) and 56–100 % of patients with prosthetic valve endocarditis (PVE) develop perivalvular extension [5].

Clinicians should be aware of clinical features pointing towards the potential for extension of infection. Such signs include the presence of a new murmur, persistent swinging fevers, acute onset of CCF and electrical conduction disturbances [22]. In one series, the presence of a new AV block had a positive predictive value (PPV) of 83 % for the detection of periannular complications [21]. If perivalvular complications are suspected then TOE is the imaging modality of choice to confirm the diagnosis [11, 23].

Resistant or Difficult to Treat Organisms

Some organisms causing IE are now found to be multi-drug resistant (such as methicillin resistant staphylococcus aureus or vancomycin resistant enterococci) and the only hope of cure in these cases is by surgical intervention.

Fungal IE often causes very large vegetations and significant complications such as valvular extension and CCF whereby treatment with antimicrobial agents is difficult and so surgery should be offered in these cases [24]. Surgery in fungal IE has been shown to improve outcomes but should be combined with ongoing anti-fungal prophylaxis for maximum survival benefit [25].

In cases of *Staphylococcus aureus* IE, complications readily occur and early surgical intervention should be considered if there is no immediate response to antimicrobial therapy. Prognosis is otherwise poor [18, 26].

In some rarer causes of IE it is also appropriate to consider early surgical intervention. Infection by *Brucella*, for example, can cause significant valve destruction and so surgery is indicated early in the course of the disease [27]. Infections with *Pseudomonas aeruginosa* and *Coxiella burnetii* may also be better managed with surgical intervention [28, 29], and a prolonged course of antibiotics is indicated post operatively in cases of *Coxiella burnetii* IE [30].

Systemic Embolism

Occurring in up to 50 % of patients with IE, systemic embolism is a particularly serious complication and often life threatening [31]. The brain is the most common site of embolic events and often embolism affects the territory of the middle cerebral artery [32]. Other sites in the body with a large vascular supply are also frequently affected (such as the spleen, or, in the case of right sided IE, the lungs) although embolism can be "silent" in around 20 % of cases [32].

Most commonly, embolic events occur early in infection (and often before formal diagnosis) and the event rate declines sharply upon starting anti-microbial therapy [32] with most occurring within the first two weeks of antimicrobial treatment [33]. Correct timing of surgical intervention is therefore crucial in preventing systemic embolism and identifying those patients at risk of this complication can guide management.

Echocardiographic findings may identify those at greater risk of embolism. Vegetation size, length, mobility and location all play a role in increasing the risk of embolism from IE [31–35]. Indeed a vegetation length of greater than 1 cm confers a significantly increased risk of systemic embolism [31, 32, 34]. Other factors increasing the risk of embolism include certain organisms [33], biochemical markers [35] and a previous embolic event [33].

Surgery should be considered early in those patients at risk of developing systemic embolism as a result of IE. One trial has shown a significant benefit to early surgery in those patients with IE and large vegetations by preventing systemic embolism [36].

Neurological Complications

Neurological complications are common and occur in around 20-40 % of cases [37, 38]; the predominant cause is embolism and the presence of neurological complications is associated with poorer outcomes including increased mortality [37]. Many manifestations exist including stroke (both ischemic and hemorrhagic), transient ischemic attack (TIA), silent embolism, abscess formation, seizures and meningitis.

The European Society of Cardiology currently recommend that if neurological symptoms are found in a patient with IE investigations including non invasive imaging of the brain (CT or MRI) are performed [5]. The occurrence of a TIA or silent cerebral embolism should prompt urgent surgery if an indication remains and the presence of a stroke should not delay surgery for other indications provided that there is no evidence of intracerebral hemorrhage.

If there is evidence of intracranial hemorrhage then surgery should be postponed for one month [5, 33] although the timing of surgery is otherwise debated. Overall, it appears that there is no advantage to delaying surgery after neurological

events and early surgery for these patients may be beneficial [39, 40].

Other scenarios and Specific Subgroups

Prosthetic Valve Endocarditis

Of all cases 10-30 % of IE occur in the context of prosthetic heart valves [10, 41]. Around half of cases require surgical intervention and in-hospital mortality is high at up to 30 % [10]. Prosthetic valve endocarditis (PVE) is defined as early or late depending on whether it arises within or after 1 year following valve replacement. This definition places focus on the likely causative organisms involved at different time points.

Early PVE is often caused by *Staphylococcus aureus* or coagulase-negative staphylococci [10]. Surgical intervention should always be considered and in cases of PVE caused by *Staphylococcus aureus* early surgical intervention is crucial [42, 43]. Late PVE tends to be caused by the same organisms as NVE and non-surgical treatment in this group may be effective.

Device Related Endocarditis

Although rare, the incidence of this complication of implanted devices is increasing due to their increasingly widespread use. Estimates of incidence vary but it is a serious complication that is often difficult to diagnose and carries with it significant mortality [44, 45]. Management strategies for complete eradication require anti-microbial therapy together with device removal [45]. New systems can be implanted once infection has been eradicated.

Right Sided Endocarditis

Infections of right sided heart valves make up 5–10 % of the total cases of IE [5] and are most commonly associated with intravenous drug users [46]. Surgery should be avoided in right sided NVE due to the success of conservative management strategies although it may be considered in cases of severe right heart failure, difficult to treat organisms or large vegetations giving rise to recurrent pulmonary emboli [5].

Endocarditis in the Elderly

As our population ages, IE is becoming more frequent in those aged over 70 [47] with trends towards worsening outcomes [48]. Diagnosis is often made later in the course of the disease as a result of more indolent presentations and this undoubtedly contributes to poorer outcomes.

Mortality of IE in elderly patients is higher than in younger patients and age, cerebral embolism and PVE have been shown to be risk factors for increased mortality [49]. Surgical intervention in elderly patients is associated with lower in hospital mortality – moreover, complications and mortality in elderly patients undergoing surgery are similar to those in younger groups [49]. Age, therefore, should not be a contra-indication to surgery where other indications for surgery exist.

Anticoagulation and Antiplatelets

Although the majority of complications of IE occur as a result of embolization, there is no evidence that anticoagulation or antiplatelet therapy reduce this risk. In fact, data suggest that patients already on anticoagulants who develop prosthetic valve endocarditis are at higher risk of hemorrhagic transformation [50]. A double-blind randomized controlled trial of high-dose aspirin in all patients with IE demonstrated no benefit of antiplatelet therapy with an accompanying increase in bleeding risk [51].

Current European guidelines indicate that antiplatelet therapy can be continued if there is no evidence of bleeding, that oral anticoagulants should be switched to unfractionated heparin should an ischemic stroke occur, and that anticoagulation should be withheld entirely if an intracranial bleed occurs [5].

The role of the Multi-disciplinary team

There is an increasing body of evidence indicating that the systematic involvement of a specialist multi-disciplinary team of experts (including cardiology, cardiothoracic surgery and microbiology) helps improve outcomes for patients with IE. A study in an Italian centre found that outcomes over a four-year period during which strict guidelines for diagnosis, surgical indications and follow-up were implemented, were improved with mortality rates dropping from 18.5 % to 8.2 % ($p=0.008$) [52]. These findings were recently borne out in a different centre in Italy with outcomes measured before and after introduction of a multi-disciplinary approach [53]. In this study, patients were assessed within 12 hours of admission with surgery performed within 48 hours where indicated. Patients were then assessed frequently and operated on if and when indications arose. This approach resulted not only in reduced mortality in-hospital (28 % to 13 %, $p=0.02$) and at three years (34 % to 16 %, $p=0.0007$) but also reduced occurrence of culture-negative endocarditis, reduced rates of renal dysfunction and improved surgical outcomes. This strategy was effective in both native and prosthetic valve IE [54].

These interesting data certainly advocate the management of these complex patients by an experienced specialist team

from the outset, and provides further support for the role of early surgery.

Conclusion

Infective endocarditis remains a serious disease with ongoing treatment challenges. The mainstay of treatment remains prompt diagnosis and appropriate use of antimicrobial agents. The role of surgery is critical and close team working between cardiologists, microbiologists and cardiac surgeons will ensure that the management of each patient is considered closely and carefully. The benefits of surgery must be weighed against the risks and these will differ on a patient to patient basis. Clear indications exist where early surgery has proven benefit and wider awareness of these indications should ensure prompt referral for surgical intervention. The timing of surgery for maximum benefit and minimal risk is debated but it is likely that more robust evidence for early surgical intervention will continue to appear aiding more straightforward decision making.

Compliance with Ethics Guidelines

Conflict of Interest Aneil Malhotra, Jenny Rayner, Timothy M. Williams, and Bernard Prendergast declare that they have no conflict of interest.

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