CURRENT CONTROVERSIES IN INFECTIVE ENDOCARDITIS

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ABSTRACT

Infective endocarditis (IE) remains a devastating disease with a high mortality. Its microbiology is changing with increasing incidence of *Staphylococcus aureus* infection, which often does not present with the typical signs that are incorporated into diagnostic criteria. With expanding indications for the implantation of cardiac devices, such as cardiac resynchronisation pacemakers and defibrillators, the incidence of device-related endocarditis is also increasing rapidly. The European Society of Cardiology (ESC) provides evidence-based guidelines regarding prophylaxis, diagnosis, and management of IE, the most recent of which were published in 2009. The aim of this review is to identify topical areas of controversy, where new research developments have shed some light since the last publication of these guidelines. The review focuses on antibiotic prophylaxis, investigating potential IE in *S. aureus* bacteraemia, and management of cardiac device-related IE. It is notable that not 1 in over 80 recommendations in the latest ESC guidelines is backed by data that are level of evidence A. Whilst it is clearly unethical to perform trials in this area of medicine against placebo, treatment algorithms and approaches to management can readily be compared with each other in a randomised way, and data using this approach are emerging. Increasing the quantity and quality of evidence when it comes to IE remains a significant challenge.

Keywords: Infective endocarditis, *Staphylococcus aureus*, prophylaxis, cardiac devices, guidelines.

INTRODUCTION

Infective endocarditis (IE) is a devastating disease with an incidence estimated between 30-100 episodes per million patient-years.[1-4] Since its first description by the case series from Sir William Osler in 1885, the epidemiology of IE has evolved from predominantly a disease of young adults with rheumatic valve disease, to a disease also affecting the elderly (aged between 70-80), and those with prosthetic valves and intra-cardiac devices. A smaller group of challenging patients also exists who are on long-term renal dialysis, are intravenous drug abusers, HIV positive, or have complex congenital heart disease.[5-7] There have also been changes in the microbiology of IE with increasing incidence of *Staphylococcus aureus* infection and multi-drug resistant bacteria. In the latest cohort study from 2,781 inpatients across 52 different hospitals around the world (ICE-PCS), 42% of IE cases were caused by *Staphylococcus*, of which 31% were *S. aureus*.[8] These changes in demographics and epidemiology of IE likely contribute to the persistently high inpatient mortality (around 20%) with the worst outcomes in elderly patients, *S. aureus* infection, prosthetic valve involvement, and those at high operative risk.[6,8] The European Society of Cardiology (ESC) provides evidence-based guidelines regarding prophylaxis, diagnosis, and management of IE, the most recent of which were published in 2009.[9] Many controversial areas remain in the management of IE and it is clearly impossible to touch on all of these. The aim of this review is to identify topical areas of controversy, where new research developments have shed some light since the last publication of these guidelines.

PROPHYLAXIS

Prophylaxis for the prevention of IE following invasive or dental procedures has been under intense debate for >50 years and remains standard practice in many parts of the world. Evidence for bacterial prophylaxis to prevent IE came from early observational studies which showed bacteraemia following dental procedures,[10] and animal studies where prophylaxis with amoxicillin prevented development of IE in animals inoculated with *Streptococcus*.[11] Later evidence demonstrated that bacteraemia was more common following routine dental brushing, and therefore, far more frequent than that of dental procedures (particularly in those with periodontal disease and prolonged brushing),[12,13] and that the risk of IE from dental procedures was extremely low at 1:14,000,000.[14] Furthermore, the existing evidence has failed to demonstrate any efficacy of widespread antibiotic prophylaxis in the prevention of IE. Following comprehensive reviews, three professional bodies, the ESC, the American Heart Association (AHA), and the British Society for Antimicrobial Chemotherapy (BSAC) have recommended restricting antibiotic prophylaxis to use in high-risk patients. (Table 1).[4,15,16] For patients in the highest risk groups, in particular those with prosthetic valves, there is evidence for the use of antibiotic prophylaxis. It should be noted though that common native valve diseases including bicuspid valve, mitral valve prolapse, and calcific aortic stenosis are not considered high risk.

A recent review by the UK National Institute of Health and Clinical Excellence (NICE) took the matter further and recommended stopping antibiotic prophylaxis for all patients.[17] NICE did recognise the high-risk patient groups as suggested by the other guidelines, but chose not to separate the groups in the interest of simplicity and population economics. The published recommendations from NICE were received with mixed reactions from clinicians addressing risk-benefit considerations of individual patients, and a call was made for both national and international monitoring of IE outcomes.[18] A questionnaire sent in 2012 to cardiologists, cardiothoracic surgeons, infection specialists, and dentists showed 39% of cardiologists and cardiothoracic surgeons did not follow the NICE guidelines; even amongst dentists with the highest rate of acceptance (87%), 36% still prescribed antibiotic prophylaxis following the guideline publication.[19] Similar trends were observed in North America where despite 75% satisfaction with AHA guidelines, 70% of dentists still had patients on antibiotics before dental procedures.[20] Studies are now also emerging on the impact of the new guidelines on IE admission and complications. In one North American study of 1,157 paediatric IE admissions (age <18), there was no significant change in either admission trends or incidence of oral streptococci IE.[21] Similar findings were observed in another North American study where no perceivable increase was observed in the incidence of viridans group streptococci.[22]

Table 1: Cardiac conditions of patients at highest risk of infective endocarditis (IE) and recommendations for antibiotic prophylaxis.

Recommendations	Class	Level
Antibiotic prophylaxis should only be recommended for patients at highest risk of IE.		
1. Patients with a prosthetic valve or any prosthetic material used for cardiac valve repair,	IIa	C
2. Patients with previous IE,		

3. Patients with congenital heart disease (CHD):
    a. Cyanotic CHD with or without previous interventions,
    b. CHD with complete repair (surgical or percutaneous) for the next 6 months,
    c. When a residual defect persists after cardiac surgery or percutaneous technique.		

Antibiotic prophylaxis is no longer recommended in other forms of valvular or CHD.	III	C

Modified from Habib G et al.[44]
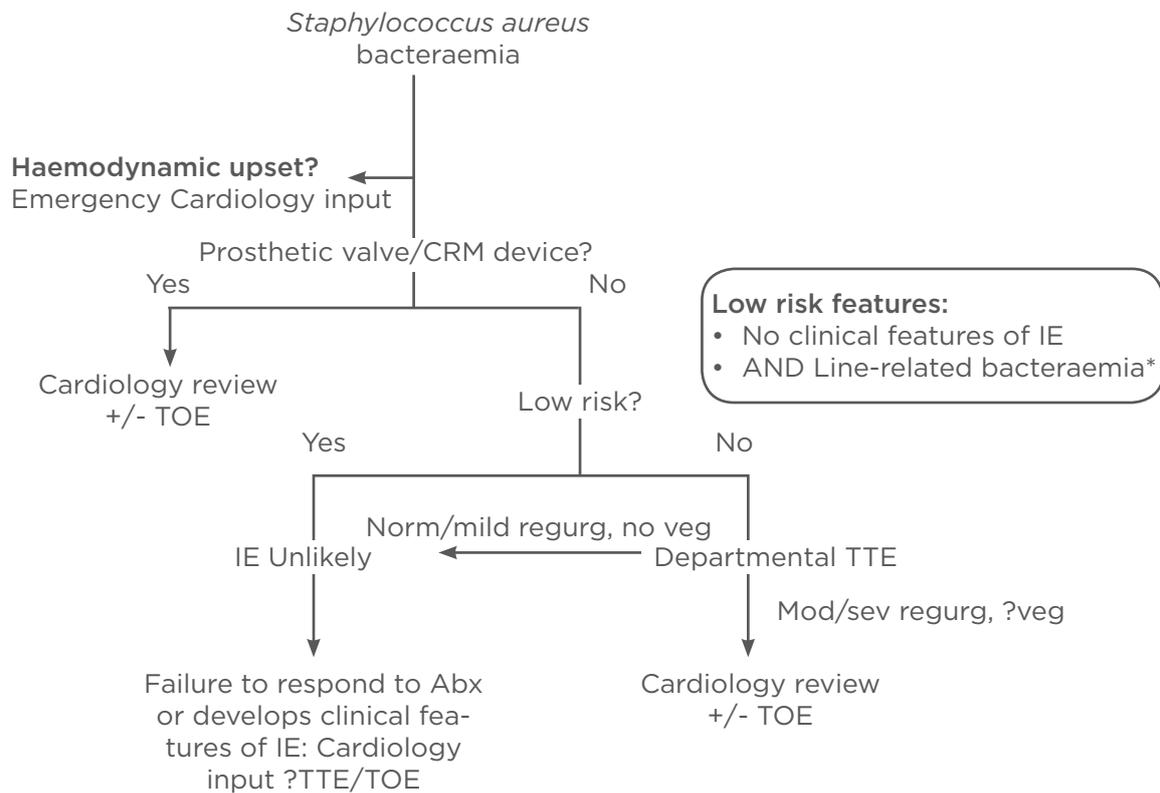
Figure 1: Proposed algorithm for prioritisation of echocardiography in the setting of *Staphylococcus aureus* bacteraemia.
CRM: cardiac rhythm management; TOE: transoesophageal echocardiography; IE: infective endocarditis; TTE: transthoracic echocardiography; Abx: antibiotics.
Modified from Joseph et al.[32]

In the UK, a recent study that examined all patients admitted with IE did not show a significant increase in the incidence of IE cases or deaths from IE 2 years after implementation of the NICE guidelines, despite 78.6% reduction in the prescription of antibiotic prophylaxis.[19] These studies suggest that reducing antibiotic prophylaxis had no adverse impact on IE although all are limited by inclusion of patients, including those at high-risk. All guidelines agree that regular dental surveillance to promote good oral hygiene and reduce the need for invasive procedures is important, and the lack of access in many countries, including the UK, remains a significant problem.[23]

IMAGING IN *S. AUREUS* BACTERAEMIA (SAB)

S. aureus is an increasingly common cause of IE and associated with significantly higher mortality due to its propensity to cause deep-seated and metastatic infections.[6,8] IE is a frequent complication of SAB,[24] and recent BSAC guidelines have recommended echocardiography as a routine investigation for all cases of SAB.[25] Evidence to support routine screening of patients with SAB for associated IE came first from a study by Fowler et al.[26] which found 25% of 103 patients with SAB had echocardiographic evidence of IE despite the presence of clinical features in only

7% of the patients. Subsequent studies using echocardiography in patients with SAB found similar results.[27,28] Guidelines, however, differ on the timing and modality of echocardiography that should be used. Transthoracic echocardiography (TTE) has the advantage of being widely accessible with no risk to the patient but, despite advances in imaging technology, good quality TTE remains less sensitive (82-89%) when compared to transoesophageal echocardiography (TOE).[29] The quality of TTE can also vary depending on patient factors such as body mass index and concurrent lung disease, and identifying vegetations in patients with metallic valves and intra-cardiac devices is difficult with TTE due to imaging artefact. Imaging can also identify coincidental pathology, such as minor aortic valve thickening, which can confuse the diagnostic process and lead to further investigations. TOE on the other hand is a limited resource, costly, and poses a small procedural risk to the patient. If imaging is carried out very early in the course of the illness, it is also possible that small vegetations could be missed, and no guidance exists on whether repeated imaging is beneficial. Some clinicians are reluctant to perform TOE in patients with SAB and have no features of IE, who show prompt clinical response to antimicrobial treatment, and have the focus of infection (e.g. a central intravenous catheter) promptly removed.

Several studies in the last few years have identified groups of patients who are at high or very low-risk of having echocardiographic evidence of IE. Those patients with intra-cardiac material, such as prosthetic valves or cardiac rhythm management devices, have up to a 5-fold higher risk of IE,[26,30-32] and patients with community acquired compared to hospital acquired SAB infection have up to a 3-fold higher risk of IE.[28,31-33] Those patients with prolonged bacteraemia on repeated blood cultures of >4 days are also at higher risk of developing IE.[30] Conversely, patients with strictly defined line-related infections have a particularly low risk of IE,[31] particularly when the high-risk features described above are also absent.[32] Those patients with a TTE which demonstrates no or mild valvular regurgitation only, and no evidence of IE, are also at low risk of developing IE.[32,33] A recent publication has suggested a diagnostic approach incorporating these features, suggesting that imaging can be prioritised appropriately in patients with SAB; we summarise this approach in Figure 1. This algorithm relies on early and continued input from a specialist infectious disease/microbiology

and cardiology multidisciplinary team.[34] Imaging should be of the best quality and performed by an experienced operator, with guidance and interpretation overseen by the cardiology team in the context of the individual clinical case.

TIMING OF SURGERY

Almost half of patients with IE need surgical treatment due to complications.[5,8,35] The three main indications for surgery are heart failure, uncontrolled infection, and prevention of embolic events (Table 2). It is not clear, however, when surgery should be performed, and this remains a hotly contended topic. The benefits of early surgery may also depend on the point at which it is measured, as there is an initial increase in mortality due to the operation itself before the longer term advantages become apparent. A recent meta-analysis by Chatterjee et al.[36] included 10 studies totalling 3,758 patients who had early surgery compared to conventional medical treatment and showed significantly less long-term all-cause mortality in the early surgical cohort compared to conventional treatment (OR 0.53, 95% CI 0.37-0.75, p=0.0004). However, the studies were heterogeneous - with the definition of early surgery ranging from within 48 hours to up to 60 days - included both native valve and prosthetic valve infection, and excluded the large recent cohort study from ICE-PCS.[37] In order to provide a more accurate overview of the role of early surgery we have separated native from prosthetic valve IE (PVE).

Native valve IE remains the most common presentation, accounting for two-thirds of all IE admissions.[8] Most of the observational studies, to date, favour early surgery (Figure 1). This is supported by a randomised controlled trial (RCT) from Kang et al.[38] where patients with native valve endocarditis were randomised to either surgery within 48 hours of admission (37 patients) or to conventional medical treatment (39 patients). The study demonstrated a significant reduction in the primary end-point of in-hospital death and new embolic events in patients who underwent early surgery (3%) compared to conventional treatment (23%). This important difference persisted at 6-month follow-up. Furthermore, in a recent observational study of 212 patients (73 had surgery within 2 weeks and 139 had medical therapy), survival at a median of 5.5-years follow-up was significantly higher in the early surgery group when

compared to medical therapy (94% versus 82%) with reduced cardiac events (12% versus 32%).[39] Altogether, these data suggest that early surgery is beneficial for patients with native valve IE; whether surgery should be performed within 48 hours of admission as suggested by Kang et al.[38] or later is still under debate. It is also important to note that in the study by Kang et al.[38] all patients undergoing early surgery had severe valvular disease, so results may not apply to other groups (such as those with embolic disease only). The organisms in their cohort were also not typical of those seen at other centres and the timing of embolic events not clear.

PVE accounts for 21% of all IE and is associated with significantly greater mortality.[8] Given the greater and more severe complications of PVE, one could reasonably suspect that early surgery would be beneficial in these patients. Evidence for the role of early surgery in PVE is sadly limited to

three observational studies (Figure 2). The largest study (1,025 patients: 490 early surgery [median 8 days], 535 medical therapy alone), ICE-PCS, showed significantly lower mortality in patients treated with early surgery compared to medical therapy but only in the highest risk quintile. In the overall cohort there was no survival benefit associated with early surgery, either in-hospital (HR 0.9, 95% CI 0.76-1.07) or at 1-year follow-up (HR 1.04, 95% CI 0.89-1.23). The two smaller studies showed similar findings (Figure 2). The apparent difference for early surgery in native and PVE is difficult to explain, but the greater complexity and frequency of complications associated with PVE surgery may be contributory. In addition, organisms vary between endocarditis contracted soon after valve implantation compared to those contracted later. The presence of local and distant complications as well as the level of co-morbidities also adds to the risk of undertaking surgery.

Table 2: Indications and timings of surgery in left-sided native valve infective endocarditis (IE).

Recommendations: Indications for surgery	Timing	Class	Level
A. HEART FAILURE (HF)			
Aortic or mitral IE with severe acute regurgitation or valve obstruction causing refractory pulmonary oedema or cardiogenic shock.	Emergency	I	B
Aortic or mitral IE with fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema or cardiogenic shock.	Emergency	I	B
Aortic or mitral IE with severe acute regurgitation and persisting HF or echocardiographic signs of poor haemodynamic tolerance (early mitral closure or pulmonary hypertension).	Urgent	I	B
Aortic or mitral IE with severe acute regurgitation and no HF.	Elective	IIa	B
B. UNCONTROLLED INFECTION			
Locally uncontrolled infection.	Urgent	I	B
Persisting fever and positive blood culture >7-10 days.	Urgent	I	B
Infection caused by fungi or multiresistant organisms.	Urgent/elective	I	B
C. PREVENTION OF EMBOLISM			
Aortic or mitral IE with large vegetations (>10mm) following one or more embolic episodes, despite appropriate antibiotic treatment.	Urgent	I	B
Aortic or mitral IE with large vegetations (10mm) and other predictors of complicated course (HF, persistent infection, abscess).	Urgent	I	C
Isolated very large vegetations (>15mm)	Urgent	IIb	C

Modified from Habib G et al.[44]
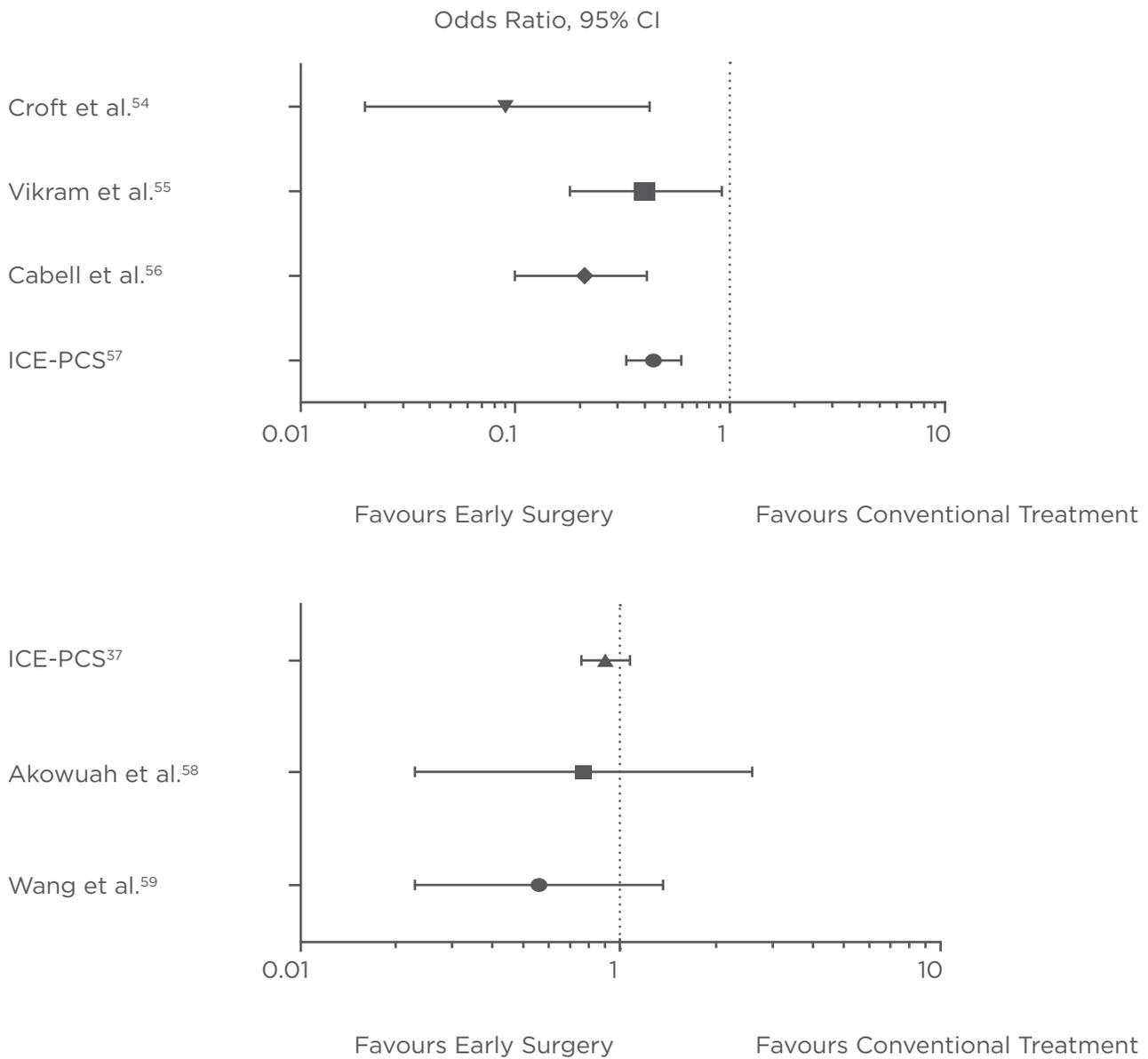
Figure 2: All-cause mortality odds ratio with 95% confidence interval (CI) for A) patients with native valve infective endocarditis (IE) comparing early surgery versus conventional therapy;[54-57] B) patients with prosthetic valve infective IE comparing early surgery versus conventional therapy.[37,58,59]

Future RCTs are needed before we conclusively know the benefit of early surgery in PVE.

CARDIAC DEVICE-RELATED ENDOCARDITIS (CDE)

CDE is a serious complication of bacteraemia in patients with permanent pacemakers or implantable cardioverter defibrillators (ICDs), and is associated with high mortality.[40] The number of implantable devices continues to increase substantially with the advent of primary prevention indications for ICDs and the expanding indications for implantation of cardiac resynchronisation

devices as a treatment for heart failure. With infection rates of 1.9 per 1,000 device years, CDE now accounts for 7% of all IE and this is expected to rise substantially further.[41] In a recent study 177 patients from a cohort of 2,760 patients with IE were diagnosed with CDE with in-hospital mortality of 14.7% and 24% at 1 year.[42] This was similar to a previous study from Michigan, which found mortality of 18% in patients with CDE.[43] The diagnosis of CDE is made using a combination of clinical symptoms, echocardiography, and blood cultures. Once diagnosed, the current guidelines recommend prolonged antibiotic treatment and total device extraction.[44] This can be distinguished

from generator/pocket infections, although in most cases infection here also involves the leads and so device extraction is routinely carried out.[45] Superficial skin wound infection is often treated with antibiotics alone, but with a low threshold for pocket exploration/extraction if the infection does not resolve.

The evidence for treatment of CDE is mostly extrapolated from cardiac device infection studies, and for CDE there are only two recently published studies that report the mortality of device extraction and antibiotic treatment compared to antibiotic treatment alone.[40,43] These studies confirmed the guideline recommendations, demonstrating reduced mortality (HR 0.44, 95% CI 0.2-0.96;[46] HR 0.42, 95% CI 0.22-0.8240) in patients treated with device extraction and antibiotics compared to antibiotic therapy alone. A further study from Spain that examined 33 patients with CDE showed that failure to undertake device extraction was significantly correlated with treatment failure (p<0.0001).[47] Current ESC guidelines recommend that for vegetations of <25 mm in diameter, especially when there is no destruction of the tricuspid valve, transvenous lead extraction can be attempted without need for thoracotomy. A recent observational single centre study incorporating 1,838 lead extractions over a 16-year period suggested that 21% of patients had lead associated vegetations detected on TOE.[48] All leads were removed percutaneously despite some vegetations being as large as 40 mm (mean diameter 16 mm). Only two vegetations embolised and these were both >20 mm.

Transvenous lead extraction still carries a significant risk, with major life-threatening complications occurring in up to 3.5% of patients and operative mortality in up to 0.8%.[49] The 30-day mortality in patients with lead associated vegetations has been reported as being as high as 10%.[48] Extraction should therefore be carried out in a specialist centre by experienced operators, with appropriate monitoring and cardiothoracic surgical support within the facility. The European Heart Rhythm Association (EHRA) has recently produced guidelines on training and accreditation for this procedure.[49]

Other areas of uncertainty in the management of these difficult cases relate to the duration of antibiotic treatment length and the timing of new device re-implantation. 6 weeks of anti-microbial treatment have been suggested by several previous studies,[42,50,51] but a 4-week duration has been advocated recently.[52] The current guidelines from the AHA and ESC suggest 4-6 weeks depending on patient characteristics and clinical response to treatment.[44,53] The question of when to re-implant the new device is based on expert opinion: current advice is to wait for 14 days after the first negative blood culture.[52] It is important to remember that the original indications for device implantation may no longer be relevant and re-implantation may therefore not be required. However, for those patients who require a device, the new system is usually inserted via the contralateral side. With the continual increase in cardiac device implantation, it is important that further studies and databases are established to evaluate approaches to treatment. The prospective European Lead Extraction ConTRolled (ELECTRa) Registry involves 100 centres in 25 countries, and aims to evaluate the short and long-term safety of transvenous lead extraction and provide a mechanism for verification and potential adjustment of standards for lead extraction procedures.

CONCLUSION

IE remains a deadly disease with high mortality and many areas of its management remain controversial. New methods and treatments are emerging, which aim to accelerate diagnosis, reduce delays, optimise treatment, and improve multi-disciplinary specialist involvement. Delay in diagnosis and involvement of specialist centres is still a leading cause of morbidity. Moreover, it is notable that not 1 in over 80 recommendations within the latest ESC guidelines is backed by data that are level of evidence A (i.e. from multiple randomised clinical trials). Whilst it is clearly unethical to perform trials in this area of medicine against placebo, treatment algorithms and approaches to management can readily be compared with each other in a randomised way, and data using this approach are emerging. It would be particularly useful to initiate studies in areas such as: the use of new molecular techniques for microbiological diagnosis; the choice and duration of antibiotic therapy; identifying appropriate groups for outpatient intravenous antibiotic therapy; imaging and treatment of IE in complex congenital heart disease; and the timing of surgery in prosthetic valve endocarditis and following cerebral events. Increasing the quantity and quality of the evidence base when it comes to IE remains a significant challenge.

Acknowledgements

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