Infective endocarditis in the adult patient

JAT Sandoe

RW Watkin

TSJ Elliott

MJ Dayer

Abstract

Infective endocarditis (IE) is an uncommon disease with a high morbidity and mortality. The basic pathology involves adherence of microorganisms to areas of endothelial damage or associated implanted medical devices, such as prosthetic valves or pacemakers, resulting in localized infection and formation of vegetations. Complications include sepsis, valvular failure and embolization. Staphylococci and streptococci are the predominant causes of IE. Blood cultures and echocardiography are key diagnostic tests, but a diagnosis of IE can still be difficult to establish. Serological tests, particularly for fastidious microorganisms, can assist when blood cultures are negative. The Duke criteria can aid diagnosis but lack sensitivity, particularly when blood cultures are negative or transthoracic echocardiography images are non-diagnostic. Antibiotics are the mainstay of treatment, but surgical debridement and valvular surgery are frequently required. Recent changes in antibiotic prophylaxis for those considered to be at risk of IE have reduced the number of patients given antimicrobials by dental practitioners. This article summarizes how to diagnose IE and outlines current antibiotic treatment regimens.

Keywords Antibiotics; cardiac; endocarditis; infection; MRCP; prophylaxis; treatment

Key points

- Infective endocarditis remains a disease with a high morbidity and mortality
- The role of antibiotic prophylaxis continues to be debated
- New investigations, such as positron emission tomography/computed tomography (PET/CT) and cardiac CT, have been incorporated into diagnostic guidelines, but blood cultures, taken correctly, remain the most important diagnostic test
- Empirical antibiotic therapy should be avoided if possible until blood cultures have been taken or (ideally) a microorganism identified
- Multidisciplinary teams, including cardiologists, infection specialists and cardiothoracic surgeons, are key to good management of cases
- The role of surgery continues to be refined, and surgery is recommended earlier in the course of the disease than previously

JAT Sandoe ***FRCPath PhD*** *is a Consultant Microbiologist at Leeds Teaching Hospitals NHS Trust, UK. Competing interests: JATS is Chair of the British Society for Antimicrobial Chemotherapy Endocarditis Working Party, has received research funding, honoraria and/or travel sponsorship from Pfizer, Merck Sharp and Dohme, Abbott, Novartis and Astellas.*

RW Watkin ***MD MRCP*** *is a Consultant Cardiologist at the Heart of England NHS Trust, Birmingham, UK. Competing interests: RWW is a Member of the British Society for Antimicrobial Chemotherapy Endocarditis Working Party, and advisor for Medtronic, Abbott Vascular and Cordis, has received education grants from Boston Scientific, Abbott Vascular, Cordis and Astra Zeneca and is PI for commercial studies sponsored by Daiichi Sankyo, Roche, Novartis and OrbusNeich.*

TSJ Elliott ***MRCP FRCPath PhD DSc*** *is a Consultant Microbiologist at University Hospital Birmingham, NHS Foundation Trust, UK. Competing interests: TSJE is a Past Member of the British Society for Antimicrobial Chemotherapy Endocarditis Working Party, British Gastroenterology Working Party on antibiotic prophylaxis and International Collaborative Group on Endocarditis, and a Past Member of the BNF Formulary Committee. TSJE has received research funding, honoraria and travel sponsorship from Becton Dickenson, CareFusion, Copper Development Association and 3M.*

MJ Dayer ***PhD FRCP*** *is a Consultant Cardiologist at Taunton and Somerset NHS Trust, UK. He is a Consultant Cardiologist at Musgrove Park Hospital, Taunton, UK, and has a long-standing interest in infective endocarditis. He has published a number of articles on the subject and spoken on the subject at national and international meetings. He was a non-voting member for the most recent revision of the NICE guidelines. Competing interests: in the past 5 years, he has received fees for speaking from Pfizer, Bristol-Myers Squibb, Boehringer-Ingelheim, Roche and Biotronik. He has attended advisory boards for Bayer, Daiichi-Sankyo, St Jude and ResMed, and received educational support from Bayer and Biotronik.*

Infective endocarditis (IE) is an uncommon condition with a recently reported incidence of 7.7 cases per 100,000 population per year in the USA. There is uncertainty over whether the incidence is increasing, some population-based analyses reporting a stable or falling incidence but others an increase. IE remains a serious problem with an in-hospital mortality of 20%. Infection can involve any part of the endocardium; native heart valves are most often affected, but implanted medical devices such as prosthetic heart valves, intravascular conduits and implantable cardiac electronic devices are increasingly involved.

The pathological hallmark of IE is a 'vegetation', composed of microorganisms, usually of one species, enmeshed in fibrin, platelets and other host-derived products. Vegetations usually form on heart valves, and infection can spread to adjacent structures. Vegetations are more common on the left side of the heart and on the free margins of incompetent valves, especially the atrial side in mitral regurgitation and the ventricular side in aortic regurgitation. Right-sided IE involving the tricuspid and pulmonary valves occurs more commonly in patients who are intravenous drug users, or

Please cite this article in press as: Sandoe JAT, et al., Infective endocarditis in the adult patient, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.08.004

have pacemakers or long-term indwelling vascular access devices, such as haemodialysis patients.

A clinical diagnosis of IE can be difficult to establish because of the non-specific symptoms or presentation with extracardiac complications. The modified Duke criteria, recently extended by the European Society of Cardiology (ESC),[1] provide a probabilistic approach to the diagnosis and an objective means of appraising clinical evidence to support a diagnosis, which still remains challenging. The criteria are, however, limited when blood cultures are negative or transthoracic echocardiography (TTE) is inconclusive.

Peripheral clinical manifestations of IE, such as Janeway lesions (haemorrhagic macular plaques, most often seen on the palms and soles), Osler's nodes and splinter haemorrhages, are less common than previously reported, occurring in <10% of cases.[2] Gram-positive bacteria, in particular streptococci and staphylococci, are the predominant causative microorganisms. Recent international registry data have suggested that staphylococci are now the leading cause of IE, accounting for 31% of all cases.[2]

Pathogenesis and prevention of infective endocarditis

To appreciate the rationale for measures aimed at preventing IE, it is necessary to understand its pathogenesis.

Approximately 50% of patients with a diagnosis of IE have an underlying cardiac predisposition.[2] Based on animal model work on native heart valve infection, it is thought that abnormal intracardiac blood flow resulting from structural heart disease or the presence of an intracardiac device causes endothelial damage and microthrombus formation. In the presence of bacteraemia or fungaemia, these microthrombi can become colonized with microorganisms, and vegetations can subsequently form. The vegetation enlarges because of recurrent fibrin deposition and microbial multiplication. IE related to an indwelling device or prosthetic valve can result from microbial contamination at the time of implantation as well as seeding via the bloodstream (in the same manner as native valve infection).

Many invasive medical and non-medical procedures, such as tooth extraction, urinary tract catheterization or body piercing, have the potential to cause the transient presence of microorganisms in the bloodstream that can subsequently seed a damaged endocardium. Historically, prophylactic antibiotics were given to patients at risk of IE undergoing procedures such as dental operations, which are associated with possible bacteraemia. There are multiple case reports of IE occurring after dental operations such as extractions, and it is well recognized that oral pathogens can cause IE and antibiotics can prevent IE in animal models. Consequently, over the last 50 years or so, antibiotic prophylaxis has been recommended by expert groups from around the world for many groups of patients at risk of IE undergoing dental procedures. Antibiotic prophylaxis has also been recommended for non-dental invasive procedures, especially involving the gastrointestinal, genitourinary or respiratory tract. In Europe and the USA, it is still recommended that antibiotic prophylaxis is given for dental and some other procedures in patients perceived to be at high risk of complications from IE, for example with prosthetic valves, complex congenital heart disease or a history of IE.

However, it is now considered that bacteraemias resulting from daily activities are so frequent that they are more likely than an isolated procedure to be the cause of IE, although this does not exclude the possibility that procedures can cause a small proportion of cases. In the UK, the National Institute for Health and Care Excellence Clinical Guideline no. 64 on the prevention of IE recommended in 2008 that antibiotic prophylaxis should not be given to at-risk patients undergoing dental and non-dental procedures. The recommendation was slightly modified in 2016, stating that antibiotic prophylaxis should not be given routinely to at-risk patients, following a report of an increase in rates of IE above the baseline trend. The discrepancy in advice that exists worldwide reflects the fact that there has never been a randomized controlled clinical trial to settle the question of whether antibiotic prophylaxis is truly effective.

Healthcare-associated IE now comprises approximately 25% of all episodes.[2] This substantial group of potentially preventable infections should be a prime target for preventive measures. The emergence of these infections probably relates to an increasing prevalence of patients with either a cardiac device *in situ* or an indwelling vascular access device, for example haemodialysis or cancer patients, which increases the risk of bacteraemia and IE.

Traditional views about preventing IE through antimicrobial prophylaxis for dental procedures and invasive procedures are changing, as outlined above. Emphasis on prevention of IE has shifted towards a need for improved dental health in patients at risk of developing IE.[3] However, it should also probably include more attention to infection prevention practices. These include optimal antimicrobial prophylaxis when inserting cardiac devices and the use of enhanced aseptic procedures during the insertion and subsequent care of vascular access devices.

Establishing a diagnosis of infective endocarditis

The Duke criteria are used to aid in the diagnosis of IE (Table 1). They have recently been modified by the ESC to take account of new imaging techniques.[1] The clinical diagnosis of IE continues to be difficult to establish because the symptoms are often non-specific or non-cardiac. The most common presenting symptoms are loss of appetite, night sweats and fatigue. There should be a low threshold for considering IE in patients with any of the following sets of clinical findings:

- febrile illness and a new cardiac murmur of valvular regurgitation
- febrile illness, a pre-existing at-risk cardiac lesion and no clinically obvious site of infection
- febrile illness associated with any of the following vascular or immunological phenomena: embolic event, stroke, splinter haemorrhages, Janeway lesions, Roth's spots, Osler's nodes or peripheral abscesses of unknown cause
- prolonged history of sweats, weight loss, anorexia or malaise.

Blood cultures are a key means of establishing a diagnosis of IE. Multiple positive blood cultures remain the most important diagnostic indicator and are a major Duke criterion.[4] The subsequent choice and duration of antimicrobial treatment are based on several factors, including the causative microorganism and its susceptibility to antimicrobial agents.

Please cite this article in press as: Sandoe JAT, et al., Infective endocarditis in the adult patient, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.08.004