Infective endocarditis: changing aetiology of disease

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ABSTRACT

Infective endocarditis (IE) is an evolving disease resulting in high morbidity and mortality. Despite medical and diagnostic advances, the incidence of the disease has remained unchanged, reflecting the changing epidemiological and microbiological profile of IE. Classical risk factors such as rheumatic heart disease have now been overtaken by new risk factors including an ageing population, degenerative valve disease and intravenous drug use. The routine use of invasive procedures, implantable cardiac devices and prosthetic heart valves has served to increase the number of at-risk patients. The microbiology of IE mirrors the changing risk factors, with staphylococcal infections predominating over viridans streptococci. An overview of this rare disease is given describing current understanding, investigation and changing epidemiology and microbiology of IE.

KEY WORDS: Heart disease.
Infective endocarditis.
Risk factors.

Introduction

Endocarditis is a rare condition that causes inflammation of the endocardium, and usually involves the heart valves (native or prosthetic). The disease is caused by infection with microorganisms, usually bacteria, and is termed infective endocarditis (IE).[1] The condition is lethal if not treated promptly with either antibiotics or surgery, or a combination thereof.[2]

Infective endocarditis can develop in many ways, having several clinical presentations as first described by William Osler in 1885. However, four fundamental pathophysiological elements remain constant: continuous bacteraemia with the invading microorganism(s), predisposing factors, endomyocardial involvement, and vascular phenomena.[3]

The study of IE was once difficult due to the rarity of the disease and absence of a precise case definition.[2] Over the past 30 years, however, our understanding of the epidemiology of the disease, investigation and management of IE has changed radically.[4] The introduction of the modified Duke criteria[5] for diagnosis, together with modern diagnostic techniques, non-invasive imaging, molecular diagnostic methods, potential curative surgery and antimicrobial therapy have aided disease management.[4] However, despite improvements in healthcare, the incidence of disease has remained unchanged over the past two decades.[6]

The lack of impact of modern medicine reflects a change in the aetiology of IE,[4] perhaps as a consequence of social transformation in Western populations.[3] Changes include an ageing population, the increasing role of degenerative valve disease in the elderly, the virtual disappearance of rheumatic heart disease (once a common cause of IE), intravenous drug misuse, longer hospital stays and increasing use of invasive therapies.[3]

These transformations have also been mirrored by a change in the microbiology of the disease. Increasing staphylococcal infections and those caused by fastidious organisms have overtaken viridans streptococci as the predominant cause of infection.[6] Furthermore, previously undetected pathogens are now being identified by molecular techniques such as the polymerase chain reaction (PCR). In addition, multidrug-resistant bacteria are becoming a challenge to conventional treatment regimens.[4]

This review aims to describe current understanding, investigations and changing trends associated with IE, with particular focus on the changing epidemiology and microbiology of the disease.

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Epidemiology

Overall incidence of IE is approximately 1.7–6.2/100,000 patient years in the USA and Europe[6] and may be increasing,[7] particularly in at-risk cohorts such as intravenous drug users (IVDU).[4] Infective endocarditis is an evolving disease and this is reflected in the changing risk factors associated with the disease.[8]

Classical risk factors include rheumatic heart disease in the young following group A streptococcal infection; however, advances in medicine have significantly reduced the incidence of rheumatic disease, which is no longer seen in developed countries.[9] However, it remains a major risk in developing countries that are not medically privileged.[4]

Ironically, medical progress has resulted in the emergence of new risk factors associated with IE. Underlying degenerative aortic valve and mitral valve disease now predominate over rheumatic disease.[9] Furthermore, the

availability of indwelling intravascular or implantable cardiac devices (e.g., pacemakers, implantable cardioverter defibrillators [ICD]) and prosthetic heart valves have increased the number of patients at risk from IE.[9]

Gender and age have an effect on the incidence of IE, with males more often affected than females in a ratio of 2:1.[10] Owing to medical intervention, longevity has been increased and given rise to increased incidence of degenerative valve disease, becoming the most common risk for developing IE.[1] The incidence of the disease increases with age.[10]

Infective endocarditis has been divided into four categories: native valve endocarditis (NVE), prosthetic valve endocarditis (PVE), IE in IVDU, and healthcare-associated IE.[10] The categories describe both the clinical condition and causative microorganisms.[2]

Native valve endocarditis, traditionally termed subacute endocarditis (long incubation) and acute endocarditis (short incubation) describes both the rate of progression and severity of disease. Owing to the low incidence of rheumatic heart disease, the incidence of subacute endocarditis has decreased while acute endocarditis has increased in incidence.[10] Almost all cases of IE seen locally (in Merseyside) are acute cases, with most patients having normal valves and no previous diagnosis of heart disease (Dr Rittoo, consultant cardiologist, Wirral University Teaching Hospitals, personal communication).

Prosthetic valve endocarditis is classified into early or late, depending on when infection occurs.[10] Early PVE occurs within two months of surgery, while late PVE occurs more than two months after surgery.[10] This accounts for 0.1–2.3% of IE cases. The type of valve, mechanical or bioprosthesis, appears equally susceptible to infection.[6]

Infective endocarditis in IVDU affects individuals of a younger age (median: 30–40 years) and is increasing in incidence due to increasing drug misuse.[2] The tricuspid valve is involved in 50% of cases with mixed right sided and left sided IE. Infecting organisms tend to originate from the skin where drug injection takes place.[2] The majority of people in this category have no known pre-existing cardiac disease.[6]

Healthcare-associated IE is rapidly increasing in incidence and is a major problem because mortality within this category is more than 50%.[6] Medical advances have led to its increased incidence.[2] A major at-risk subgroup of this category is haemodialysis patients, with IE being second only to cardiovascular disease as the leading cause of death in this group.[11] Episodes of bacteraemia are frequently encountered in these patients as a result of indwelling vascular catheters, and infection is usually from the patients' own cutaneous flora.[11] The patients in this subgroup are two to three times more likely to develop IE than the general population.[2]

It is apparent that the epidemiology and associated risk factors for IE are changing. In a study conducted in 2007, 203 IE episodes were examined.[7] The findings included increasing number of IE episodes in older patients, increase in PVE and healthcare-associated IE, with reduced incidence of subacute and increased incidence of acute endocarditis. Other studies show similar findings.[2]

In addition, the microbiological profile of IE has changed, with staphylococcal infections predominating over viridans streptococci.[12]

Microbiology

The microbiology of IE depends on the source of infection, whether the disease affects the native valve or prosthetic valve, and whether it is hospital-acquired or community-acquired.[10] Gram-positive bacteria are most frequently identified as the causal agents of IE, due to their greater propensity to adhere to the heart valves.[2] *Staphylococcus aureus, Streptococcus* spp. and *Enterococcus* spp. account for more than 80% of all cases of the disease.[2,10]

Staphylococcus aureus has emerged as the most common cause of IE, overtaking viridans streptococci,[10] and this has been the finding in several studies.[35,36] In 2006 a retrospective study of 326 episodes of IE treated during 1980–2004 in Finland, observed that IE due to *S. aureus* was predominating over viridans streptococci.[36] Studies conducted in France[35] and Argentina[37] also observed such findings together with an increase in coagulase-negative staphylococci (CNS) IE. Possible reason for this trend maybe an increase in cutaneous port of entry as a result of increasing invasive medical procedures[10] and intravascular lines.[25]

S. aureus is the most common cause of all forms of IE, with a mortality rate of 40–50%, and many of the isolates are methicillin-resistant.[25] Acquisition of methicillin-resistant *S. aureus* (MRSA) due to classic risk factors such as hospitalisation, surgery or recent antimicrobial therapy is termed hospital-associated-MRSA (HA-MRSA).[38] However, over the past decade, acquisition of MRSA not associated with classic risk factors has been reported among young, previously healthy individuals in the community, and this is termed community-associated-MRSA (CA-MRSA).[38] Both strains differ in their genetic background, pathogenicity and epidemiology,[39] with CA-MRSA producing virulence factors such as Panton-Valentine leucocidin (PVL),[40] which can result in septic shock in severe infections.[39] Infective endocarditis due to involvement of CA-MRSA has been described and is particularly associated with the IV drug user population.[39]

A group of Gram-negative bacteria known collectively as the HACEK group (*Haemophilus* sp., *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens* and *Kingella kingae*), and also *Bartonella* spp., *Coxiella burnetii, Legionella pneumophila* and *Tropheryma whipplei* are an important subgroup associated with culture-negative IE.[15] These fastidious organisms account for 1–4% of IE cases,[10] and a reason for their emergence may be improved molecular techniques such as PCR, with subsequent sequencing to detect or identify bacteria from patients with IE, improving aetiological diagnosis.[41]

Coagulase-negative staphylococci such as *Staphylococcus epidermidis* and *S. lugdenensis*[42] are most commonly isolated from cases of early PVE[6] as a result of valve implantation[2] or following cardiac catheterisation.[42] This is followed by infection with *S. aureus* and *Enterococcus* spp.[10] Late PVE, on the other hand, is largely community-acquired and mirrors NVE in its microbial aetiology (e.g., *S. aureus* and the HACEK group).[2]

Healthcare-associated IE is emerging as the most common form of *S. aureus* IE,[43] and in haemodialysis patients *S. aureus* accounts for more than 50% of all cases.[10] This emerging trend is due to the increase in medical procedures and implantable devices such as pacemakers and defibrillators, with an *S. aureus*:CNS ratio of 3:1.[10]

Furthermore, implantable devices bring the added risk of IE due to non-HACEK Gram-negative bacteria such as *Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella* species, once considered to cause IE almost exclusively in IVDU.[44] The mortality rates with non-HACEK Gram-negative endocarditis are high, with a combination of antibiotics and surgery failing to improve the outcome for the patient.[44]

Enterococcus spp. are the third most common cause of IE,[25] with *E. faecalis* and *E. faecium* most commonly isolated.[19] *Enterococcus* spp. account for 5–18% of IE cases, and the incidence appears to be increasing[8] in association with procedure-related IE such as urogenital and gastrointestinal procedures.[10]

Incidence of IE is markedly higher in IVDU than in the general population and the changing microbiological epidemiology of IE, with *S. aureus* surpassing viridans streptococci, has also been noted among this cohort.[45]

The causative organisms among IVDU usually originate from the skin, which explains the predominance of *S. aureus*.[2] In addition to this, pathogens such as *P. aeruginosa* and fungi (e.g., *Candida* and *Aspergillus* spp.) are also frequently isolated.[10,19]

Cases of IE due to more than one pathogen (polymicrobial) are relatively uncommon among the other categories of IE (e.g., NVE, PVE and healthcare-associated endocarditis). It is, however, most frequently associated with IVDU and it may even be increasing in incidence due to an increase in IVDU.[8]

Among IVDU with human immunodeficiency virus (HIV) infection, the risk of IE is most common in those with a low CD4 count (<500 cells/μL) and mortality increases significantly.[15] In cases such as this, unusual pathogens are sometimes isolated (e.g., *Bartonella* and *Salmonella*).[10]

Pathogenesis

Direct contact between blood and subendothelial components as a result of haemodynamic or mechanical stress produces a small clot or sterile thrombotic vegetation.[1,4] These vegetations are considered to be the initiating lesions in the development of IE,[1] as they promote bacterial adherence to the damaged endothelium during transient bacteraemia.[6] Normally the intact endothelium resists colonisation by microorganisms, reflecting the rarity of endocarditis.[1]

Microorganisms gain entry to the circulation due to trauma (e.g., trauma to the oral mucosa, genitourinary or gastrointestinal tract).[1] Conversion of thrombotic, non-bacterial endocarditis to IE takes place through bacterial persistence and growth within the cardiac lesion.[1]

The formed lesion on the damaged endothelium consists of large quantities of fibrinogen, fibrin, fibronectin, plasma protein and platelet proteins.[2] Such host factors have been shown to be important in bacterial adhesion in addition to bacterial factors.[1]

Gram-positive bacteria adhere to the lesion more avidly than do Gram-negative bacteria. This explains the predominance of Gram-positive organisms as the aetiological agents of IE.[1]

Adherent bacteria attract and activate monocytes to produce cytokines and tissue factors in a continuous cycle, resulting in the progressive enlargement of the vegetative lesion.[4] In response to local inflammation, endothelial cells express β1 integrins. These transmembrane proteins bind fibronectin to the endothelial surface. *Staphylococcus aureus* carries fibronectin binding proteins on its surface, binding to fibronectin on the endothelium and providing an adhesive surface for subsequent circulating staphylococci to attach.[2]

Resultant local extension and tissue damage can often lead to complications,[6] most frequently congestive heart failure due to acute or semi-acute valvular insufficiency.[8] The second most frequently encountered complication is embolisation which may result in stroke. Emboli can also invade other systemic organs including the liver, spleen and kidney. Abscess formation arises due to extension of the infection outside the valve, which often requires surgical intervention.[8]

Clinical presentation

Infective endocarditis can often be a difficult condition to diagnose due to the presentation of fairly non-specific symptoms,[13] including fever and cardiac and non-cardiac manifestations.[14] The severity of symptoms depends on the infecting organism and tends to be more severe in individuals with pre-existing heart conditions.[2]

Fever is the most common symptom presenting in up to 90% of cases.[13,15,16] Systemic symptoms such as anorexia, weight loss, malaise and night sweats may also accompany fever.[14] Cardiac manifestations including new or changing heart murmur can be found and in one study this was the case in 82% of patients.[13]

Classical signs of IE (e.g., Osler's nodes [painful subcutaneous lesions in distal fingers] and Janeway lesions [painless haemorrhagic cutaneous lesions on palms and soles]) may still be seen in the developing world where presentation is often delayed.[4] However, peripheral stigmata associated with IE are increasingly uncommon elsewhere because patients generally present earlier in the disease course.[15] Similarly, two studies reported that only a small proportion of patients presented with these symptoms, providing evidence that they are an uncommon finding in developed countries.[13,16]

Vasculitic phenomena include splinter haemorrhage, Roth spots and glomerulonephritis.[15] In 30% of patients. emboli to the brain, lung or spleen are often the presenting feature.[4]

In the elderly and immunocompromised, atypical presentation is common with patients often presenting without fever.[15] This group of patients can be difficult to diagnose due to prior use of antibiotics, resulting in negative blood cultures. Therefore, a high index of suspicion and low threshold for specialist investigations are essential in these patients and other high-risk groups.[4] Manifestations in childhood may also differ.[17,18]

Diagnosis

For patients presenting with classical manifestations associated with IE, such as immunological vascular phenomena, particularly the subacute form, diagnosis is fairly straightforward. In developed countries, however, most cases of IE are acute, with disease evolving too quickly for classical symptoms to develop.[19]

Variation in clinical presentation of IE requires an approach to diagnosis that is both sensitive for disease detection and specific to exclude the disease.[19] Current diagnosis has evolved from the von Reyn[20] and modified Duke criteria[5] to utilise a multifaceted approach involving clinical suspicion, microbiological, biochemical and echocardiographic information.[15,17,21–23] Non-specific laboratory findings such as anaemia, leucocytosis, raised C-reactive protein and increased procalcitonin levels (a marker of systemic bacterial infection) act as valuable additional diagnostic markers.[15] Diagnosis of IE centres on two tests, namely blood culture and echocardiography.[14]

Blood culture

Blood culture (BC) is vital to the diagnosis of IE. Positive culture enables isolation of the causative organism and permits susceptibility testing.[15] Current guidelines suggest three sets of BC be taken one hour apart before administration of antibiotics,[4] and in more than 90% of cases the first two sets are positive.[15] The BC set consists of one aerobic and one anaerobic bottle.[24] Anaerobic bacteria are an uncommon but important cause of IE, accounting for 2–16% of all cases, with organisms such as *Bacteroides fragilis*.[25]

Negative BC accounts for 2.5–31% of all IE cases,[15] delaying diagnosis, treatment and resulting in potentially adverse clinical outcome.[4] The most frequent cause of negative BC is previous antimicrobial treatment.[24] Another increasingly common cause is infection with intracellular or fastidious pathogens including *Coxiella burnetii, Legionella* spp., *Brucella* spp. (associated with fatal cases of IE – a risk to laboratory personnel), *Bartonella* spp., the HACEK group and fungi such as *Candida* and *Histoplasma*.[24,26,27] Investigations that may be carried out for rare causes of culture-negative endocarditis include PCR, serology and immunohistology.[15]

In the event of such a situation, BC were once given an extended incubation period of up to 10 days,[15] although there is now evidence to suggest that prolonged incubation is unnecessary and even increases the likelihood of contamination.[27] Alternative methods such as serology and PCR are now preferred for the detection of difficult-to-culture organisms.[24,26,28]

Echocardiography

Echocardiography is a non-invasive visualisation technique used to investigate and aid diagnosis of endocarditis. In patients with a high degree of clinical suspicion of IE, transthoracic echocardiography (TTE) is the initial technique of choice.[29] Normal TTE confirms that endocarditis is unlikely and investigations should be focused elsewhere.[4]

Transoesophageal echocardiography (TOE) is cost-effective[6] and has increased sensitivity (90–100%) and specificity over TTE, with a sensitivity of 40–63%.[29] It should be used in all cases of PVE[6] and is particularly useful in high-risk groups[4] or when TTE is negative or inconclusive.[29] In addition to this, TOE can be used to investigate complications of IE (e.g., perivalvar abscesses[29] or the mechanism of valvular regurgitation).[4]

The two forms of non-invasive imagery work in synergy, complementing one another. Transthoracic echocardiography should be used as an initial screen if the patient is suspected of having IE. If negative TTE results are obtained and suspicion remains high, TOE should then be used.[29]

Table 1. Modified Duke criteria (adapted from Beynon RP, Bahl VK, Prendergast BD. Infective endocarditis. *BMJ* 2006; **333**: 334–9).

Pathological criteria
• Positive histopathology or microbiology of pathological material obtained at autopsy or cardiac surgery (e.g., valve tissue, vegetations, embolic fragments, or intracardiac abscess content)
Major criteria
• Two positive blood cultures showing typical organisms consistent with infective endocarditis (e.g., *Streptococcus viridans* and the HACEK group)
OR
• Persistent bacteraemia from two blood cultures taken >12 h apart or three or more positive blood cultures where the pathogen is less specific (e.g., *Staphylococcus aureus* and *S. epidermidis)*
OR
• Positive serology for *Coxiella burnetii*, *Bartonella species* or *Chlamydia psittaci*
OR
• Positive molecular assays for specific gene targets
• Positive echocardiogram showing oscillating structures, abscess formation, new valvular regurgitation or dehiscence of prosthetic valves
Minor criteria
• Predisposing heart disease
• Fever >38°C
• Immunological phenomena such as glomerulonephritis, Osler's nodes, Roth spots, or a positive rheumatoid factor
• Microbiological evidence not fitting major criteria
• Elevated C-reactive protein or erythrocyte sedimentation rate
• Vascular phenomena such as major emboli, splenomegaly, clubbing, splinter haemorrhages, petechiae or purpura
Definite infective endocarditis
• Pathological criteria present
OR
• Two major criteria
OR
• One major and two minor criteria
OR
• Five minor criteria

Diagnostic criteria

The original von Reyn diagnostic criteria for IE were based on clinical, pathological and microbiological findings.[20] The criteria have now been surpassed by the Duke criteria to incorporate the increasing role of imaging technology such as echocardiography.[5,30] Several studies have been conducted to evaluate Duke criteria and found it more sensitive than von Reyn criteria.[21,31] However, limitations do exist, particularly when BC are negative, reducing the sensitivity of Duke criteria.[17] It is also of lower value in groups with PVE, pacemakers or with IE affecting the right heart.[30]

In 1997, Lamas and Eykyn[32] proposed a number of modifications to the Duke criteria (the 'St Thomas' modifications) in response to the deficiencies mentioned

above. Further modifications have since been made to Duke criteria (Table 1) to include the role of Q fever, the increasing incidence of staphylococcal infection and widespread use of TOE.[30]

Histological and immunological techniques

Histological examination of the removed heart valve is one of the major Duke criteria for the diagnosis of definite IE.[30] Various stains are utilised (e.g., Ziehl-Neelsen and periodic acid Schiff) to identify the causative organism.[33] Furthermore, it may enable guided antimicrobial treatment to be administered.[30]

Immunological techniques have proved successful in the detection of fastidious organisms such as *Coxiella burnetii* and *Chlamydia* spp. from valvular tissue.[33] Several techniques are available including indirect immunofluorescence and enzyme-linked immunosorbent/immunofluorescent assays (ELISA/ELIFA).[33]

Electron microscopy, although time-consuming and expensive, has high sensitivity and may detect microorganisms that are undetectable by molecular or immunological methods.[33]

Molecular techniques

Molecular techniques for the detection and analysis of nucleic acid targets have been assessed for the detection and identification of pathogens in a wide variety of diseases.[22] They have become routine in developed countries and are generally used in the following circumstances: identification of the infective agent in a culture-negative situation; characterisation of the cultured agent; and determination of antibiotic resistance.[15]

The most widely used technique is PCR, in which trace amounts of nucleic acid target of microbial DNA in host tissue is amplified,[30] enabling the identification of new causative agents and the determination of genetic structures of resistant organisms.[15] Suggestions have been made to incorporate PCR into the major Duke criterion with much support; however, limitations with the technique exist. These include the risk of sample contamination and generation of false-negative results due to the presence of PCR inhibitors in the clinical sample. Results should therefore be interpreted carefully and the technique should be used in combination with other techniques (e.g., BC).[30]

Antimicrobial treatment

In order to treat this potentially devastating disease,[10] many treatment guidelines have been developed.[46,47] The most well known of these guidelines are the recommendations made by the American Heart Association,[19] giving guidance on the treatment of the most common pathogens.[4]

Treatment and successful outcome of IE rely on a multidisciplinary approach involving cardiologists, microbiologists and cardiac surgeons.[6] Isolated pathogens from BC dictate the choice and length of treatment given to the patient.[4] Long-term treatment of four to six weeks is usually required, although shortened courses (two weeks) of a combination of antibiotics have been found to be safe and efficient for patients with sensitive organisms.[6]

If BC have already been taken and it is deemed necessary to start antimicrobial therapy while awaiting culture results, then the patient should be started on empirical broad-spectrum treatment. Once the causative organism has been identified and antibiotic susceptibility testing has been performed, the patient should be switched to the appropriate antibiotic agent.[4]

A major problem challenging current therapeutic regimens is that of bacterial resistance to conventional antibiotics.[6] Bacterial resistance has emerged due to overuse of antibiotics and also treating empirically with inappropriate antibiotics. Examples of resistant organisms include MRSA, which is a problem in hospital and community environments, and multidrug-resistant enterococci and streptococci that are resistant to penicillin and other β-lactam antibiotics.[6]

Surgery

Surgery for IE is extremely important and potentially life-saving.[4] Surgery is required in approximately 50% of IE cases and decisions to operate should be made by a team including cardiologists and cardiac surgeons.[2] Indications for surgery include: refractory cardiac failure caused by valvular insufficiency;[2] persistent fever and bacteraemia despite antimicrobial treatment; abscess or fistula formation due to local spread of infection; infection with highly resistant bacteria that do not respond to treatment, or fungal IE.[6] Overall, surgical mortality in active IE is 8–16%, with actuarial survival rates of 75–76% at five years and 61% at 10 years.[2]

Prophylaxis

The prevention of IE via antibiotic prophylaxis remains a controversial topic.[6] The role and efficacy of prophylaxis has been poorly investigated, with studies limited to experimentation in animals only.[2] However, in high-risk patients (e.g., prosthetic valves, previous IE and congenital heart disease), prophylaxis is considered to be effective.[4]

Invasive procedures such as dental procedures were once thought to provoke bacteraemia and be a risk factor for acquisition of IE.[8] However, many papers suggest that this factor has been over-emphasised[4] because the bacterial load associated with dental procedures is much lower than that involved in everyday activities like tooth brushing and chewing.[2] This is reflected in the American Heart Association guidelines, in which prophylactic therapy prior to dental procedures is now not recommended.[19] However, cases of subacute endocarditis caused by viridans streptococci, classically triggered by dental extraction in patients with underlying valve lesions, continue to be recorded (Dr Rittoo, consultant cardiologist, Wirral University Teaching Hospital, personal communication), highlighting that dental procedures can and will cause endocarditis in patients with pre-existing valve lesions.[2]

Preventative measures such as good dental care and skin hygiene, together with the avoidance of unnecessary procedures,[6] are now recommended to reduce the likelihood of spontaneous bacteraemia that may result in IE.[2]

Future developments

Progression towards improved prevention and treatment of IE is made due to several developments, including vaccinations designed to target bacterial adhesins inhibiting valve colonisation,[4] and new antimicrobial agents attenuating invasive properties of virulent bacteria such as *Staphylococcus aureus*.[6] Finally, the risk of developing IE may be reduced in patients with artificial heart valves as a result of the use of modified biomaterials.[4] However, despite such developments, IE remains an evolving disease that continues to present challenges in its diagnosis and treatment.

Discussion

Infective endocarditis is a rare but lethal condition if not treated promptly and aggressively. Over the past 30 years the profile of IE has changed considerably. Medical advances have virtually eradicated classical risk factors previously associated with the disease in developed countries. However, medical progress such as increasing invasive therapies and implantable devices, together with changing social trends in Western populations (e.g., increased IVDU) has given rise to new risk factors and actually increased the number of people at risk of IE.

As a consequence of changing risk factors it is not surprising that the microbiology of the disease has also altered. Staphylococcal infections, particularly *S. aureus*, have surpassed viridans streptococci as the predominant cause of IE in developed countries, possibly due to an increase in cutaneous ports of entry. Similarly, the emergence of fastidious Gram-negative bacteria (e.g., the HACEK group) as a cause of IE has also occurred. Improved molecular techniques such as PCR may be a reason for their detection as a result of improved identification. Worryingly, non-HACEK Gram-negative bacteria (e.g., *Pseudomonas aeruginosa*) have been identified more recently as a cause of IE. These organisms result in high rates of mortality and were once associated exclusively with IE in IVDU. However, due to the increased use of implantable devices they have now been isolated from IE cases in non-IVDU.

Despite improvements in healthcare, diagnostic techniques and treatment, IE remains an evolving and challenging condition to manage. There is a substantial literature and various studies describe IE and give guidance on treatment and management of the disease.[48] □

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