Occasional articles

Changing trends in infective endocarditis

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Introduction

Infective endocarditis was formerly known as bacterial endocarditis but the nomenclature has changed with the recognition that fungi, rickettsia, and chlamydia can also cause endocarditis. Infective endocarditis is an infection of the heart valves which may sometimes involve the endocardium of patients with congenital defects.

It usually occurs at the site of a predisposing heart lesion or congenital defect where the velocity of blood passing through it is such as to cause turbulence, resulting in damage to the endocardial surface. On such surfaces a platelet-fibrin clot is deposited. This clot, initially sterile, acts as a nidus for any micro-organisms released into the bloodstream from dental or other sources. Thereafter the clot may become an avascular "infected vegetation".

The disease used to be described as "acute" or "subacute", this being based on the progression of the untreated disease. The acute form followed a fulminant course with fever, toxicity, and death usually within six weeks. It was commonly associated with infection with *Staphylococcus aureus*, *Streptococcus pneumoniae*, or *Streptococcus pyogenes*. The subacute form was associated with a low grade fever, night sweats, weight loss and malaise. This form of the disease was usually caused by the viridans streptococci and resulted in death after about three months. This terminology is now no longer used. Instead, it is preferable to describe the disease in terms of the causative micro-organism. Such terminology may imply the nature of the endocarditis, the probable underlying cardiac status and often the appropriate antimicrobial treatment.

This disease has always been of great interest to clinicians, pathologists and microbiologists. This interest was generated over 100 years ago by William Osler who presented the Gullstonian lectures on Malignant Endocarditis to the Royal College of Physicians in 1885.¹ In these lectures he summarised the state of knowledge of what, at that time, was a poorly understood disease. Some years later in 1909 Horder published a classic paper on infective endocarditis with an analysis of 150 cases.² In this excellent paper he described clearly the clinical features, established the importance of streptococci as the usual causative agents, and also correlated the clinical and pathological findings of the disease. At this time, the disease had a mortality of 100% and it remained so until the advent of antibiotics in the 1940s.

There was then a dramatic decline in mortality which was further reduced in the 1970s with the introduction of cardiac surgery. However, despite effective antimicrobial treatment and surgical intervention, mortality today is still about 30%.

Since the advent of antibiotics and cardiac surgery the natural history of the disease has altered. It is difficult to obtain accurate figures on the incidence of infective endocarditis but even with the availability of antibiotics, there seems to have been little change in the numbers of cases.^{3,4} It is estimated that about 20 cases per million population a year can be expected. However, prognosis has improved with antibiotics and cardiac surgery. Antibiotics have decreased the incidence of acute rheumatic fever and valve replacement has increased the chances of survival in patients with congenital heart disease. However, two new "at risk" groups have emerged. These are patients with prosthetic heart valves and intravenous drug abusers. All of these factors have contributed to a changing pattern in infective endocarditis. Over the past 25 years many studies have reflected on these changes.⁵⁻¹⁷

This article considers the changing pattern of infective endocarditis with particular emphasis on the causative micro-organisms, the patient population and their underlying diseases, the clinical presentation, the diagnosis, treatment and management of the disease.

The types of micro-organisms that can infect the heart and its valves have changed dramatically. In the pre-antibiotic era the viridans streptococci were by far the main causative micro-organisms, but recently the incidence of staphylococcal endocarditis has dramatically increased. One of the main reasons for this is the emergence of a new population "at risk" of infective endocarditis, namely intravenous drug abusers. *Staphylococcus aureus* is the causative organism in up to 70% of these patients, who usually develop endocarditis involving the tricuspid valve. Mortality is high for *S aureus* endocarditis on native or prosthetic valves but the right sided endocarditis seen in drug misusers usually responds well to appropriate antibiotics. Another reason for the increase in staphylococcal endocarditis is the emergence of coagulase negative staphylococci as clinically important hospital pathogens. They are partic-

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ularly associated with prosthetic devices, such as heart valves.¹⁸ In early prosthetic valve endocarditis (which occurs within two months of surgery) the coagulase negative staphylococci are responsible for most cases.^{19, 20} Prosthetic valve endocarditis with these bacteria responds poorly to antibiotics and valve replacement is often necessary.¹⁹

Streptococci remain important causative organisms. The viridans group of streptococci are still the predominant cause of endocarditis in patients with rheumatic fever, albeit fewer in number. Such cases usually respond well to medical treatment alone. *S pneumoniae* endocarditis, although now less prevalent than in the pre-antibiotic era, usually occurs in patients with pneumonia, meningitis, and also in alcoholics. Faecal streptococci remain an important cause of endocarditis especially after gastrointestinal or genitourinary surgical intervention in elderly men. These patients often have no previously identified valve disease. Such cases do not normally respond well to antibiotics. *S bovis* endocarditis is associated with carcinoma of the colon.²¹ Other streptococci responsible for endocarditis are the β -haemolytic streptococci and anaerobic streptococci. There has recently been an increase in endocarditis caused by the group B streptococcus (*S agalactiae*) in non-puerperal adults.²²

Gram negative micro-organisms are becoming more common as causative agents of infective endocarditis, especially in patients with diabetes or in intravenous drug misusers. Fungi, especially *Candida* sp, have become a recognised, but relatively uncommon, cause of endocarditis in both patients with prosthetic heart valves and intravenous drug misusers. Mortality is high for fungal endocarditis even with effective antifungal treatment and valve replacement, which is an essential component of treatment. *Coxiella burnetii* is a known but rare cause of endocarditis. In addition to occasional isolated cases, there have been clusters of such cases associated with outbreaks of Q-fever.

In the pre-antibiotic era a low grade febrile illness was the commonest presentation of subacute bacterial endocarditis. It usually occurred in patients with rheumatic heart disease. Characteristic clinical features included night sweats, anorexia, weight loss, finger clubbing and splenomegaly. The classic signs of endocarditis splinter haemorrhages, Osler nodes, Roth spots and Janeway lesions were often present.^{10, 23} These features were originally attributed to micro-emboli but it is now known that they are due to deposition of immune complexes. The infection usually progressed relentlessly with increasing weight loss and eventually the patient died usually from cardiac failure or from a major embolism. Nowadays, the classic features are frequently absent and the presenting clinical symptoms are often more subtle with perhaps only a heart murmur and fever. Sometimes these symptoms may be accompanied by malaise, anorexia, and weight loss.²⁴ Indeed, with the low grade pathogens such as coagulase negative

staphylococci and diphtheroids, both of which can cause prosthetic valve endocarditis, clinical signs of infection may be minimal.

The very nature of the disease has itself changed. One of the major features is the change in the age of the patients. In the 1930s most patients were less than 40 years old, but nowadays infective endocarditis, with exception of the intravenous drug misusers, is a disease of the middle aged and elderly.²⁵ The reasons for this age shift are an increase in average lifespan, decreased incidence of rheumatic fever, and longer survival of patients with rheumatic fever and congenital heart disease. Surgery for valve replacement itself has provided a new "at risk" group for infective endocarditis. Early prosthetic valve endocarditis has an incidence of less than 1% but a mortality of about 70%. The potential sources of infection are numerous and include the prosthesis itself, intravascular lines, pacing wires, theatre air and the skin of both staff and the patients themselves. With late prosthetic valve endocarditis, which occurs more than two months after surgery, the causal organisms are usually streptococci. Unlike early prosthetic valve endocarditis where the source of infection is often never identified, these late infections are usually associated with episodes of transient bacteraemia resulting from dental instrumentation or a minor invasive surgical procedure.

With the recognition of the consequences of these bacteraemias, guidelines for antibiotic prophylaxis covering dental and other instrumentation have now become widely recommended.²⁶ Prophylaxis with antibiotics is recommended not only for patients with prosthetic valves but also for those with pre-existing valvular disease. When adequate prophylaxis is given infective endocarditis rarely occurs. However, evidence suggests that the importance of dental procedures in infective endocarditis is not as great as was originally perceived^{10, 12, 13} and also that endocarditis can occur in patients with no previously known heart disease.^{27, 28} Bayliss and colleagues confirmed these two important observations in a series of papers reporting results of the most comprehensive study ever undertaken in the United Kingdom in which cases of infective endocarditis during 1981 and 1982 were investigated retrospectively.²⁹⁻³¹ While reaffirming the need for prophylaxis for dental and other surgical procedures in "at risk" patients, they also highlighted the dilemma of prevention of endocarditis in the group of patients (43% in their survey) with normal or apparently normal hearts who develop endocarditis. Within this group elderly patients are at particular risk. Other groups at enhanced risk included diabetics, alcoholics, the immunosuppressed, intravenous drugs misusers and patients with malignant disease. Bayliss *et al* also showed that a significant number of cases of endocarditis were related to poor dental hygiene and they emphasised the need for better routine dental care.²⁹

Infective endocarditis is a disease in which close collaboration between microbiologists

Figure GRI = Glasgow Royal Infirmary Glasgow 1976-1981 modified from Whitby and Fenech.¹⁵

and clinicians is essential because prompt diagnosis and early treatment are imperative for survival. Blood cultures remain the cornerstone of diagnosis and must be taken whenever there is clinical suspicion of endocarditis. Bacteraemia is consistent and low grade.³² Blood cultures should be taken before antibiotic treatment is started but in seriously ill patients this must not be delayed until blood culture results are available.

Echocardiography is a useful investigative technique and a complementary diagnostic aid in infective endocarditis. It can detect vegetations on heart valves and also assess the haemodynamic status of the patient. The diagnostic sensitivity of echocardiography varies from 20 to 80%,³³ dependent on the echocardiographic techniques used, the size of the vegetations and also at what time during the infection it is performed. However, failure to show vegetations on echocardiography does not exclude the diagnosis of infective endocarditis, and the presence of vegetations does not imply that the disease is active. The recent introduction of transoesophageal echocardiography has greatly improved the sensitivity of the technique.^{34 35}

With the isolation and identification of the causative micro-organism, the microbiologist can advise on appropriate antibiotics and monitoring of this treatment. Recommendations for treatment of streptococcal and staphylococcal endocarditis have been made by the Endocarditis Working Party of the British Society for Antimicrobial Chemotherapy (BSAC).³⁶ Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) tests are necessary to guide dose of antibiotics and to ensure adequate serum antibiotic concentrations. The serum bactericidal test remains widely used to assess the

response to treatment but there is little evidence that it is of any prognostic value.³⁷ However, there is apparent correlation between bactericidal titres of greater than one in eight after antibiotic dosing and bacteriological cure.³⁸ Now that rapid tests are available, measurements of C-reactive protein in endocarditis have been shown to be useful in monitoring the response to treatment and also to detect intercurrent infections and complications.^{39 40} In our experience the optimal management of infective endocarditis is a team approach involving the clinician, microbiologist, cardiac surgeon and dentist. Patients failing to make a good clinical response to appropriate antimicrobial treatment should be considered for early cardiac surgery.

Many of the features described above are illustrated by our experience in a prospective study of 69 episodes of endocarditis in 66 patients between 1984 and 1989 at the Glasgow Royal Infirmary. The overall mortality in the series was 28% and the average age was 45 years (age range 14-73 years). When the 16 episodes of endocarditis in IVDA were removed from the series the average age was increased to 52 years.

It is interesting to compare the causative micro-organisms in this study of 69 cases with a previous retrospective study of 71 cases of endocarditis in Glasgow (also over a five year period but from 1976 to 1981).¹⁵ The figure shows that in the earlier study the viridans streptococci were, at 45% of the total, the predominant causative organisms; in the later study they represented only 20%. There was a pronounced increase in the numbers of both *S aureus* (from 14% to 36%) and coagulase negative staphylococci (from 5% to 15%) in the 1984-1989 series compared with the 1976-1981 study.

In our series there are approximately equal numbers of *S aureus* (36%) and streptococci (35%) if the viridans streptococci enterococci and other streptococci are considered together. This, in part, may be explained by the large number of cases of *S aureus* endocarditis in drug misusers. Another contributory factor may be that as our hospital is a tertiary referral centre, we perhaps do not see cases of streptococcal endocarditis successfully treated in other hospitals. Nevertheless, our series confirms that staphylococci are now important causative agents in endocarditis. Table 1 details the predisposing cardiac conditions in the 69 episodes. Thirty one of the patients had no previously suspected heart disease. Of these, 15 were intravenous drug misusers, two acquired the infection from an infected catheter, one had mitral valve prolapse, one was a

Table 1 Infective endocarditis Glasgow Royal Infirmary 1984-1989

Predisposing cardiac conditions	
None previously suspected	31*
Prosthetic valve	24
Congenital heart disease	10
Rheumatic	4
Total	69

* 15 intravenous drug misusers

Table 2 Infective endocarditis Glasgow Royal Infirmary 1984-1989

Prosthetic valve endocarditis causative micro-organisms

	Early*	Late†
Coagulase negative staphylococci	5	5
<i>Staphylococcus aureus</i>	1	4
Viridans streptococci		4
<i>Candida</i> sp	3	
Streptococci (Lancefield group B)		1
Culture negative		1
	9	15

* Endocarditis within two months of surgery

† Endocarditis more than 2 months after surgery.

diabetic, one developed endocarditis from an infected pacemaker and one had florid atopic dermatitis. Table 2 shows that coagulase negative staphylococci were the main cause of prosthetic valve endocarditis.

In conclusion, infective endocarditis is a continually changing and evolving disease with many of the contributory factors being inter-related. Clinicians must recognise and maintain an increased awareness of this serious and potentially fatal disease. In particular, they must recognise "at risk" patients, discover prior instrumentation or invasive procedures in any clinical history, be aware of the non-specific clinical symptoms and also have a high index of suspicion of endocarditis in any patients with staphylococci or streptococci in their blood cultures.

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