

Clinical review

Infective endocarditis

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The investigation and management of infective endocarditis in the developed world have changed radically over the past 30 years.¹ Non-invasive imaging, molecular science, diagnostic protocols, and curative surgery have all become commonplace, yet the incidence remains unchanged and annual mortality approaches 40%.²

The lack of impact of modern medicine reflects important changes in the causes of the disease. In Western populations in particular, chronic rheumatic heart disease is now an uncommon antecedent, whereas degenerative valve disease in elderly people, intravenous drug misuse, preceding valve replacement, or vascular instrumentation have become increasingly frequent, coinciding with an increase in staphylococcal infections and those due to fastidious organisms. Furthermore, previously undetected pathogens are now being identified with the disease, and multidrug resistant bacteria challenge conventional treatment regimens. Meanwhile, rheumatic valve disease remains endemic in the developing world, where modern investigations and management are the privilege of the well off few who live in large urban areas.^{3 w1 w2} In this review, we outline the modern understanding, investigation, and management of this perplexing and enigmatic condition.

Who gets infective endocarditis?

The incidence of infective endocarditis is approximately 1.7-6.2 cases per 100 000 patient years,⁶ although rates are higher in at risk cohorts such as intravenous drug users.^{w3} Men are more often affected than women (in a ratio of 2:1), and the incidence progressively increases with age. Underlying degenerative aortic and mitral valve disease now predominate over rheumatic disease,^{w1} although in one recent French study 47% of patients with infective endocarditis presented without previous knowledge of an underlying cardiac disorder.⁷ The relation to dental surgery has been overemphasised in the past, and infective endocarditis is now more likely in the context of previous valve surgery or as a consequence of iatrogenic or nosocomial infection.⁸

What is the underlying pathophysiology?

Ulceration on the valvular endothelial surface promotes bacterial adherence by two possible mechanisms⁹:

- Direct contact between blood and subendothelial components results in production of a coagulum or small clot. Pathogens associated with infective

Summary points

Endocarditis remains an important clinical problem with the rise of intravenous drug misuse, degenerative valve disease, and nosocomial infection

Successful management requires a multidisciplinary approach involving microbiologists, cardiologists, and cardiothoracic surgeons

Well validated diagnostic criteria have improved diagnostic sensitivity and specificity

New serological and molecular techniques have an important role in the diagnosis of culture negative patients

Treatment often requires prolonged antibiotic regimens of up to six weeks' duration

Persistent infection, haemodynamic compromise, repeated embolic events, or perivalvular complications are indications for urgent surgery

Antibiotic prophylaxis remains important for patients with high risk cardiac conditions

endocarditis circulating in the bloodstream as a result of transient bacteraemia bind avidly to the coagulum and in turn attract and activate monocytes to produce cytokines, resulting in progressive enlargement of an infected vegetation

- Local inflammation promotes cells to express trans-membrane proteins that bind fibronectin. Pathogens such as *Staphylococcus aureus* carry fibronectin binding proteins on the surface. Staphylococcal endocarditis is often seen in patients with previously normal valves, and micro-ulcerations are thought to be responsible for endocarditis by this mechanism.

How do patients present?

Registry data suggest that up to 90% of patients present with a fever,^{w5} often associated with systemic symptoms of chills, poor appetite, and weight loss. Heart murmurs are found in up to 85% of patients.



Extra references are on bmj.com

Sources and selection criteria

We incorporated the latest consensus from systematic reviews and publications identified by a literature search through Medline with specific emphasis on randomised controlled trials and English language articles on infective endocarditis. The European Society of Cardiology, American College of Cardiology, and American Heart Association provide comprehensive guidelines for the prevention, diagnosis, and treatment of infective endocarditis,^{4,5} and further articles came from a personal collection of recently published work

Classic textbook signs may still be seen in the developing world, although peripheral stigmata of infective endocarditis (Osler's nodes, Janeway lesions) are increasingly uncommon elsewhere, as patients generally present at an early stage of the disease (fig 1). However, vasculitic phenomena such as splinter haemorrhages, Roth spots, and glomerulonephritis remain common, and emboli to brain, lung, or spleen occur in 30% of patients and are often the presenting feature. Mycotic aneurysms may result from systemic emboli and are seen more frequently in the developing world, where presentation is often delayed.⁶

Atypical presentation is common in elderly or immunocompromised patients, in whom fever is often absent. This group may be difficult to manage, as previous administration of antibiotics may inhibit growth in blood cultures. A high index of suspicion and low threshold for specialist investigation are therefore essential in these and other high risk patients.

How to investigate endocarditis: take blood cultures first, treat later

Blood cultures

Given the need for prolonged antibiotic treatment in most patients with infective endocarditis, positive microbiological cultures and sensitivities are vitally important for successful management. Current guidelines recommend that three sets of blood cultures are drawn one hour apart before the introduction of antibiotic treatment⁴—the first two sets are positive in more than 90% of cases (fig 2). No evidence suggests that cultures should be taken coincident with peaks of temperature, as bacteraemia is constant. However, cultures should not be taken from indwelling lines because of the high likelihood of contamination. Although



Fig 1 Cutaneous manifestations in infective endocarditis. (Left) Osler's nodes in patient with streptococcal endocarditis and underlying hypertrophic obstructive cardiomyopathy. (Right) Severe purpuric lesions in woman with staphylococcal endocarditis arising on an implanted pacemaker. (Reproduced with permission from Habib G. *Heart* 2006;92:124-30)

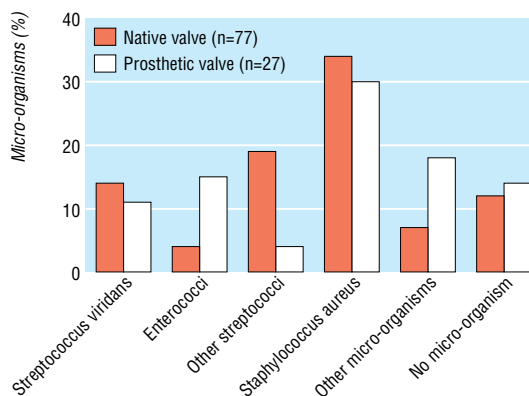


Fig 2 Micro-organisms responsible for native valve and prosthetic valve endocarditis in recent European survey. (Reproduced courtesy of P Tornos and the Euro heart survey)

infective endocarditis secondary to anaerobic infection is uncommon, cultures should be sent for both aerobic and anaerobic incubation. In patients with a high likelihood of infective endocarditis who have already started antibiotic treatment, the risks of stopping treatment to allow fresh culture specimens to be taken may be outweighed by the advantages of identifying the causative organism. Early liaison with the local microbiology team is essential when infective endocarditis is suspected, particularly when specialised investigation seems necessary (see below).

What to do when the cultures are negative

Blood cultures are negative in 14% of cases of endocarditis, often delaying diagnosis and the start of treatment with profound impact on clinical outcome. Negative cultures are most commonly related to the previous administration of antibiotics,¹⁰ but they may also be associated with fastidious pathogens, including *Legionella*, *Coxiella*, the HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*), and fungi such as *Candida*, *Histoplasma*, and *Aspergillus* species. Serological testing can be particularly useful for investigating the possibility of *Coxiella burnetii* (Q fever) and *Bartonella* infection and should be done in all patients who are initially culture negative. Histological techniques may also be useful when infected tissue is available from cardiac surgery or retrieval of embolic material, and the advent of molecular techniques, notably polymerase chain reaction, has much improved the detection of fastidious and non-culturable agents.¹¹ Polymerase chain reaction uses nucleic acid target or signal amplification, alone or in combination with sequence analysis, and may be done on blood or tissue samples. The technique is particularly useful when negative cultures are caused by previous administration of antibiotics (as the technique is culture independent) or the presence of a fastidious organism and to identify the culprit organism in polymicrobial infection.

Echocardiography

Transthoracic echocardiography is the initial technique of choice for investigating infective endocarditis. In low risk patients, a normal transthoracic echocardiogram provides confirmation that endocarditis is

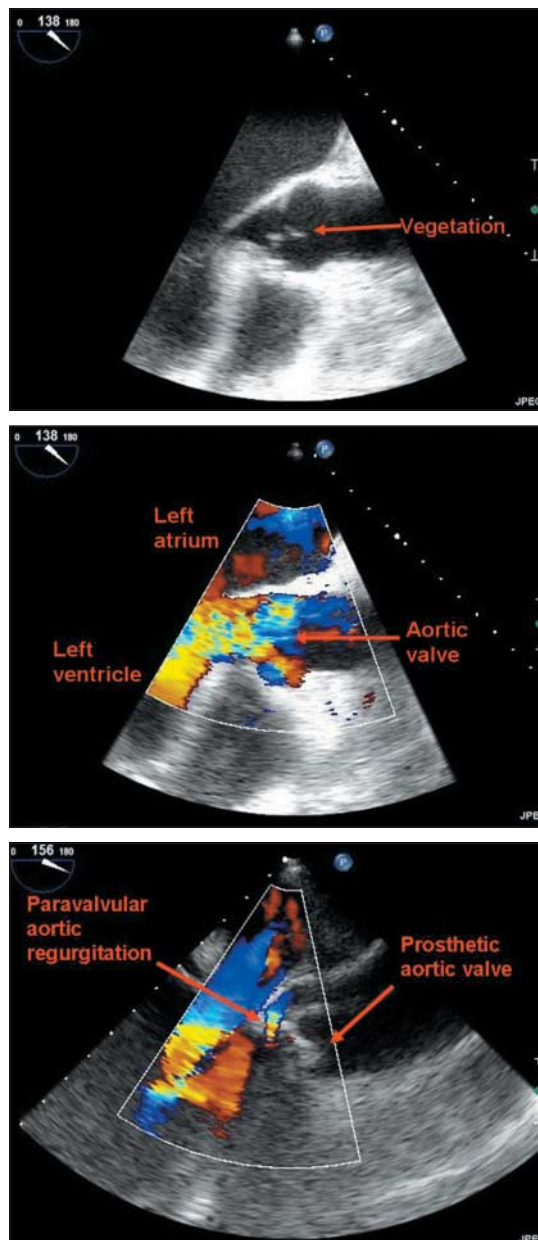


Fig 3 Role of transoesophageal echocardiography in investigation and management of endocarditis. Top: small vegetation on tip of a coronary cusp undetected by transthoracic echocardiography. Middle: same patient as above, showing resultant severe aortic regurgitation. Bottom: paravalvular aortic regurgitation in patient with endocarditis affecting a prosthetic aortic valve

unlikely and suggests that investigations should be directed elsewhere. In high risk groups, transoesophageal echocardiography, with its higher sensitivity and specificity, may be needed if the transthoracic echocardiogram is normal and suspicion of infective endocarditis remains high. Transoesophageal echocardiography is also used to investigate potential complications of infective endocarditis (fig 3, fig 4, fig 5). For example, the mechanism of significant valvular regurgitation is often best assessed with transoesophageal echocardiography, and paravalvular abscesses are often detected by transoesophageal echocardiography when the transthoracic echocardiogram is normal. Demands on non-invasive cardiac services are high in the United Kingdom and elsewhere, and requests to “exclude

endocarditis” in patients with a low clinical likelihood of the disease are increasingly common, with resultant poor diagnostic yield. For example, in one recent study examining 500 consecutive referrals for transthoracic echocardiography to exclude infective endocarditis, the diagnosis was confirmed in only 43 (8.6%) of the patients. Furthermore, the absence of five clinical variables—a prosthetic valve, intravenous drug use, positive blood cultures, central venous access, or signs of embolic phenomena—made the likelihood of infective endocarditis zero (box 1).¹²

Diagnostic criteria

The diagnosis of infective endocarditis requires a multifaceted approach involving clinical suspicion and examination, laboratory investigation by means of inflammatory markers and microbiological analysis, and imaging with echocardiography. The need for robust diagnostic criteria uniting these means of investigation was shown by the original Von Reyn criteria, published in the early 1980s^{w7} and subsequently superseded by the Duke criteria in the 1990s in the light of improved echocardiographic techniques.¹³ Despite the high sensitivity and specificity of these original criteria, subsequent modifications have been suggested to acknowledge the role of Q fever, the increasing prevalence of staphylococcal infection, the widespread adoption of transoesophageal echocardiography, and increasing use of polymerase chain reaction.^{w8} These modified Duke criteria¹⁴ (box 2) have now been adopted in the latest guidelines from the European Society of Cardiology.⁴ Nevertheless, the sensitivity of these criteria is significantly weakened in culture negative patients and in countries where echocardiography, modern serology, and molecular techniques remain poorly resourced.

Antimicrobial treatment

The choice and length of treatment are dictated by the pathogen isolated from cultures and require the close collaboration of microbiologist and physician. In deprived communities, the lack of microbiological support encourages empirical use of inappropriate (though readily available) antibiotics, with predictable adverse impact on outcome.

If blood cultures have been taken and empirical antibiotic treatment is thought necessary while awaiting the results, patient related risk factors and local bactericidal resistance patterns should be considered when choosing a regimen. Patients should be switched to the appropriate antibiotic as soon as cultures and sensitivities are available. Recommendations for the treatment of most of the common pathogens have been published, and treatment is needed for four to six weeks in most cases.¹⁵ Short course antibiotic treatment (two weeks) has been investigated in patients with right sided infective endocarditis and uncomplicated infective endocarditis secondary to *Streptococcus viridans* and found to be safe and efficacious without significant valvular complications.^{w9} Selected patients with streptococcal infective endocarditis may also be suitable for once daily dosing regimens with ceftriaxone, allowing consideration of outpatient treatment.^{w10}

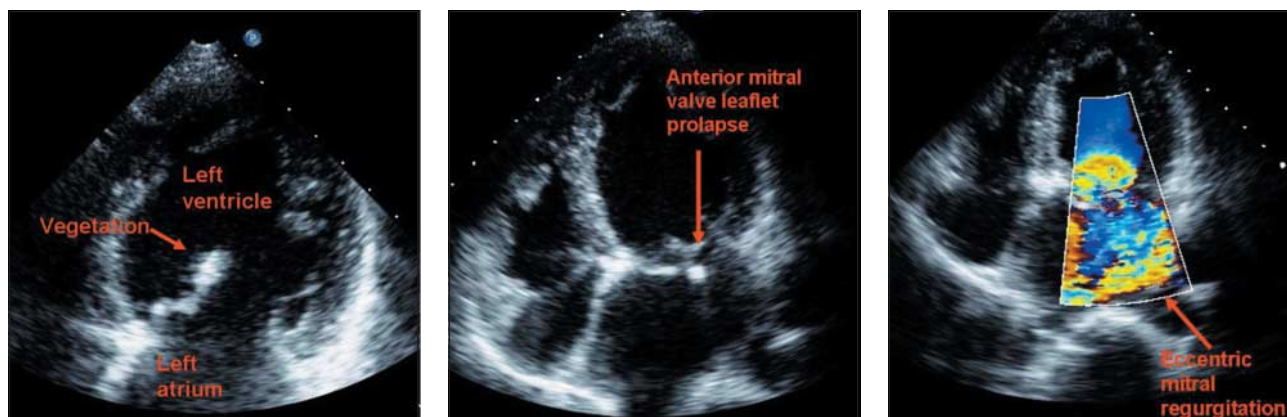


Fig 4 Left: large vegetation on tip of anterior mitral valve leaflet. Middle: prolapsing mitral valve leaflet in same patient. Right: resultant severe eccentric mitral regurgitation

Special subgroups

Prosthetic valves

The incidence of prosthetic valve endocarditis ranges from 0.1% to 2.3% a year^{w11} and accounts for 10-15% of cases. Transoesophageal echocardiography is almost always needed for investigation, as vegetations are often small and imaging is made difficult by artefacts related to previous surgery and “acoustic shadows” cast by a metallic prosthesis. Prosthetic valve endocarditis may be classified as early or late in onset according to the timing of symptoms in relation to the original valve surgery, and a distinct shift in the pattern of infecting organisms is seen one year after surgery. Staphylococci predominate in early onset prosthetic valve endocarditis, whereas the microbiological spectrum in late onset prosthetic valve endocarditis mirrors that of native valve endocarditis.^{w12} Complications are common, and aortic root abscess is a particularly frequent finding when prosthetic valve endocarditis involves the aortic valve. Treatment is difficult, requiring prolonged use of antibiotics, and surgery, when needed, is technically demanding. Overall mortality remains worryingly high at 40-50%, and specialist care is mandatory (box 3).

Intravenous drug users

The incidence of infective endocarditis in intravenous drug users is 1-5% a year and seems to be rising steadily in the UK population. Infection occurs with equal

frequency on right sided and left sided valves, and *Staph aureus* is the most common pathogen.^{w13} These patients present particular management difficulties because of their drug seeking behaviour and poor compliance with treatment. They often struggle with prolonged hospital stays as a result. Furthermore, the incidence of recurrent infective endocarditis is high because of repeated drug misuse after successful treatment, and cardiac surgeons may be reluctant to offer surgery in this setting. Mortality is substantial.

Who needs cardiac surgery?

Surgery for infective endocarditis is potentially life saving.¹⁶ Morbidity and mortality associated with infective endocarditis are related to valvular regurgitation and abscess formation secondary to tissue destruction, heart failure, and embolic complications. Rarely, vegetations may become sufficiently large to cause valve obstruction. Overall, surgery is needed in approximately 50% of patients who develop infective endocarditis, and careful timing is essential to ensure a good outcome. In most stable patients, surgery is best delayed until antibiotics are completed to reduce the risk of perioperative complications and early prosthetic valve endocarditis. Unstable patients with haemodynamic or perivalvular complications have a poor prognosis and are best transferred to a specialist centre at the earliest opportunity. When deemed necessary (box 4), surgery should not be delayed to allow completion of an arbitrary course of preoperative antibiotic treatment, as mortality rises quickly with increasing comorbidity.

Surgery is often difficult and associated with high risk, not least because patients are frequently extremely sick with multisystem disease. Furthermore,

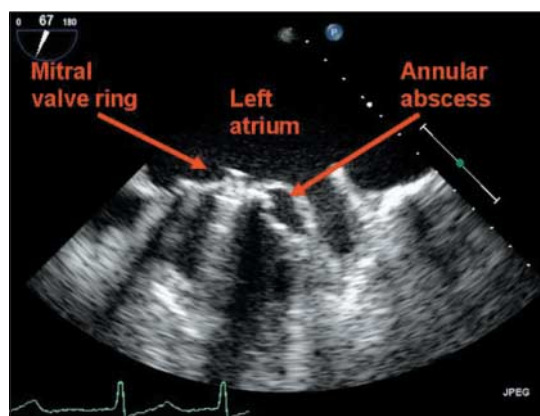


Fig 5 Severe prosthetic valve endocarditis with large abscess cavity surrounding a mitral annuloplasty ring

Box 1: Use of echocardiography

The absence of

- a history of valve replacement or intravenous drug misuse AND
- signs of embolic phenomena AND
- central venous access AND
- positive blood cultures

indicates a near zero possibility of endocarditis¹²

Box 2: Modified Duke criteria

Pathological criteria

- Positive histology or microbiology of pathological material obtained at autopsy or cardiac surgery (valve tissue, vegetations, embolic fragments, or intracardiac abscess content)

Major criteria

- Two positive blood cultures showing typical organisms consistent with infective endocarditis, such as *Streptococcus viridans* and the HACEK group OR
- Persistent bacteraemia from two blood cultures taken > 12 hours apart or three or more positive blood cultures where the pathogen is less specific, such as *Staphylococcus aureus* and *Staph epidermidis* OR
- Positive serology for *Coxiella burnetti*, *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 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 positive OR
- Two major criteria OR
- One major and two minor criteria OR
- Five minor criteria

in the developing world scarce resources and limited access to surgical care may affect management decisions. Overall surgical mortality in active infective endocarditis is 8-16%, with actuarial survival rates of 75% at five years and 61% at 10 years.¹⁴ Surgical technique commonly involves valve replacement with a metallic or biological prosthesis, but valve sparing techniques with chordal preservation or partial leaflet resection are becoming more widespread. Valve replacement with a homograft or use of the Ross procedure (aortic valve replacement using the patient's own pulmonary valve combined with a pulmonary homograft) have particular attractions in patients with infective endocarditis affecting the aortic valve, especially when complicated by abscess formation. However, application of these techniques may be limited by difficulties with valve procurement or available surgical expertise.

Box 3: Who needs tertiary care?

- Patients in whom diagnosis remains uncertain (especially when transoesophageal echocardiography is unavailable)
- Patients whose progress is poor despite appropriate antibiotic treatment
- Patients who develop complications needing surgery (see text)
- Patients with prosthetic valve endocarditis

Box 4: Who needs surgery?

Urgent surgery should be considered in the following circumstances (descending order of priority):

- Haemodynamic compromise due to valve destruction
- Persistent fever despite appropriate antibiotic treatment
- Development of abscesses or fistulas due to perivalvular spread of infection
- Involvement of highly resistant organisms (aggressive staphylococcal strains, *Coxiella burnetti*, *Brucella* species, fungi)
- Prosthetic valve endocarditis (particularly in the early postoperative phase)
- Large vegetations with high embolic potential (> 10 mm or on the mitral valve)

Prophylaxis

The role of prophylaxis has been poorly investigated, and, although it is widely accepted, uptake remains poor in both developed and developing nations.^{17 w15} Guidelines are extensively published,^{18 w16} and the *British National Formulary* devotes a section to a summary of accepted practice. Very recent publications have questioned the need for routine prophylaxis before dental procedures in many patients, though these views remain controversial.^{19 w17} Overall, the benefits of prophylaxis are likely to be considerable in high risk patients (prosthetic valves, previous infective endocarditis, congenital cyanotic heart disease) and relatively small in low risk groups such as patients with mitral valve prolapse. The importance of scrupulous dental and skin hygiene should be reinforced in all patients at risk of infective endocarditis.

International collaboration

To date, knowledge of the clinical features and natural history of infective endocarditis has relied largely on small, uncontrolled, outdated studies; modern, well designed registries and trials reflecting current disease patterns are long overdue. The recently elaborated International Collaboration on Endocarditis will contribute greatly to our current and future knowledge of infective endocarditis, allowing the development of new diagnostic and treatment strategies.²⁰ Involving 39

What do general practitioners need to consider?

- Patients with prosthetic valves, congenital heart disease, intravenous drug misuse, or a history of infective endocarditis are at high risk. Unexplained fever should prompt further investigations (including blood cultures) before antibiotics are administered
- Patients with known valvular heart disease are at moderate risk of infective endocarditis. A history of prolonged unexplained fever, sweats, chills, weight loss, or anaemia should prompt consideration of further investigations, including blood cultures and echocardiography
- The presence of a new cardiac murmur and unexplained fever in previously fit patients should raise the possibility of infective endocarditis

Additional educational resources

Horstkotte D, Follath F, Gutschik E, Lengyel M, Oto A, Pavie A, et al. Guidelines on prevention, diagnosis and treatment of infective endocarditis: executive summary. *Eur Heart J* 2004;25:267-76 (www.escardio.org/knowledge/guidelines/)—A comprehensive document covering all aspects of the investigation and management of infective endocarditis

Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Bolger AF, Levison ME, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. (circ.ahajournals.org/cgi/content/full/111/23/e394)—Up to date American Heart Association guidelines on the management of endocarditis

British National Formulary (www.bnf.org)—Detailed explanation of current prophylaxis recommendations
International Collaboration on Endocarditis (endocarditis.org/ice/index.html)

Information for patients

American Heart Association patient information sheet (www.americanheart.org/presenter.jhtml?identifier=4436)—A good basic guide written for non-medical personnel

American National Institute for Health information sheet (www.nlm.nih.gov/medlineplus/ency/article/000681.htm)—A brief description of infective endocarditis from a patient's perspective

Patient UK (www.patient.co.uk/showdoc/27000162/)—A simple description of infective endocarditis from a UK based site (partially funded by advertisements)

sites in 16 countries, the initial merger of existing databases has yielded a primary group of 2200 well characterised patients with definite infective endocarditis by the Duke criteria, allowing the assessment of regional differences in presentation and outcome. Indeed, analysis of the dataset has already enabled valuable insight into emerging epidemiological patterns of the disease and its clinical presentation.^{w18-w21} In future, this platform will provide the basis for sorely needed adequately sized randomised clinical trials in the management and treatment of infective endocarditis.^{w22 w23}

The future

Several exciting developments offer the prospect of improved prevention and treatment of infective endocarditis. Vaccines targeted at specific bacterial adhesins may inhibit valve colonisation, and newer antibacterial agents with novel effects may attenuate the invasive properties of virulent organisms such as *Staph aureus*.¹ Finally, modified biomaterials in development may reduce the risk of infective endocarditis in patients with artificial heart valves or other intracardiac prosthetic material. However, despite these advances, the diagnosis and management of infective endocarditis remain a considerable challenge across the range of medical disciplines.

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Corrections and clarifications

Pressure relieving support surfaces (PRESSURE) trial: cost effectiveness analysis

This research article by Cynthia Iglesias and colleagues (*BMJ* 2006;332:1416-8, 17 Jun) should have included the trial registration identifier Current Controlled Trials ISRCTN78646179.

Correction for Nixon et al

In the correction (*BMJ* 2006;333:30, 1 Jul) to the article "Randomised, controlled trial of alternating pressure mattresses compared with alternating pressure overlays for the prevention of pressure ulcers: PRESSURE (pressure relieving support surfaces) trial" (*BMJ* 2006;332 1413-5, 17 Jun), we incorrectly referred to haemoglobin levels rather than odds ratios. We should have said: "In table 4 of the full version on bmj.com (table 2 of the abridged version), the odds ratio for haemoglobin levels on admission or preoperatively should be 0.89 (0.82 to 0.97), and the corresponding P value should be 0.01."