

MINI-SYMPOSIUM

Diagnostic criteria and problems in infective endocarditis

B D Prendergast

Heart 2004;90:611–613. doi: 10.1136/hrt.2003.029850

Few diseases present greater difficulties in the way of diagnosis than malignant endocarditis, difficulties which in many cases are practically insurmountable. It is no disparagement to the many skilled physicians who have put their cases upon record to say that, in fully one-half the diagnosis was made post mortem. — *William Osler 1885*

Osler's portentous words are as relevant now as when originally published. Despite improved preventive strategies, rational antibiotic prescribing, advances in imaging, and increasing use of early life saving cardiac surgery, the incidence of infective endocarditis remains high at 1.7–6.2 per 100 000 person years in the USA and Europe, with a one year mortality approaching 40%.¹ The classical patient with infective endocarditis described in textbooks no longer represents the majority of cases in practice. The emergence of staphylococcal infection, often associated with indwelling devices, co-existent medical conditions and resistant to conventional antibiotic regimes, a variety of other atypical organisms, and the persistent syndrome of culture negative endocarditis make diagnosis and treatment as great a challenge as ever.

DIAGNOSTIC CRITERIA AND THEIR LIMITATIONS

The original von Reyn diagnostic criteria for infective endocarditis,² based upon clinical and microbiological features, have now been surpassed by the Duke criteria³ which emphasise the role of echocardiography, the key imaging tool for both diagnosis and assessment of prognosis. Many studies have now demonstrated the superiority of the Duke criteria and a recent scientific statement of the American Heart Association concluded that they should be adopted as the primary diagnostic schema in the clinical evaluation of patients in whom infective endocarditis is suspected.⁴ Nevertheless, clear deficiencies remain. Thus, in one series⁵ of 93 patients with pathologically confirmed infective endocarditis (affecting a native valve in 63 and a prosthetic valve in the remainder), 22 were misclassified as "possible" cases using the Duke criteria, yielding a sensitivity of only 76%. Echocardiographic major criteria were present in 19 patients but blood cultures were negative in 21. The cause of negative blood cultures was prior antibiotic treatment in 11 patients and Q fever endocarditis detected by positive serology in three. The Duke criteria have also been shown to be of lower value in other important patient groups, including those with infection affecting a prosthetic valve or pacemaker lead and the right heart in drug abusing patients.

CULTURE NEGATIVE INFECTIVE ENDOCARDITIS AND ATYPICAL ORGANISMS

Negative blood cultures occur in 2.5–31% of all cases of infective endocarditis, often delaying diagnosis and the onset of treatment with profound impact on clinical outcome. Moreover, the sensitivity of the Duke criteria, which rely heavily on microbiological indices, is diminished in this setting. Negative cultures arise most commonly as a consequence of prior antibiotic administration, but an

increasingly common scenario is infection by fastidious organisms with limited proliferation under conventional culture conditions, or requiring specialised tools for identification. Such pathogens include *Coxiella*, *Legionella*, the HACEK group (*Haemophilus* species, *Actinobacillus actinomyces* *temcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*), *Chlamydia*, *Bartonella*, *Tropheryma whippelii*, and fungi, including *Candida*, *Histoplasma*, and *Aspergillus* species, and *Torulopsis glabrata*. These organisms may be particularly common in cases of infective endocarditis affecting patients with prosthetic valves, indwelling venous lines, pacemakers, renal failure, and immunocompromised states.

MODIFIED CRITERIA AND NEW DIAGNOSTIC TECHNIQUES

In 1997, Lamas and Eykyn proposed a number of clinical modifications to the Duke criteria to include newly diagnosed splenomegaly or clubbing, elevated inflammatory markers, haematuria, and the presence of central and peripheral venous lines ("the St Thomas modifications").⁶ Simultaneously, recognition of the role of Q fever, a worldwide zoonosis caused by *Coxiella burnetii* and a particularly frequent cause of infective endocarditis in France, increasing prevalence of staphylococcal infection, and widespread use of transoesophageal echocardiography resulted in further modifications; these involved incorporating the acceptance of positive Q fever serology or bacteraemia caused by *Staphylococcus aureus* (regardless of its source) as major criteria and the elimination of minor echocardiographic criteria (table 1).^{7,8} A recent study compared these modifications in pathologically proven yet culture negative cases.⁹ Only 21% were classified as definite by the original Duke criteria, while 32% were definite by the modified Duke criteria, and the St Thomas modifications classified 62% correctly. Interestingly, the four additional cases identified correctly by the modified Duke criteria were upgraded on account of positive Q fever serology. Furthermore, careful scrutiny led to identification of the causative organism in almost 50% of culture negative cases, achieved by serology (*C burnetii*, *Bartonella*, *Chlamydia psittaci*) in 24%, culture of the excised valve in 14%, microscopy of the excised valve in 5%, and non-valve culture in 6%.

Histological/immunological techniques

Histological findings are included in the Duke and von Reyn diagnostic criteria and pathological examination of resected valvar tissue or embolic fragments remains the gold standard for the diagnosis of infective endocarditis. Pathological examination may also guide antimicrobial treatment if the causative agent can be identified by means of special stains or immunohistological techniques, and allow distinction from conditions whose echocardiographic features mimic infective endocarditis (for example, myxomas, fibroelastomas, and rheumatoid nodules). It should be noted that specimens are potentially infectious to the examiner, particularly when Q fever is suspected. The pathological hallmark of endocarditis

Table 1 Duke criteria for the diagnosis of infective endocarditis and proposed modifications

Duke criteria	Suggested modifications
Pathological criteria Microorganisms demonstrated by culture or histological examination Active endocarditis demonstrated by histological examination	
Major criteria Positive blood cultures -typical microorganisms consistent with endocarditis from two separate blood cultures -microorganisms consistent with endocarditis from persistently positive blood cultures Evidence of endocardial involvement -echocardiography: oscillating structures, abscess formation, new partial dehiscence of prosthetic valve -new valvar regurgitation	<i>To be added:</i> -positive serology for <i>Coxiella burnetii</i> ^{7,8} -bacteraemia due to <i>Staphylococcus aureus</i> ⁸ -positive molecular assay for specific gene targets and universal loci for bacteria and fungi ¹³ -positive serology for <i>Chlamydia psittaci</i> ⁹ -positive serology for <i>Bartonella</i> species ⁹
Minor criteria -predisposing heart disease -fever >38°C -vascular phenomena -immunological phenomena -microbiological evidence (no major criterion) -suspect echocardiography (no major criterion)	<i>To be omitted:</i> Suspect echocardiography (no major criterion) ⁸ <i>To be added:</i> Elevated CRP, elevated ESR, splenomegaly, haematuria, clubbing, splinter haemorrhages, petechiae and purpura ⁴ Identified IE organism from metastatic lesions ¹²
Categories	
Definite: Pathological criteria positive or 2 major criteria positive or 1 major and 2 minor criteria positive or 5 minor criteria positive	
Possible: All cases which cannot be classified as definite or rejected	1 major and 1 minor criterion positive ⁸ 3 minor criteria positive ⁸
Rejected: Alternative diagnosis Resolution of the infection with antibiotic treatment for ≤4 days No histological evidence	

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IE, infective endocarditis.
Adapted with permission from Naber CK, Erbel R. *Heart* 2003;**89**:241-3.

is the demonstration of inflammatory changes in valvar tissue and/or vegetations, characteristically at the site of attachment or base of a vegetation. This finding is not specific, however, and inflammation is also a feature of degenerative and other valve pathology. Electron microscopy has high sensitivity and may help to characterise new microorganisms. However, it is time consuming and expensive and therefore reserved for cases in which other techniques fail to detect an organism. Histological criteria for the diagnosis of endocarditis have been proposed (table 2) and a variety of specialised stains and immunohistological techniques (immunoperoxidase staining, enzyme linked immunosorbent (ELISA) and immunofluorescent (ELIFA) assays, and direct immunofluorescence using fluorescein conjugated monoclonal antibodies) are now available to allow the identification of elusive bacteria and fungi (table 3).¹⁰⁻¹¹ *C burnetii* and *Bartonella* species are the most common aetiological agents in culture negative endocarditis and may be easily detected by serological testing using indirect immunofluorescence or ELISA. Immunological analysis of urine may also allow detection of microorganism

degradation products and ELISA detection of *Legionella* species has been described using this technique. However, the incorporation of these techniques into accepted diagnostic criteria awaits prospective validation.

Molecular techniques

Several molecular approaches have been assessed for the detection and identification of pathogens in a wide variety of infectious diseases. The polymerase chain reaction (PCR) utilising nucleic acid target or signal amplification, alone or in combination with sequence analysis, is most widely used and allows rapid and reliable detection of fastidious and non-culturable agents in blood and surgical material of patients with infective endocarditis.¹² It may also be of value when phenotypic characterisation is essential following isolation of two or more organisms in separate cultures (most commonly caused by contamination with skin commensals during sampling or polymicrobial infection in intravenous drug abusers). Indeed, the incorporation of such techniques as a major Duke diagnostic criterion has been proposed with widespread support.¹³ Specific primers are now available

Table 2 Proposed histological criteria for diagnosis of infective endocarditis

Major criteria
Vegetation
Active endocarditis, including inflammatory infiltrates with polymorphonuclear cells
Microorganisms demonstrated in tissues by histology or immunohistology
Minor criteria
Mononuclear cell infiltrate (macrophages and lymphocytes) of the valve
Necrosis
Neovascularisation
Fibrosis
Calcification
Definite IE: 2 major or 1 major and 3 minor criteria
Possible IE: 1 major and 2 minor criteria
Rejected IE: No major criterion

IE, infective endocarditis.
Reproduced from Lepidi *et al*⁰ with permission.

Table 3 Main histological stains used for the diagnosis of infective endocarditis

Tissue stain	Detected microorganism
Acridine orange	Any bacterium
Giemsa	Any bacterium
Tissue Gram	
Brown-Hoops	Gram positive bacteria
Brown-Brenn	Gram negative bacteria
Periodic acid-Schiff	<i>Tropheryma whippelii</i> , fungi
Warthin-Starry	<i>Bartonella</i> species
Ziehl-Nielsen	Acid-fast bacilli
Gimenez	<i>Coxiella burnetti</i> , <i>Legionella</i> species
Kinyoun, Mchivavello	<i>Chlamydia</i> species
Gomori-Grocott	Fungi

Reproduced from Houpijian *et al*¹¹ with permission.

for many bacterial agents including *T whippelii*, *C burnetti*, and species of *Bartonella*, *Chlamydia*, *Brucella*, *Legionella*, *Mycobacteria*, and *Mycoplasma*. Future improvements include the possibility of quantitation by real time PCR eliminating the need for gel electrophoresis with faster, more accurate results, and the possibility of investigating common antimicrobial resistance genes enabling a targeted approach to antibiotic treatment.¹⁴

In a recent validation study of these molecular methods, Grijalva and colleagues¹⁵ reported the investigation of valvar specimens of 15 patients with definite, though culture negative, infective endocarditis undergoing surgery. The causative organism was identified in 14 (93%) of the culture negative cases (streptococci 3, staphylococci 2, enterobacter 1, *T whippelii* 1, *Borrelia burgdorferi* 1, *Candida albicans* 1, *Aspergillus* species 2, unspecified 3) while 13 matched controls yielded negative results. Analysis was complete within 8 hours and within 48 hours if sequencing was required.

PROPOSED APPROACH

Optimal antiseptic skin preparation is important and at least 10 ml of blood (less in children) should be obtained for each culture. Bacteraemia is usually continuous and there is no rationale for timing blood cultures to coincide with peaks of pyrexia. If there is a history of prior antibiotic treatment, maximum diagnostic yield may be achieved by diluting the culture broth and considering the use of sodium polyanethol-sulfonate or a dedicated adsorbent resin, both of which inactivate antimicrobial effects. Multiple separate blood cultures are required and most guidelines recommend at least two, and most usually three sets. Although endocarditis caused by anaerobes is uncommon, blood cultures should be incubated in both aerobic and anaerobic atmospheres to detect organisms such as *Bacteroides* or *Clostridium* species.

If all blood cultures remain negative at five days but infective endocarditis remains likely on clinical grounds, subculture onto chocolate agar plates may allow identification of an atypical organism, although prolonged culture for up to 2–3 weeks is associated with rising likelihood of contamination. At this stage, therefore, serum should be analysed for antibodies to organisms that cannot be cultured by routine methods, and, if available, antibodies to Gram positive bacterial cell walls. Excised valves, vegetations or other relevant material should undergo microscopy, culture, histopathology, and relevant molecular techniques (usually PCR) which can also be applied to newly acquired blood samples or the original growth negative blood culture substrate.

CONCLUSIONS

To date, definitive studies of infective endocarditis have been difficult to perform because of its heterogenous nature. Launched in 1999, the International Collaboration on Endocarditis was conceived to develop a large global database of patients whose clinical, echocardiographic, and microbiological findings have been characterised using standard methodology. The associated network of investigators and organisational infrastructure will provide the platform for large randomised trials to test therapeutic strategies.¹⁶ This resource offers the opportunity for major advances in our understanding and treatment of infective endocarditis over the next two decades.

Modification of the original Duke criteria is now proposed to enhance diagnostic sensitivity, especially in culture negative cases. Increased emphasis on symptoms and signs⁶ coupled with improved likelihood of identification of a causative pathogen using serology,⁷ additional culture,¹¹ or newer histological¹⁰ and molecular techniques¹² will improve the sensitivity of the diagnosis and increase therapeutic specificity. These measures, combined with close collaboration and communication between the cardiologist, cardiac surgeon, and microbiologist, are essential to ensure optimal diagnosis and management and a favourable impact on patient outcome.

Correspondence to: Dr Bernard D Prendergast, North-West Regional Cardiothoracic Centre, Wythenshawe Hospital, Southmoor Road, Manchester M23 9LT, UK; bernard.prendergast@smuht.nwest.nhs.uk

REFERENCES

- 1 Cabell CH, Jollis JG, Peterson GE, *et al*. Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med* 2002;**162**:90–4.
- 2 von Reyn CF, Levy BS, Arbeit RD, *et al*. Infective endocarditis: an analysis based on strict case definitions. *Ann Intern Med* 1981;**94**:505–17.
- 3 Durack DT, Lukes AS, Bright DK, *et al*. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. *Am J Med* 1994;**96**:200–9.
- 4 Bayer AS, Bolger AF, Taubert KA, *et al*. Diagnosis and management of infective endocarditis and its complications. *Circulation* 1998;**98**:2936–48.
- 5 Habib G, Derumeaux G, Avierinos J-F, *et al*. Value and limitations of the Duke criteria for the diagnosis of infective endocarditis. *J Am Coll Cardiol* 1999;**33**:2023–9.
- 6 Lamas C, Eykyn SJ. Suggested modifications to the Duke criteria for the clinical diagnosis of native valve and prosthetic valve endocarditis: analysis of 118 pathologically proven cases. *Clin Infect Dis* 1997;**25**:713–9.
- 7 Fournier PE, Casalta JP, Habib G, *et al*. Modification of the diagnostic criteria proposed by the Duke endocarditis service to permit improved diagnosis of Q fever endocarditis. *Am J Med* 1996;**100**:629–33.
- 8 Li JS, Sexton DJ, Mick N, *et al*. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;**30**:633–8.
- 9 Lamas CC, Eykyn SJ. Blood culture negative endocarditis: analysis of 63 cases presenting over 25 years. *Heart* 2003;**89**:258–62.
- 10 Lepidi H, Durack DT, Raoult D. Diagnostic methods. Current best practices and guidelines for histologic evaluation in infective endocarditis. *Infect Dis Clin N Am* 2002;**16**:339–61.
- 11 Houpijian P, Raoult D. Diagnostic methods. Current best practices and guidelines for identification of difficult-to-culture pathogens in infective endocarditis. *Infect Dis Clin N Am* 2002;**16**:377–92.
- 12 Lisby G, Gutschik E, Durack DT. Molecular methods for diagnosis of infective endocarditis. *Infect Dis Clin North Am* 2002;**16**:393–412.
- 13 Millar BC, Moore JE, Mallon P, *et al*. Molecular diagnosis of infective endocarditis—a new Duke's criterion. *Scand J Infect Dis* 2001;**33**:673–80.
- 14 Moore JE, Millar BC, Yongmin X, *et al*. A rapid molecular assay for the detection of antibiotic resistance determinants in cause of infective endocarditis. *J Appl Microbiol* 2001;**90**:719–26.
- 15 Grijalva M, Horvath R, Dendis M, *et al*. Molecular diagnosis of culture negative infective endocarditis: clinical validation in a group of surgically treated patients. *Heart* 2003;**89**:263–8.
- 16 Cabell CH, Abrutyn E. Progress toward a global understanding of infective endocarditis. Early lessons from the International Collaboration on Endocarditis investigation. *Infect Dis Clin North Am* 2002;**16**:255–72.