Prophylaxis and treatment of infective endocarditis in adults: a concise guide

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ABSTRACT – Infective endocarditis (IE) is a life-threatening disease with substantial morbidity and mortality which affects individuals with underlying structural cardiac defects who develop bacteraemia, often as a result of dental, gastrointestinal, genitourinary, respiratory or cardiac invasive/surgical procedures. Prompt recognition of the clinical diagnosis by a wide variety of medical personnel, early involvement of specialist cardiologists, cardiac surgeon and a microbiologist, and prompt treatment with the most appropriate antimicrobial agents offer the greatest chance of improving the outcome for these patients. The guidance given here to clinicians involved in the management of patients with IE briefly covers diagnosis, antibiotic prophylaxis, medical treatment and the indications for surgery.

KEY WORDS: antibiotics, guidelines, infective endocarditis, prophylaxis, surgery

Background

Infective endocarditis (IE) is associated with substantial morbidity and mortality, despite improved techniques to aid diagnosis and modern antibiotics and surgical therapies.[1] It affects individuals with structural cardiac defects who develop bacteraemia as a result of dental, gastrointestinal, genitourinary, respiratory or cardiac invasive/surgical procedures.[2] Most organ systems can be involved and the fact that IE may present to doctors in a variety of specialties means that they must be made aware of IE as a potential diagnosis warranting prompt specialist investigation and treatment. Guidelines for diagnosis and treatment are therefore important and worthy of widespread dissemination, such as those produced by the European Society of Cardiology: www.escardio.org/knowledge/guidelines/Guidelines_Infective_Endocarditis.htm

Symptoms and diagnosis

When to suspect infective endocarditis

Infective endocarditis should be suspected in ill patients with known cardiac disease or new cardiac murmurs, especially if there is a history of recent dental, invasive diagnostic or surgical treatment and/or signs of embolic or vasculitic complications.

Clinical features

- *Systemic features*: high remitting pyrexia, rigors, anorexia, weight loss, arthralgia and fatigue.[3]
- *Cardiac manifestations*: new or worsening cardiac murmurs – typically due to valvular regurgitation; or the development of cardiac failure. Abscesses of the heart and fistulous connections between cardiac structures are serious complications.[4]
- *Extracardiac manifestations* consist of *embolic* as well as *vasculitic* phenomena.[5] All major vessels may be the recipient of infected emboli from valve vegetations. Renal, splenic and neurological complications may be particularly serious. Right-sided IE results in pulmonary infarcts and abscesses and is often associated with iv drug abuse, infected pacemakers or central iv lines.[6] Culture-negative IE, including fungal IE, often have specific clinical features.[7,8]
- *The Duke criteria* form the basis of the diagnosis of which blood cultures, echocardiography and sometimes serology are most important.[9,10]

Bacteriology

The majority of native valve IE and of late prosthetic valve endocarditis (PVE) is caused by viridans streptococci (50–70%), *Staphylococcus aureus* (25%) and enterococci (10%). In early PVE, *S. epidermidis* and *S. aureus* are the commonest organisms. Gram-positive and Gram-negative bacilli, the HACEK group of organisms (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella* and *Kingella* species) and fungi are less common but serious causes of IE.

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Box 1. Guideline development process. These guidelines were developed in accordance with the principles laid down by the AGREE (Appraisal of Guidelines for REsearch and Evaluation Instrument) Collaboration (www.agreecollaboration.org/). The guidelines are presented in more detail, with a full reference list, on the Royal College of Physicians (RCP) website: www.rcplondon.ac.uk. An extensive referenced document is also available on the British Cardiac Society's website: www.bcs.com

SCOPE AND PURPOSE	
Overall objective of the guidelines	To provide practical advice on the diagnosis, prevention and treatment of IE in adults.
The patient group covered	• Individuals at risk of developing IE, eg those with congenital heart disease, valvular heart disease, prosthetic heart valves, previous IE or IV drug abuse. • Individuals presenting with the symptoms/signs of IE (eg pyrexia, new or changing heart murmurs, positive blood cultures/serology or evidence of vegetations) who have recently undergone a dental, invasive diagnostic or therapeutic procedure or surgery.
Target audience:	• Health professionals who are responsible for treating patients with cardiac disease, or undertaking procedures in those at increased risk of developing IE. • Clinicians likely to be involved in its first presentation, who should be alerted to the possibility of this life-threatening condition.
Clinical areas covered:	• How does IE present clinically? • What are the diagnostic criteria? • How can IE be prevented? • Once diagnosed, how do we treat IE medically? • What are the indications for cardiac surgery?
STAKEHOLDER INVOLVEMENT	
Guideline Advisory Group	A multidisciplinary group of clinicians with patient representation (for full list, see end of article).
Funding	Development of the guidelines was supported by the British Cardiac Society (BCS).
Conflicts of interest	No conflicts of interest existed and the writing group had full editorial independence.
RIGOUR OF DEVELOPMENT	
Evidence gathering	The recommendations reflect an extensive review of the literature (Medline and PubMed 1964–2003) and the personal knowledge and experience of the members of the Guideline Advisory Group.
Links between evidence and recommendations	The strength of evidence and the recommendations drawn from it were classified according to the definitions used by the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk). The recommendations were graded independently by four reviewers (see end of article). *Given the lack of controlled trial data from which to draw, the guidelines reflect expert consensus opinion, supported by published reports where available.*
Piloting and peer review	The guidelines were reviewed by two senior UK cardiologists, both members of the BCS.
IMPLEMENTATION	
Tools for application	No specific audit tools have been developed so far.
Plans for update	The guidelines are due for review in 2007 by the Endocarditis Working Group of the BCS.

Table 1. Patients considered to be at moderate or high risk for developing IE.[a]

High risk
Previous IE
Prosthetic heart valves
Mitral valve prolapse with mitral regurgitation or thickened valve leaflets[b]
Complex congenital heart disease
Surgically constructed systemic pulmonary shunts or conduits
Moderate risk
Acquired valvular heart disease, eg rheumatic valve disease
Non-cyanotic congenital cardiac defects, eg patent ductus arteriosus, coarctation of aorta, ventricular septal defect, primum atrial septal defect, bicuspid aortic valve
Other structural cardiac abnormalities, eg hypertrophic obstructive cardiomyopathy, aortic root replacement

[a] Antibiotic prophylaxis is recommended for up to 12 months after atrial septal defect/patent foramen ovale/patent ductus arteriosus catheter-based closure procedures.
[b] Mitral regurgitation should be obvious clinically or deemed to be more than physiological on Doppler echocardiography.
NB: If there is uncertainty as to the nature of the heart murmur and the need for prophylaxis, an opinion from a cardiologist should be sought. In an emergency or when it is difficult to obtain specific advice, then prophylaxis should be given prior to dental or surgical treatment.

Box 2. Guidelines on infective endocarditis: prophylaxis, diagnosis and treatment.

Recommendation	Grade
Prophylaxis	
In order to prevent IE, prophylactic antibiotic treatment is recommended prior to dental or other 'surgical' procedures for those at moderate or high risk of developing IE, should bacteraemia be induced (Table 1). A list of dental and 'surgical' procedures requiring antibiotic prophylaxis is provided in Appendix 1, available in the more detailed guidelines on www.rcplondon.ac.uk	
1 Patients should be informed of their risk of IE and the need for antibiotic prophylaxis, and be told to inform any doctor or dentist who is responsible for providing care. They should be given a card to carry indicating the type of cardiac lesion, the risk and how to avoid IE.[11–14]	C
2 Patients at moderate-risk or high-risk of IE should be given antibiotic prophylaxis with appropriate antibiotics based upon the type of dental or surgical procedure being performed (Table 2).[11,12,15–18]	C
Diagnosis	
When IE is suspected, the following recommendations should be followed to establish the presence or absence of the Duke criteria (Table 3).	
3 Admit the patient to hospital for full and careful investigation, including: • *blood cultures*, • recording of *temperatures*, • haematological and biochemical investigation, • ECG, chest X-ray and • *comprehensive transthoracic echocardiography* (TTE).[3,9,19,20]	C
4 Take three sets of blood cultures at intervals of >1 hour within the first 24 hours when clinical evidence suggests the diagnosis is highly likely in a sick patient.[18,21–24]	D
5 If the patient is not acutely ill or when the diagnosis is not obvious clinically, six sets of blood cultures should be taken within the first 24–48 hours.[21–23]	D
6 If the diagnosis is confirmed by blood culture, the patient should be referred to a cardiologist.[25–28]	D
7 A microbiologist should be involved from the outset.*[24]	
8 Transoesophageal echocardiography (TOE) should be: • performed if TTE is suboptimal, to obtain further information on the size, site or mobility of vegetations, abscess or fistula formation, or valve perforation etc • performed in all patients with PVE.[29–39]	B
9 Cultures which are negative for the commoner organisms (see above) (5–10%), should be closely scrutinised for unusual and slow-growing microorganisms and fungi.[19,40–43]	D
10 Serological tests for *Coxiella burnetii*, *Bartonella* spp and *Chlamydia* spp should be performed if the diagnosis is still suspected and there is still no growth after 7 days in blood cultures.[44–46]	D
11 Microscopy and culture of any excised tissue is essential. Molecular assays for specific gene targets and universal loci for bacteria and fungi are being developed.[46–50]	D

Recommendation	Grade
Treatment	
12 Once the diagnosis is established, treatment should be commenced according to the guidelines or with alternative antibiotics if microbiological tests suggest that more appropriate agents are suitable (Table 4).[11,12,51–54]	D
13 *In a sick patient,* antibiotic treatment should be commenced immediately after blood cultures have been collected and the regimen adjusted once the microbiological data are available. The initial antibiotics of choice depend on the most likely suspected organism based upon the particular clinical presentation, but should cover Gram-positive and Gram-negative organisms.[11,12,51–54]	D
14 Generally, prolonged iv antibiotic therapy is necessary (4–6 weeks), administered via a large central vein. Only the most penicillin-sensitive streptococci should be considered for treatment with shorter courses of penicillin.[11,12,51–54]	D
15 More unusual organisms, eg nutritionally variant streptococci, HACEK group and fungi, demand special regimens, and help should be sought from a microbiologist.[11,12,51–54]	D
16 Patients with a history of penicillin allergy or who develop penicillin allergy should be treated with (or changed to) vancomycin or teicoplanin, and gentamicin or other appropriate antibiotics.[11,12,51–55]	D
Follow-up	
7 Patients receiving treatment for IE need to be regularly examined by an expert team for early detection of complications, relapses or recurrence.[56]	D
18 Examination should include detailed cardiac assessment for new or changing murmurs, careful observation for embolic or immunological complications, and *repeat echocardiography*.[57-59]	D
Surgery	
19 Surgery is indicated in patients with severe valvular incompetence, annular or aortic abscess, with infections resistant to antibiotics and with fungal IE. Large, mobile vegetations, recurrent emboli after antibiotic therapy and PVE are indications for surgery.[60–66]	D
20 In haemodynamically stable patients, early consultation with a cardiac surgeon is recommended in case surgery is suddenly required.[67–72]	D
21 Patients with life-threatening congestive heart failure, pulmonary oedema or cardiogenic shock due to treatable valvular disease should undergo emergency cardiac surgery, if the patient has reasonable prospects of recovery and a satisfactory quality of life after surgery.[61,62,68–75]	D

*No specific evidence to support statement but a good practice point.

Table 2. Prophylactic antibiotic regimens.

Clinical situation	Drug	Regimen
Prophylactic antibiotic regimens for dental, oral, respiratory tract or oesophageal procedures		
High-risk and moderate-risk patients including patients with prosthetic heart valves*	Amoxicillin	3 g oral 1h pre-procedure or 2 g iv <30 min pre-procedure[a]
If allergic to penicillin[b]	Clindamycin[c]	600 mg oral 1h pre-procedure or 300 mg iv <30 min pre-procedure[d] then oral or iv clindamycin 150 mg 6 h later
Patients with previous infective endocarditis[e]	Amoxicillin + gentamicin	2 g iv <30 min pre-procedure and 1g iv or orally 6 h post procedure 1.5 mg/kg iv <30 min pre-procedure[a]
If allergic to penicillin[b]	Vancomycin + gentamicin or Clindamycin	1g iv over 2 h, 1-2 h pre-procedure 1.5 mg/kg iv <30 min pre-procedure[a] 300 mg iv <30 min pre-procedure[d] then iv clindamycin 150 mg 6 h later
Prophylactic antibiotic regimens for genitourinary or gastrointestinal procedures		
High-risk and moderate-risk patients	Ampicillin or amoxicillin + gentamicin	2 g iv – <30 min pre-procedure[a] and 1g iv or orally 6 h post procedure 1.5 mg/kg iv <30 min pre-procedure[a]
If allergic to penicillin[b]	Vancomycin + gentamicin	1 g iv over 2 h, 1-2 h pre-procedure 1.5 mg/kg iv <30 min pre-procedure[a]

*Particular care should be taken to ensure that patients with prosthetic heart valves are protected by prophylactic antibiotics, since the consequences of infective endocarditis are particularly serious. It is essential that they receive prophylactic antibiotics orally at least 1 hour before the procedure. If not, they should be given iv antibiotics immediately before the procedure or the procedure should be postponed.
[a] *For those undergoing general anaesthetic*, iv antibiotics should be given either on induction or within 30 min before starting the procedure; oral amoxicillin (3 g) should be given 4 hours before induction. Where oral antibiotics are not ideal and in whom iv access is difficult or impossible, eg iv drug abusers, im clindamycin 600 mg 1 hour pre-op or im teicoplanin (2 mg/kg) 1 hour pre-op may be alternative treatments.
[b] or received penicillin within last 4 weeks.
[c] Azithromycin 500 mg, as an oral suspension, given 1 hour before the procedure may be an alternative if dysphagia is a problem.
[d] Clindamycin to be infused over 10-15 min.
[e] These patients are considered to be at highest risk of IE.

Table 3. Duke criteria for diagnosis of infective endocarditis and definitions used in the modified diagnostic criteria.

Definite infective endocarditis

Pathological criteria

- Microorganisms: demonstrated by culture or histology in a vegetation that has embolised, or in an intracardiac abscess, or
- Pathologic lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis

Clinical criteria (see below)

- 2 major criteria, or
- 1 major and 3 minor criteria, or
- 5 minor criteria

Definitions

Major criteria

1 Positive blood culture for IE – from at least two separate blood cultures drawn 12 hours apart, or all of three blood cultures, or a majority of four blood cultures with first and last drawn 12 hours apart.
2 Evidence of endocardial involvement, eg echocardiogram showing mobile intracardiac mass on valve or supporting structures, abscess, new partial dehiscence of prosthetic valve or new valve regurgitation.
3 Clinical evidence of new valvular regurgitation.
4 Positive serology for Q-fever or other causes of culture-negative IE, eg *Bartonella*, *Chlamydia psittaci*.
5 Identification of a microorganism from blood culture or excised tissue using molecular biology methods.

Minor criteria

1 Predisposition: predisposing heart condition or iv drug abuse.
2 Fever: >38.0°C.
3 Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages, Janeway lesions, *newly diagnosed clubbing, splinter haemorrhages, splenomegaly.**
4 Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, +ve rheumatoid factor, *high ESR (>1.5 times upper limit of normal), high C-reactive protein level (>100 mg/l).**
5 Microbiologic evidence: positive blood culture, but not meeting major criteria as defined above.

* Additional modifications to the Duke criteria, shown in italic, appear to improve diagnostic sensitivity whilst retaining specificity. ESR = erythrocyte sedimentation rate.

Table 4. Treatment of infective endocarditis.

Antibiotic	Dose/route	Duration
Treatment of IE due to penicillin-sensitive viridans streptococci and *S. bovis* (MIC <0.1 mg/l) in adults		
Benzylpenicillin	7.2–12 g iv/24 h in 4–6 divided doses	4–6 weeks[a]
+ gentamicin[b]	3–5 mg/kg iv daily in 2-3 divided doses (max 240 mg/day)	2 weeks
For patients allergic to penicillin		
Vancomycin	30 mg/kg iv in 24 h in 2 divided doses (infused over 2 h)	4 weeks
+ gentamicin[b]	3–5 mg/kg iv daily in 2–3 divided doses (max 240 mg/day)	2 weeks
Treatment of IE due to penicillin-relative resistant viridans streptococci and *S. bovis* (MIC >0.1 mg/l) in adults		
Benzylpenicillin	12–14 g iv/24 h in 4–6 divided doses	4–6 weeks[a]
+ gentamicin[b]	3–5 mg/kg iv daily in 2–3 divided doses	2 weeks[a]
For patients allergic to penicillin, see above.		
Treatment of IE due to staphylococci on native valve		
Penicillin-sensitive (non-B-lactamase producers)		
Benzylpenicillin	12–14 g iv/24 h in 4–6 divided doses	6 weeks
+ gentamicin[b]	3–5 mg/kg iv daily in 2–3 divided doses	3–5 days
Methicillin-sensitive staphylococci (B-lactamase producer)		
Flucloxacillin	8–12 g iv/24 h in 4 divided doses	6 weeks
+ gentamicin[b]	3–5 mg/kg iv daily in 2–3 divided doses (max 240 mg/day)	3–5 days
Methicillin-resistant staphylococci[c]		
Vancomycin	30 mg/kg iv in 24 h in 2 divided doses (infused over 2 h)	6 weeks
+ gentamicin[b]	3–5 mg/kg iv daily in 2–3 divided doses	3–5 days
For patients allergic to penicillin, see above.		
Treatment of IE due to enterococci in adults		
Gentamicin-sensitive or low-level resistant organism (MIC <500 mg/l)		
Benzylpenicillin	10–12 g iv/24 h in 4–6 divided doses	4–6 weeks
or ampicillin or amoxicillin	12 g iv/24 h in 4–6 divided doses	4–6 weeks[d]
+ gentamicin[e,b]	3–5 mg/kg iv daily in 2–3 divided doses (max 240 mg/day)	4–6 weeks[d]
For those allergic to penicillin, see above.		

[a]Duration adjusted according to clinical response and advice from microbiologist.
[b]Gentamicin blood levels must be checked regularly during this period.
[c]Linezolid or Synercid[R] may be used in methicillin-resistant *Staphylococcus aureus* (MRSA).
[d]Six weeks therapy recommended for patients with symptoms for >3 months.
[e]For *strains highly resistant to gentamicin (MIC >500 mg/l),* ampicillin or amoxicillin 12 g iv per day in six divided doses or as a continuous infusion for 6 weeks is advisable, a microbiologist's opinion sought, and surgery considered early for antibiotic-treatment failure. For *ampicillin-resistant strains*, and for patients allergic to penicillin, a vancomycin + gentamicin regimen may be effective.
Gentamicin and vancomycin dose will need adjustment in renal impairment.
MIC = minimum inhibitory concentration.

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A more detailed version of these guidelines, including a full reference list, is available on the RCP website: www.rcplondon.ac.uk