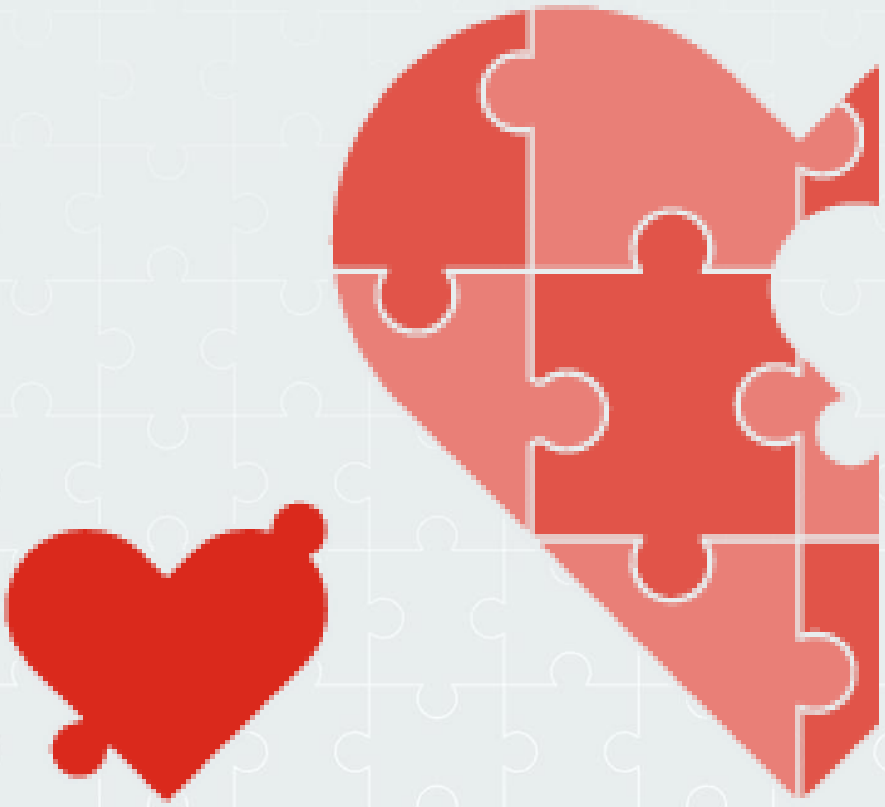
NHS
East Midlands
Congenital Heart Network

Network Guideline

Infective Endocarditis

January 2024



Governance

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The interpretation and application of this guideline remains the responsibility of the individual clinician. If in doubt contact a senior colleague or expert.

Introduction

Infective Endocarditis is a rare condition but has significant morbidity and mortality. Patients at risk of infective endocarditis are more vulnerable to 'cardiac seeding' of circulating bacteria and care should be taken if they present with a fever with no readily discernible cause.

Annual incidence is reported between 0.05 and 0.12 per 1000 paediatric admissions. Unfortunately, around 5% of these children will die despite treatment, and for some infections the risk is higher.

This guideline covers the EMCHN approach to prophylaxis, investigation of possible cases and early management in network centres. It does not cover tertiary and surgical management, nor does it cover specialist microbiological management once a diagnosis is confirmed and organism is known. Once a diagnosis is confirmed management must be carefully tailored to individual patients based on their background, cardiac status and culture results.

Prophylaxis against infective endocarditis

Prophylactic antibiotics against infective endocarditis are required for a selected group of patients undergoing a small group of procedures where there is increased risk of bacteraemia.

Antibiotic prophylaxis for patients with congenital heart disease was previously more widely used. Following NICE (2008) and Cochrane (2013) reviews this was rationalised removing all requirement for antibiotics. A further update in 2015 reinstated some prophylaxis. The EMCHN follows the guidelines published by the Scottish Dental Clinical Effectiveness Programme, these are endorsed by the BCCA, and follow the European Society of Cardiology Guidance.

Patients in whom the risk of infective endocarditis is high are listed below, these patients should receive prophylaxis or prior discussion with their named Cardiologist.

Patients at risk – give prophylaxis or discuss with named cardiologist when time permits:

1. Patients with any type of cyanotic heart disease with persisting cyanosis
2. Patients with repaired heart disease within 6 months of the repair
3. Patients with repaired heart disease where a residual shunt or regurgitation remains
4. Patients with prosthetic valvular material used to repair or replace a valve
5. Patients with a previous episode of infective endocarditis

Standard practice for all Patients with Congenital heart disease:

1. Provide and document advice on infective endocarditis including an explanation of why antibiotic prophylaxis is not routinely recommended
2. Provide and document advice on the symptoms of infective endocarditis in the post-operative period and when to seek medical help.
3. Chlorhexidine mouthwash should not routinely be given
4. Usual antibiotic therapy for any given procedure should be followed.
5. If the surgery is for suspected infection e.g. abscess, then seek microbial advice and select antibiotics that cover for dominant endocarditis pathogens (strep and staph).

Risk factors for infective endocarditis

The following patients are at significantly increased risk of infective endocarditis. Any patient with a risk factor presenting with acute or sub-acute fever and no clear source should undergo senior review and consideration for investigation of infective endocarditis

1. **Valvular heart disease** (stenosis, regurgitation or valve replacement) *
2. **Structural congenital heart disease**, including surgically corrected or palliated **
3. **Hypertrophic cardiomyopathy**
4. **Previous infective endocarditis**
5. **Indwelling Central Venous Line**

* Patients with turbulent flow around valvular apparatus particularly prosthetic or mechanical valves have some of the highest risk and should be managed with care.

** Isolated atrial septal defect, fully repaired ventricular septal defect or fully repaired patent ductus arteriosus, and closure devices more than 6 months post insertion are not considered to be at significantly increased risk.

Patients with residual right to left shunts (cyanotic congenital heart disease) are at particular risk of complications due to the risk of paradoxical embolization.

Clinical Presentation

Clinical presentation is rarely with sepsis and emboli. Subtle sub-acute infection remains the most common presentation and is easily over-looked with symptoms typical of viral infections. Persistent low-grade fever, lethargy and fatigue should be warning signs in all cases of elevated risk. These are easily missed or dismissed and consequently the mortality for this disease remains stubbornly high at 5%.

Sub-acute presentation – Non-specific fever and malaise

Typical presentation is with indolent and prolonged low-grade fevers. There may be additional symptoms of malaise, fatigue, myalgia and arthralgia, weight loss and rigors. These non-specific symptoms should raise concern in any patient with risk factors, immunosuppression or indwelling lines / prosthetic material.

Acute presentation – Sepsis or severe heart failure

Sepsis with or without embolic phenomenon. This typically has a short course with high fevers and an acutely unwell child. In these children Staph Aureus or Streptococcus are the likely organisms. Embolic phenomenon are rare during early disease and in right sided lesions e.g. pulmonary stenosis where the emboli reside in the lungs.

Rarely, the presentation may be with fulminant heart failure and acute cardiovascular collapse.

Asymptomatic presentation – Recurrent positive blood cultures

Recurrent 'contaminant' blood cultures with an identical organism in at least 3 sets of separately drawn blood cultures. This is particularly important in those who are immunocompromised, those with central lines or neonatal patients. The incidence of neonatal infective endocarditis has increased with fewer than one third having structural cardiac disease.

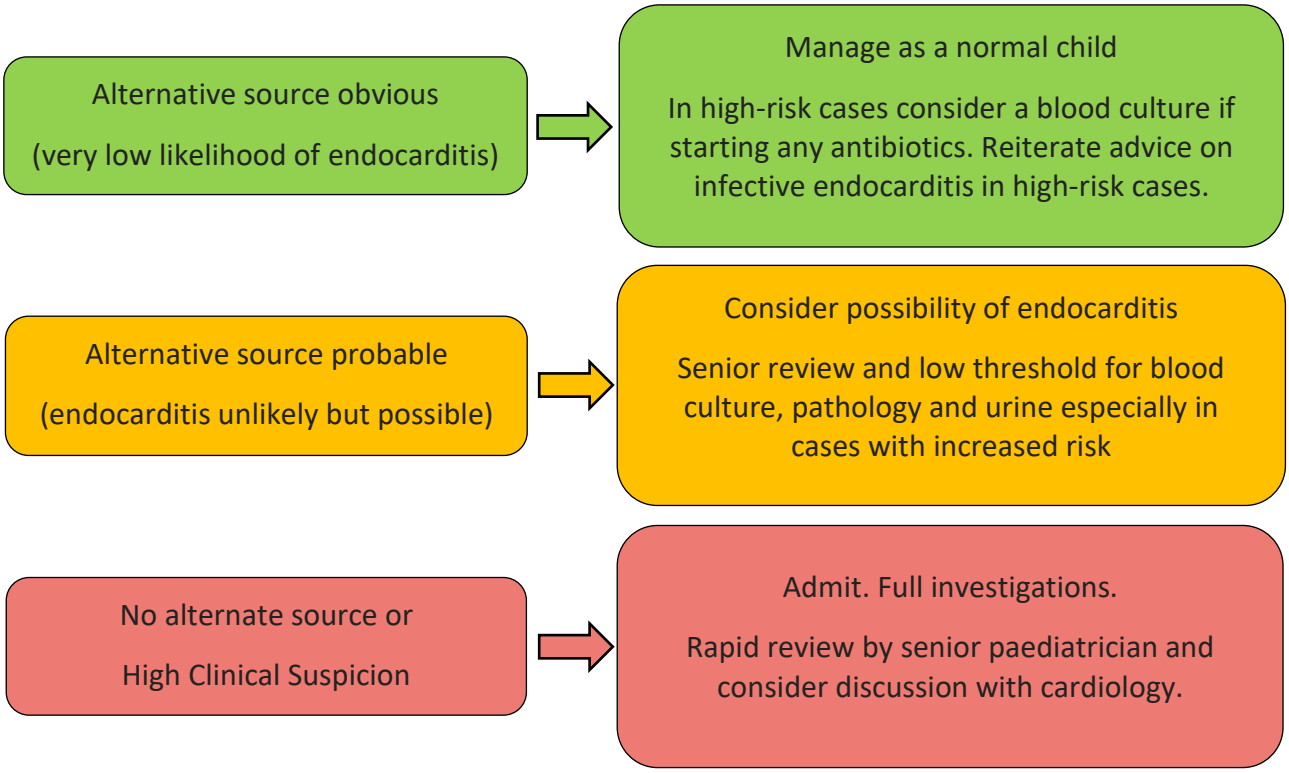
Culture negative – Immunosuppressed patients often with central lines

There is a growing recognised entity of culture negative infective endocarditis typically seen in those with immunosuppression including preterm infants. Central lines or indwelling catheters may be present but may have simply provided the original source. Persistent elevation of inflammatory markers and low-grade fever may be the only noted signs. Discussion with paediatric cardiology and microbiology in this unusual case is recommended.

Investigation of possible cases

The key role of the local paediatrician is to determine whether an alternative likely source for the symptoms is found and if not attempt to isolate a pathogen to support the clinical diagnosis. Isolation enables an effective, targeted antibiotic regime rather than a short broad-spectrum course in which the recurrence risk is high.

Children presenting with fever or sub-acute symptoms with risk factors for endocarditis



Blood Cultures

Blood cultures are the key criteria for diagnosis. A minimum of 2 cultures from separate sites are required. Culture volume must be a minimum of 1ml, preferably 3ml as yield can be low. Strict non-touch technique to avoid contaminants is required. **Treatment should not be started without positive results unless the patient is acutely septic.** When immediate treatment is necessary, at least two further cultures from more than one site should be obtained within an hour of decision to treat.

If there is no growth at 48 hours and suspicion remains high, two more cultures should be taken.

Echocardiogram

Clinicians should be aware that transthoracic echo has relatively poor sensitivity with the potential for false negative results. An echocardiogram is not required in children with a single positive blood culture (< 5% sensitive) unless the fever and bacteraemia persist despite adequate antibiotic treatment. For larger / older patients transoesophageal echo has better sensitivity.

Echo criteria:

1. 1 positive culture without source for Staph Aureus, Strep Viridans or Coxiella Burnetii
2. 2 positive cultures without source for Enterococcus or HACEK organisms*
3. 3 positive cultures at least 12hrs apart for other bacteria e.g. skin contaminants
4. Proven prolonged fever of unknown origin and a new murmur or high clinical suspicion
5. Suspicion of culture negative or fungal endocarditis after discussion with cardiologist
6. Stigmata or evidence of peripheral septic embolism

▪ Positive cultures must not come from same draw on same site e.g. red waste and sample from the same line count as a single sample

* HACEK organisms: Strep Gallolyticus, Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae

Blood Pathology & Urine Testing

Blood tests and Urine dip are helpful in determining infection and haemolysis:

1. Full blood count – normocytic anaemia, neutropaenia and commonly thrombocytopaenia
2. Renal function – immune complex glomerulonephritis is rare
3. Bilirubin & Haptoglobin – low grade haemolysis is common in infective endocarditis
4. Acute Phase Reactants (ESR and CRP) – often persistently elevated
5. Rheumatoid Factor – suggestive of chronic inflammation and part of Duke criteria
6. Urine Dip – review for evidence of haemolysis (blood) or alternative diagnosis (nitrates)

ECG

Pathological changes can occur on ECG. These include Ectopics, P-R interval prolongation, AV nodal block, complete heart block or new bundle branch block. ECG changes suggest significant pathology and require urgent referral.

Diagnosis (Modified Duke Criteria):

Diagnosis is based on the modified duke criteria separated into major and minor features. A positive diagnosis requires either 2 major OR 1 major and 3 minor OR all five minor criteria.

Major Criteria

1. **Positive Blood Culture -**

   Typical infective endocarditis organisms isolated from **2 or more blood cultures** in the absence of a focus or 2 positive cultures taken 12 hours apart. Organisms are Viridans strep, Staph aureus, Enterococci, HACEK organisms (Haemophilus, Aggregatibacter, Cardiobacterium, Elkenella, Kingella). Coxiella is the exception; this virulent organism only needs detection in 1 blood culture. **Note that Strep Viridans, Staph Aureus and Enterococci are regarded as the 'Big 3' due to the dominance in proven endocarditis**.

2. **Endocardial Involvement -**

   New regurgitant murmur or **positive echocardiogram** (vegetations, intracardiac mass, periannular abscess, dehiscence of prosthetic valve)

Minor Criteria

1. **Risk** - Predisposing risk factors as per previous list or intravenous drug use
2. **Fever** - Persistent fever > 38.0
3. **Vascular** - emboli, pulmonary infarcts, janeway lesions, conjunctival haemorrhage
4. **Immune** - glomerulonephritis, Osler nodes, Roth's Spots, Rheumatoid Factor +ve
5. **Microbiological** - Positive culture not achieving major or serological evidence of infection

Note:

Roth Spots – White centred retinal haemorrhages, only visible on fundoscopy

Osler Nodes – Painful. New red-purple small lumps typically on fingers or toes

Janeway Lesions – Painless. Flat dark red or black macules on soles and palms.

Initial Management

Infective endocarditis has complex decision making involving paediatric cardiologist, microbiologists and cardiothoracic surgeons. This is led by and generally delivered in the regional specialist centre. Infective endocarditis carries a high mortality and most patients should be transferred to the regional centre even in those who appear quite well.

Acute treatment prior to culture results

In the **unusual case of an acutely septic child** with embolic phenomenon and no culture results then empirical therapy may be warranted. The following approach is suggested:

1. **Treat urgently as sepsis** – Where criteria are met use your local protocol to treat urgently as sepsis. Antibiotic regimes will typically include two agents, a broad spectrum antibiotic such as a 3rd generation cephalosporin together with gentamicin.

2. **Take further blood cultures –** Take a minimum of 3 sets of blood cultures at 30 minute intervals when starting empiric antibiotics in high risk or suspected cases. In septic cases do not delay antibiotics but ensure subsequent adequate cultures from different sites.

3. **Discuss with on-call consultant for microbiology** – Commence treatment urgently and then discuss with the on-call microbiologist in cases of high suspicion to establish whether any known pathogens or broader cover e.g. vancomycin is required

Please note that guidance from the European Society of Cardiology currently recommends that empirical treatment use Vancomycin and Gentamicin but rates of MRSA and other resistant bacteria in the UK and particularly in Children are low. This should therefore only be followed on advice of the consultant microbiologist.

Definitive Anti-microbiological treatment:

Culture specific drugs and durations of treatment are extensively covered in the both the European Society and American Heart guidance and so not replicated here. The final choice of drug is made jointly with the responsible cardiologist and microbiology consultant. Doses above that of the BNFc may often be required and these doses should be documented in the notes and on the drug card.

Antibiotics are dosed multiple times per day resulting in potentially lengthy hospitals stays. Transition to once daily therapy (e.g. Teicoplanin or Ceftriaxone) should only be considered after discussion with a cardiologist and when stability is established. Long-term vascular access should be considered only once therapy is fully established to avoid line colonisation.

The following important treatment points should be noted:

1. **Length** - A prolonged course of therapy (at least 4 weeks and often 6–8 weeks) has been the recommended practice (Class I; Level of Evidence B).
2. **Bactericidal** – bactericidal rather than bacteriostatic antibiotic drugs should be chosen whenever possible (Class I; Level of Evidence A). This recommendation is based on past reports of treatment failures and relapses when using only bacteriostatic agents.
3. **Avoid Intramuscular** - In infants and children, one should use intravenous antibiotic drugs rather than intramuscular agents (Class I; Level of Evidence C).
4. **Outpatient (home) intravenous treatment of endocarditis** – this may be considered in selected patients after initial treatment of at least two weeks in the hospital and confirmation that these patients are hemodynamically stable, afebrile, have negative blood cultures, and are not at high risk for complications (ie, not of young age and do not have a fungal pathogen) (Class IIb; Level of Evidence C).
5. **Access to acute care** - Frequent home monitoring by a community nurse who to assess wellness, adherence to drug therapy, absence of complications, and absence of drug toxicity is part of the plan. It is reasonable that such a standard would include prompt (minutes to hours) access to medical and surgical care and cardiac follow-up should complications develop (Class IIa; Level of Evidence C).
6. **Surveillance on completion** - Additional blood cultures performed after completion of antibiotic treatment may be considered but might also result in isolation of a contaminant (Class IIb; Level of Evidence C). The evidence for this is not robust. EMCHC recommend a blood culture of at least 1ml at one week and two weeks post cessation of treatment.

Culture Negative Results

In patients started on antibiotics because of clinical suspicion but with subsequent negative cultures, it is reasonable to withhold antibiotic drugs for ≥48 hours while additional blood cultures are obtained (Class IIa; Level of Evidence C). **The patient should not have respiratory or hemodynamic compromise or change in mental status at the point of cessation of treatment.** This reiterates the importance of confirming the diagnosis at onset.

In patients with risk factors who do not meet the diagnostic criteria but where exclusion of endocarditis remains important then repeat cultures off antibiotics at 48hrs and 5-7 days are recommended. This surveillance can occur at home with appropriate and documented advice.

Further investigation

1. **CT Head -** Patients with confirmed left-sided endocarditis (or right-to-left shunts) should routinely be offered head CT to exclude abscess.
2. **CT Abdomen -** Patients with confirmed left-sided endocarditis (or right-to-left shunts) and additional symptoms such has abdominal pain or haematuria should be considered for abdominal CT to assess for embolic within the viscera (e.g. renal or splenic emboli)
3. **CT Chest -** For patients with right-sided endocarditis (or left-to-right shunts) imaging of the lungs via CT is important to both support the diagnosis and stratify risk. Chest imaging may should haemorrhagic or septic emboli together with lung lesions.

   CT Chest is typically performed without contrast although this may be considered under specialist advice to identify filling defects within the great vessels.
4. **Transoesophageal Echo (TOE) –** Transoesophageal echo has a higher sensitivity than transthoracic echo and should be considered in cases with high clinical suspicion and no vegetations on standard imaging. This is performed at the cardiac centre and involvement of a paediatric cardiologist is required.

Anticoagulation

No international recommendations exist for the initiation of anticoagulation however patients with proven infective endocarditis are at risk of haemorrhagic emboli. There is no evidence that anticoagulation can prevent this and there is evidence of increased risk of haemorrhagic transformation of embolic sites.

Infective endocarditis may also potentiate the effect of Warfarin resulting in a significantly elevated INR. Do not routinely prescribe Vitamin K to correct the INR without first discussing with the oncall consultant for paediatric cardiology and the local haematologist. INR correction is often highly sensitive in these patients and re-anticoagulation can be challenging.

Larger immobile patients should receive appropriate DVT prophylaxis but other anticoagulation should only be after tertiary MDT discussion.

Location of Cardiac Care:

Proven infective endocarditis requires the early input of a paediatric cardiologist and management outside of a tertiary centre is not recommended.

Transfer to a cardiac centre is mandated for any patient with embolic phenomenon, evidence of vegetation or with a known artificial valve and high suspicion of infective endocarditis. During initial treatment these patients should be nursed in a higher dependency environment due to the risk of septic decompensation and emboli to the pulmonary, neurological (stroke), gastrointestinal (NEC) and renal systems.

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