

# ESC Guidelines for the management of infective endocarditis

Diagnosis

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# Clinical features

- The clinical history of IE is highly variable according to the causative microorganism, the presence or absence of pre-existing cardiac disease, the presence or absence of prosthetic valves or cardiac devices and the mode of presentation
- Up to 90% of patients present with fever, often associated with systemic symptoms of chills, poor appetite and weight loss. Heart murmurs are found in up to 85% of patients. Up to 25% of patients have embolic complications at the time of diagnosis. Therefore IE has to be suspected in any patient presenting with fever and embolic phenomena

- **Atypical presentation is common in elderly or immunocompromised patients, in whom fever is less common than in younger individuals. A high index of suspicion and low threshold for investigation are therefore essential in these and other high-risk groups, such as those with CHD or prosthetic valves, to exclude IE or avoid delays in diagnosis**

# Laboratory findings

- Sepsis severity may be indicated by the demonstration of a number of laboratory investigations, including the degree of leucocytosis/leucopenia, the number of immature white cell forms, concentrations of CRP and procalcitonin, ESR and markers of end-organ dysfunction (lactataemia, elevated bilirubin, thrombocytopaenia and changes in serum creatinine concentration); however, none are diagnostic for IE

# Imaging techniques

- Imaging, particularly echocardiography, plays a key role in both the diagnosis and management of IE. Echocardiography is also useful for the prognostic assessment of patients with IE, for its follow-up under therapy and during and after surgery.
- However, the evaluation of patients with IE is no longer limited to conventional echocardiography, but should include several other imaging techniques

- Echocardiography, either transthoracic echocardiography (TTE) or TOE, is the technique of choice for the diagnosis of IE, and plays a key role in the management and monitoring of these patients.
- Echocardiography must be performed as soon as IE is suspected. TOE must be performed in case of negative TTE when there is a high index of suspicion for IE, particularly when TTE is of suboptimal quality.

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref. <sup>c</sup>
<b>A. Diagnosis</b>			
<ul style="list-style-type: none"> <li>TTE is recommended as the first-line imaging modality in suspected IE.</li> </ul>	I	B	64,65
<ul style="list-style-type: none"> <li>TOE is recommended in all patients with clinical suspicion of IE and a negative or non-diagnostic TTE.</li> </ul>	I	B	64, 68–71
<ul style="list-style-type: none"> <li>TOE is recommended in patients with clinical suspicion of IE, when a prosthetic heart valve or an intracardiac device is present.</li> </ul>	I	B	64,71
<ul style="list-style-type: none"> <li>Repeat TTE and /or TOE within 5–7 days is recommended in case of initially negative examination when clinical suspicion of IE remains high.</li> </ul>	I	C	
<ul style="list-style-type: none"> <li>Echocardiography should be considered in <i>Staphylococcus aureus</i> bacteraemia.</li> </ul>	IIa	B	66,67
<ul style="list-style-type: none"> <li>TOE should be considered in patients with suspected IE, even in cases with positive TTE, except in isolated right-sided native valve IE with good quality TTE examination and unequivocal echocardiographic findings.</li> </ul>	IIa	C	
<b>B. Follow-up under medical therapy</b>			
<ul style="list-style-type: none"> <li>TTE and TOE</li> </ul>	I	B	

### **B. Follow-up under medical therapy**

<ul style="list-style-type: none"><li>Repeat TTE and/or TOE are recommended as soon as a new complication of IE is suspected (new murmur, embolism, persisting fever, HF, abscess, atrioventricular block).</li></ul>	I	B	64.72
<ul style="list-style-type: none"><li>Repeat TTE and/or TOE should be considered during follow-up of uncomplicated IE, in order to detect new silent complications and monitor vegetation size. The timing and mode (TTE or TOE) of repeat examination depend on the initial findings, type of microorganism, and initial response to therapy.</li></ul>	IIa	B	64.72

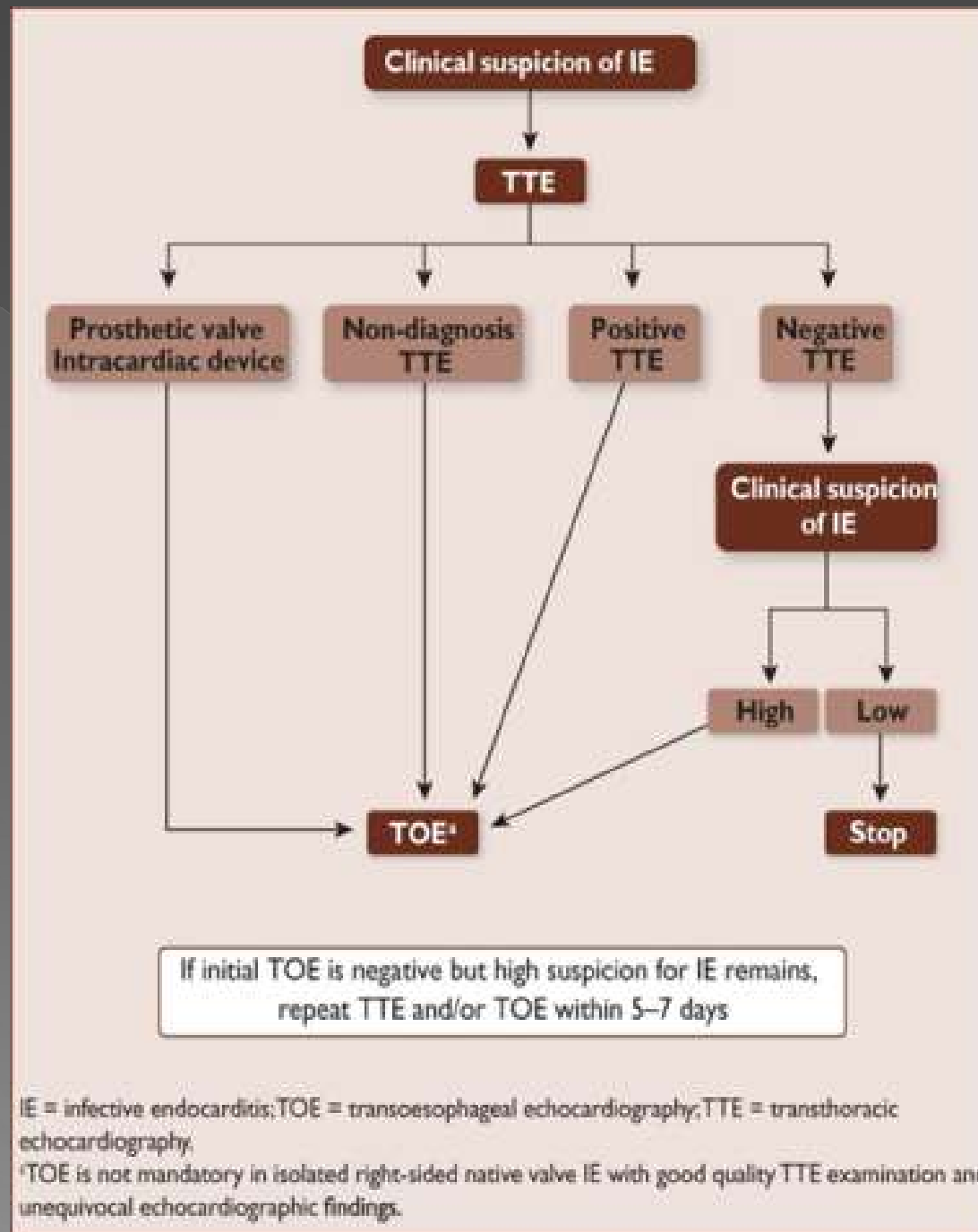
### **C. Intraoperative echocardiography**

<ul style="list-style-type: none"><li>Intraoperative echocardiography is recommended in all cases of IE requiring surgery.</li></ul>	I	B	64.73
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### **D. Following completion of therapy**

<ul style="list-style-type: none"><li>TTE is recommended at completion of antibiotic therapy for evaluation of cardiac and valve morphology and function.</li></ul>	I	C	
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IE = infective endocarditis; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

\*TOE is not mandatory in isolated right-sided native valve IE with good quality TTE examination and unequivocal echocardiographic findings.

- Three echocardiographic findings are major criteria in the diagnosis of IE: vegetation, abscess or pseudoaneurysm and new dehiscence of a prosthetic.
- Nowadays, the sensitivity for the diagnosis of vegetations in native and prosthetic valves is 70% and 50%, respectively, for TTE and 96% and 92%, respectively, for TOE. Specificity has been reported to be around 90% for both TTE and TOE.
- Identification of vegetations may be difficult in the presence of pre-existing valvular lesions (mitral valve prolapse, degenerative calcified lesions), prosthetic valves, small vegetations (< 2–3 mm), recent embolization and in non-vegetant IE.

- In cases with an initially negative examination, repeat TTE/TOE must be performed 5–7 days later if the clinical level of suspicion is still high
- Finally, follow-up echocardiography to monitor complications and response to treatment is mandatory

# Multislice computed tomography

- The potential risks of vegetation embolization and/or haemodynamic decompensation during coronary angiography (when indicated) have led to proposals to consider MSCT coronary angiography as an alternative technique for some patients with endocarditis.

- **MSCT can be used to detect abscesses/pseudoaneurysms with a diagnostic accuracy similar to TOE, and is possibly superior in the provision of information regarding the extent and consequences of any perivalvular extension, including the anatomy of pseudoaneurysms, abscesses and fistulae.**

- In aortic IE, CT may additionally be useful to define the size, anatomy and calcification of the aortic valve, root and ascending aorta, which may be used to inform surgical planning.
- In pulmonary/right-sided endocarditis, CT may reveal concomitant pulmonary disease, including abscesses and infarcts.

- In the evaluation of prosthetic valve dysfunction, one recent study has suggested that MSCT may be equivalent or superior to echocardiography for the demonstration of prostheses-related vegetations, abscesses, pseudoaneurysms and dehiscence. However, large comparative studies between the two techniques are missing, and echocardiography should always be performed first.

# Magnetic resonance imaging

- **Systematic cerebral MRI has an impact on the diagnosis of IE since it adds one minor Duke criterion in patients who have cerebral lesions and no neurological symptoms. In one study, findings of cerebral MRI upgraded the diagnosis of IE in 25% of patients presenting initially with non-definite IE, thereby leading to earlier diagnosis.**



# Microbiological diagnosis

## Blood culture–positive infective endocarditis

- Positive blood cultures remain the cornerstone of diagnosis and provide live bacteria for both identification and susceptibility testing. At least three sets are taken at 30-min intervals, each containing 10 mL of blood, and should be incubated in both aerobic and anaerobic atmospheres. Sampling should be obtained from a peripheral vein rather than from a central venous catheter (because of the risk of contamination and misleading interpretation), using a meticulous sterile technique

- **When a microorganism has been identified, blood cultures should be repeated after 48–72 h to check the effectiveness of treatment.**

## **Blood culture–negative infective endocarditis**

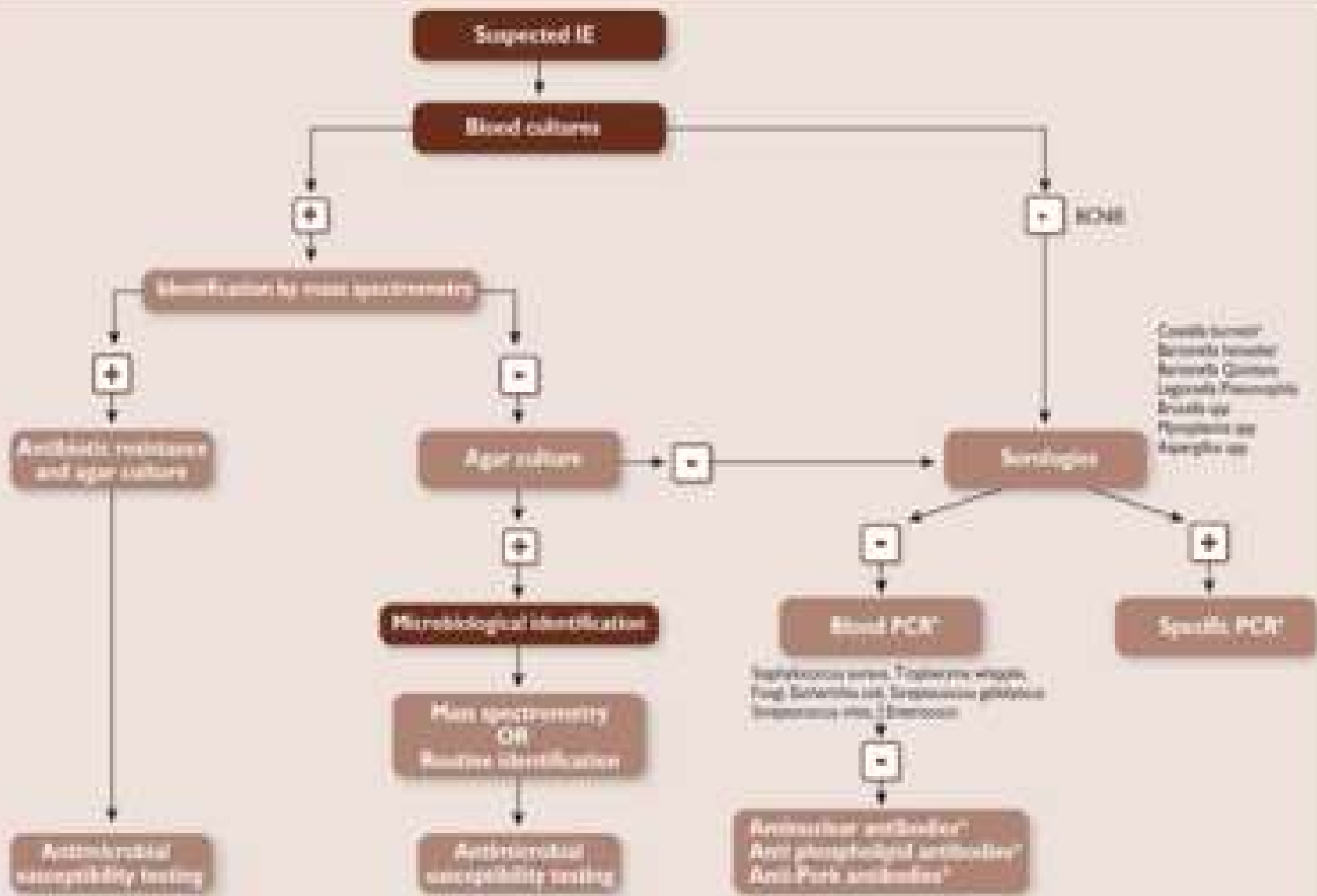
**Blood culture–negative IE (BCNIE) refers to IE in which no causative microorganism can be grown using the usual blood culture methods. BCNIE can occur in up to 31% of all cases of IE and often poses considerable diagnostic and therapeutic dilemmas**

- BCNIE most commonly arises as a consequence of previous antibiotic administration, underlying the need for withdrawing antibiotics and repeating blood cultures in this situation
- BCNIE can be caused by fungi or fastidious bacteria, notably obligatory intracellular bacteria

- When all microbiological assays are negative, the diagnosis of non-infectious endocarditis should systematically be considered and assays for antinuclear antibodies as well as antiphospholipid syndrome {anticardiolipin antibodies [immunoglobulin (Ig)G] and anti- $\beta_2$ -glycoprotein 1 antibodies [IgG and IgM]} should be performed

# Histological diagnosis of infective endocarditis

- Pathological examination of resected valvular tissue or embolic fragments remains the gold standard for the diagnosis of IE. All tissue samples that are excised during the course of the surgical removal of cardiac valves must be collected in a sterile container without fixative or culture medium. The entire sample should be taken to the diagnostic microbiology laboratory for optimal recovery and identification of microorganisms



BCBE = blood culture regime (Water endocarditis) E = infective endocarditis PCR = polymerase chain reaction.  
 \*Qualified microbiological laboratory  
 †Microbiology laboratory

- in 2000, the modified Duke criteria were recommended for diagnostic classification These criteria are based on clinical, echocardiographic and biological findings, as well as the results of blood cultures and serologies



## Definite IE

### Pathological criteria

- Microorganisms demonstrated by culture or on histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
- Pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis

### Clinical criteria

- 2 major criteria; or
- 1 major criterion and 3 minor criteria; or
- 5 minor criteria

## Possible IE

- 1 major criterion and 1 minor criterion; or
- 3 minor criteria

## Rejected IE

- Firm alternate diagnosis; or
- Resolution of symptoms suggesting IE with antibiotic therapy for  $\leq 4$  days; or
- No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for  $\leq 4$  days; or
- Does not meet criteria for possible IE, as above

- When the diagnosis remains only 'possible' or even 'rejected' but with a persisting high level of clinical suspicion, echocardiography and blood culture should be repeated and other imaging techniques should be used either for diagnosis of cardiac involvement or for imaging embolic events (cerebral MRI, whole-body CT and/or PET/CT).
- The results of these new investigations should then be integrated in the ESC 2015 modified diagnostic criteria

**\* The identification of paravalvular lesions by cardiac CT should be considered a major criterion.**

**○ In the setting of the suspicion of endocarditis on a prosthetic valve, abnormal activity around the site of implantation detected by  $^{18}\text{F}$ -FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leucocyte SPECT/CT should be considered a major criterion.**

**○ \* The identification of recent embolic events or infectious aneurysms by imaging only (silent events) should be considered a minor criterion**

### Major criteria

#### 1. Blood cultures positive for IE

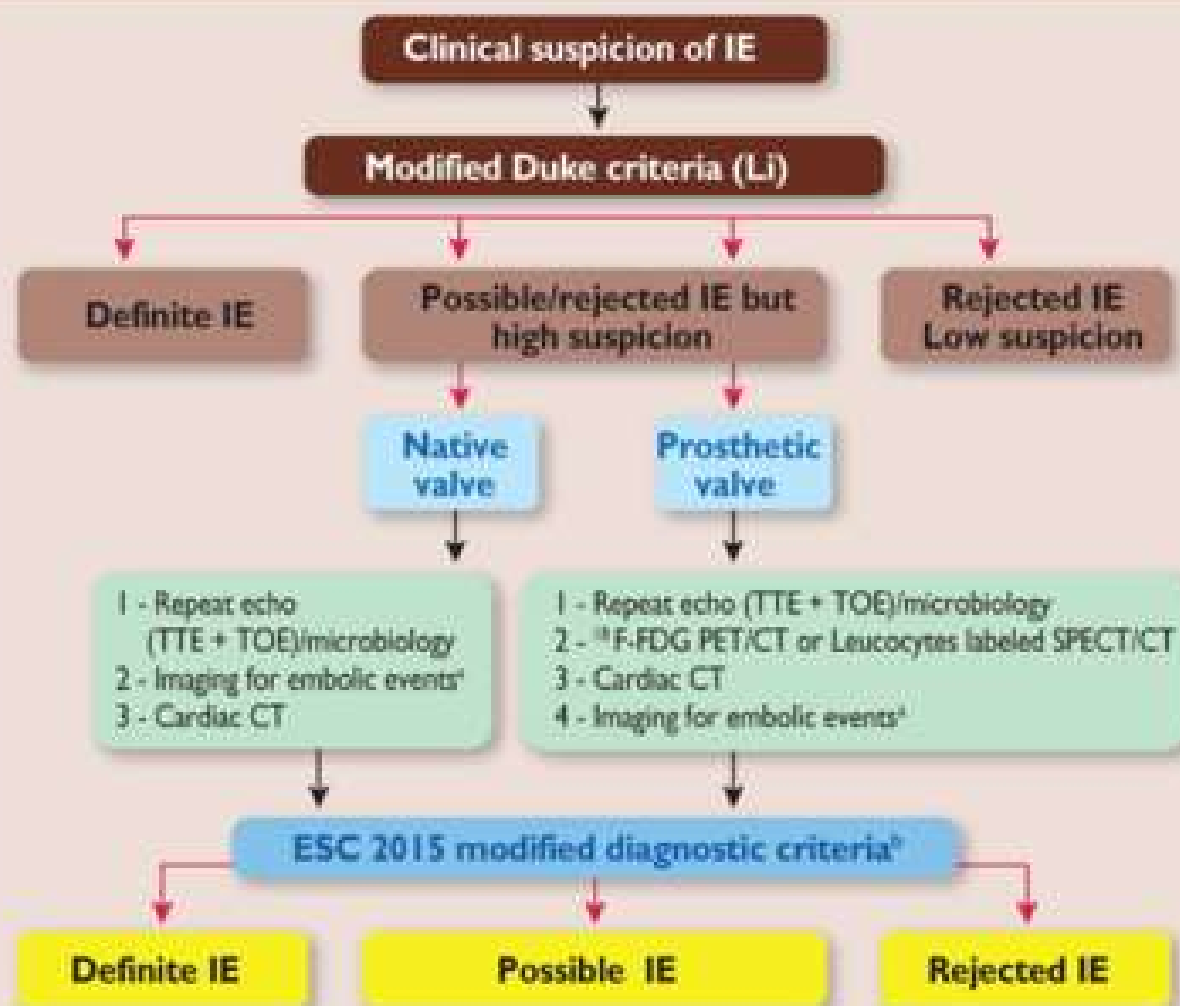
- a. Typical microorganisms consistent with IE from 2 separate blood cultures:
  - *Viridans streptococci*, *Streptococcus gallolyticus* (*Streptococcus bovis*), *HACEK* group, *Staphylococcus aureus*; or
  - Community-acquired enterococci, in the absence of a primary focus; or
- b. Microorganisms consistent with IE from persistently positive blood cultures:
  - $\geq 2$  positive blood cultures of blood samples drawn  $>12$  h apart; or
  - All of 3 or a majority of  $\geq 4$  separate cultures of blood (with first and last samples drawn  $\geq 1$  h apart); or
- c. Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titre  $>1:800$

#### 2. Imaging positive for IE

- a. Echocardiogram positive for IE:
  - Vegetation;
  - Abscess, pseudoaneurysm, intracardiac fistula;
  - Valvular perforation or aneurysm;
  - New partial dehiscence of prosthetic valve.
- b. Abnormal activity around the site of prosthetic valve implantation detected by  $^{18}\text{F}$ -FDG PET/CT (only if the prosthesis was implanted for  $>3$  months) or radiolabelled leukocytes SPECT/CT.
- c. Definite paravalvular lesions by cardiac CT.

### Minor criteria

1. Predisposition such as predisposing heart condition, or injection drug use.
2. Fever defined as temperature  $>38^{\circ}\text{C}$ .
3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions.
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.



CT = computed tomography; FDG = fluorodeoxyglucose; IE = infective endocarditis;  
 PET = positron emission tomography; SPECT = single photon emission computerized tomography;  
 TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.  
 \*May include cerebral MRI, whole body CT, and/or PET/CT.  
<sup>b</sup>See Table 14.

