Infective endocarditis

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2015 ESC Guidelines for the management of infective endocarditis

Non-specific prevention measures to be followed in high-risk and intermediate-risk patients

These measures should ideally be applied to the general population and particularly reinforced in high-risk patients:
• Strict dental and cutaneous hygiene. Dental follow-up should be performed twice a year in high-risk patients and yearly in the others.
• Disinfection of wounds.
• Eradication or decrease of chronic bacterial carriage: skin, urine.
• Curative antibiotics for any focus of bacterial infection.
• No self-medication with antibiotics.
• Strict infection control measures for any at-risk procedure.
• Discourage piercing and tattooing.
• Limit the use of infusion catheters and invasive procedure when possible. Favour peripheral over central catheters, and systematic replacement of the peripheral catheter every 3–4 days. Strict adherence to care bundles for central and peripheral cannulae should be performed.

Recommended prophylaxis for high-risk dental procedures in high-risk patients

Situation	Antibiotic	Single-dose 30–60 minutes before procedure	
		Adults	Children
No allergy to penicillin or ampicillin	Amoxicillin or ampicillin[a]	2 g orally or i.v.	50 mg/kg orally or i.v.
Allergy to penicillin or ampicillin	Clindamycin	600 mg orally or i.v.	20 mg/kg orally or i.v.

Recommended prophylaxis for high-risk dental procedures in high-risk patients

- Alternatively, cephalexin 2 g i.v. for adults or 50 mg/kg i.v. for children,

  cefazolin or ceftriaxone 1 g i.v. for adults or 50 mg/kg i.v. for children.

- Cephalosporins should not be used in patients with anaphylaxis, angio-oedema, or urticaria after intake of penicillin or ampicillin due to cross-sensitivity.

Prophylaxis for non-dental procedures

3.5.3 Dermatological or musculoskeletal procedures

- For patients undergoing surgical procedures involving infected skin (including oral abscesses), skin structure or musculoskeletal tissue, it is reasonable that the therapeutic regimen contains an agent active against staphylococci and beta-haemolytic streptococci.

Prophylaxis for non-dental procedures

3.5.5 Cardiac or vascular interventions

- Prophylaxis should be started immediately before the procedure, repeated if the procedure is prolonged and terminated 48 h afterwards. A randomized trial has shown the efficacy of **1 g intravenous (i.v.) cefazolin** on the prevention of local and systemic infections before pacemaker implantation.

Prophylaxis for non-dental procedures

3.5.5 Cardiac or vascular interventions

- Preoperative screening of nasal carriage of S.aureus is recommended before elective cardiac surgery in order to treat carriers using local mupirocin and chlorhexidine.
- Rapid identification techniques using geneamplification are useful to avoid delaying urgent surgery. Systematic local treatment without screening is not recommended.
- It is strongly recommended that potential sources of dental sepsis should be eliminated at least 2 weeks before implantation of a prosthetic valve or other intracardiac or intravascular foreign material, unless the latter procedure is urgent

Prophylaxis for non-dental procedures

3.5.6 Healthcare-associated infective endocarditis

- Healthcare-associated IE represents up to 30% of all cases of IE and is characterized by an increasing incidence and a severe prognosis, thus presenting an important health problem.
- Although routine antimicrobial prophylaxis administered before most invasive procedures is not recommended, aseptic measures during the insertion and manipulation of venous catheters and during any invasive procedures, including in outpatients, are mandatory to reduce the rate of this healthcare-associated IE.

5. Diagnosis

5.1 Clinical features

- Thus IE should be suspected in a variety of very different clinical situations. It may present as an acute, rapidly progressive infection, but also as a subacute or chronic disease with low-grade fever and non-specific symptoms that may mislead or confuse initial assessment.

- Patients may therefore present to a variety of specialists who may consider a range of alternative diagnoses, including chronic infection; rheumatological, neurological and autoimmune diseases; or malignancy.

5. Diagnosis

5.1 Clinical features

- The early involvement of a cardiologist and an ID specialist to guide management is highly recommended.
- **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.

5. Diagnosis

5.1 Clinical features

- Therefore IE has to be suspected in any patient presenting with fever and embolic phenomena.
- Classic signs may still be seen in the developing world in subacute forms of IE, although peripheral stigmata of IE are increasingly uncommon elsewhere, as patients generally present at an early stage of the disease.

5. Diagnosis

5.1 Clinical features

- However, vascular and immunological phenomena such as splinter haemorrhages, Roth spots and glomerulonephritis remain common.
- Emboli to the brain, lung or spleen occur in 30% of patients and are often the presenting feature.
- In a febrile patient, diagnostic suspicion may be strengthened by laboratory signs of infection, such as elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), leucocytosis, anaemia and microscopic haematuria.

5. Diagnosis

5.2 Laboratory findings

- In addition to specialized microbiological and imaging investigations, a number of laboratory investigations and biomarkers have been evaluated in sepsis/sepsis syndromes and endocarditis.
- The large number of proposed potential biomarkers reflects the complex pathophysiology of the disease process, involving pro- and antiinflammatory processes, humoral and cellular reactions and both circulatory and end-organ abnormalities.

5. Diagnosis

5.2 Laboratory findings

- Sepsis severity may be indicated by the demonstration of a number of laboratory investigations, including the degree of **leucocytosis/leucopoenia**, 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.

5. Diagnosis

5.2 Laboratory findings

- Further, certain laboratory investigations are used in surgical scoring systems relevant to risk stratification in patients with IE, including bilirubin, creatinine and platelet count [Sequential Organ Failure Assessment (SOFA) score]

and creatinine clearance [European Systemfor Cardiac Operative Risk Evaluation (EuroSCORE) II].

5. Diagnosis

5.2 Laboratory findings

- Finally, the pattern of increase in inflammatory mediators or immune complexes may support, but not prove, the diagnosis of IE, including the finding of **hypocomplementaemia** in the presence of elevated **antineutrophil cytoplasmic antibody in endocarditis-associated vasculitis** or, where lead infection is suspected clinically, the laboratory finding of a normal procalcitonin and white cell count in the presence of significantly elevated CRP and/or ESR

5. Diagnosis

5.3 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.
- Echocardiography is particularly useful for initial assessment of the embolic risk and in decision making in IE. **Transoesophageal echocardiography** (TOE) plays a major role both before and during surgery (intraoperative echocardiography).

5. Diagnosis

5.3 Imaging techniques

- However, the evaluation of patients with IE is no longer limited to conventional echocardiography, but should include several other imaging techniques such as MSCT, MRI, 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) or other functional imaging modalities.

5.3 Imaging techniques

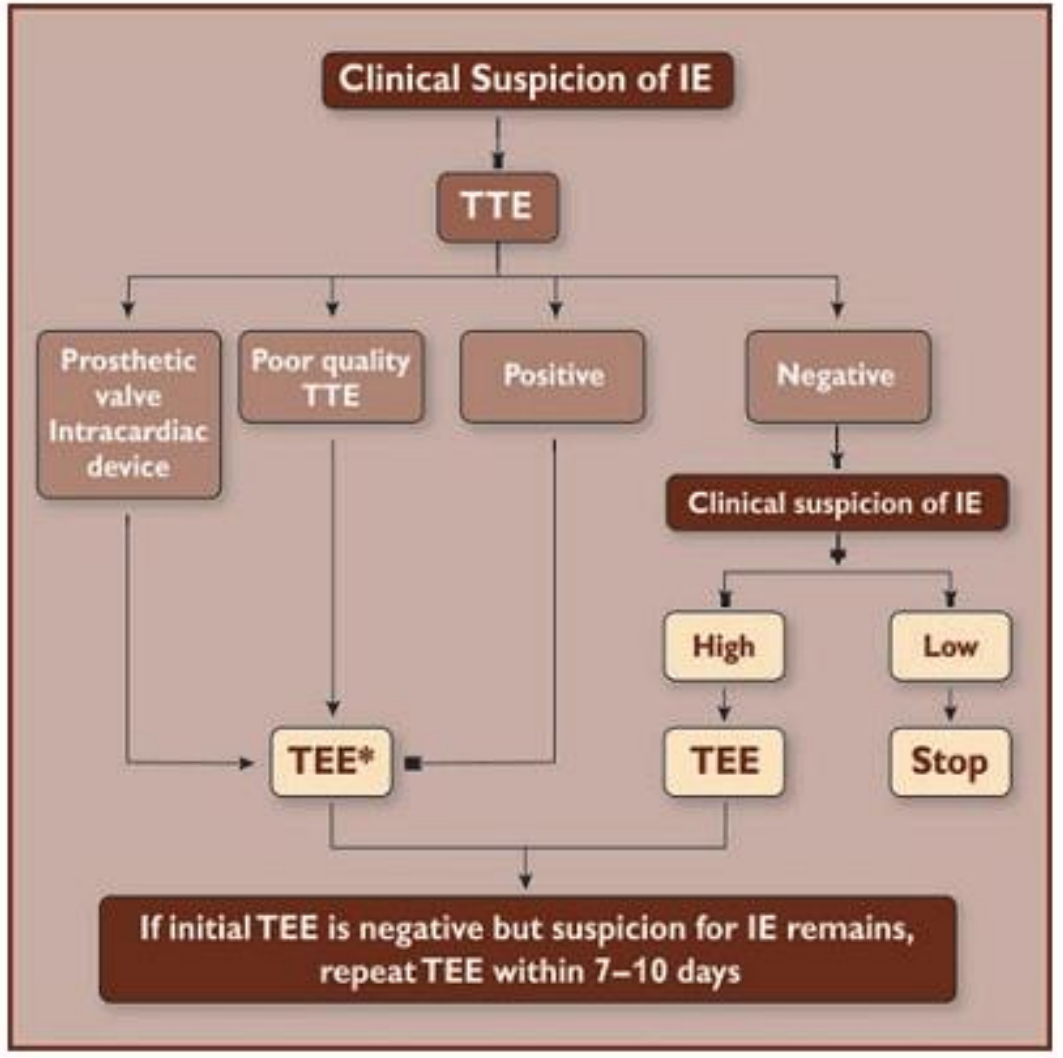
5.3.1 Echocardiography

- 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.

Echocardiography

Echocardiographic findings in IE

- Vegetation
- Abscess
- Pseudoaneurysm
- Perforation
- Fistula
- Valve aneurysm
- Dishence of prosthetic valve



5.3 Imaging techniques

5.3.1 Echocardiography

- 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.
- Diagnosis may be particularly challenging in IE affecting intracardiac devices, even with the use of TOE.

5.3 Imaging techniques

5.3.1 Echocardiography

- False diagnosis of IE may occur, and in some instances it may be difficult to differentiate vegetations from thrombi, Lambl's excrescences, cusp prolapse, chordal rupture, valve fibroelastoma, degenerative or myxomatous valve disease, strands, systemic lupus (Libman – Sacks) lesions, primary antiphospholipid syndrome, rheumatoid lesions or marantic vegetations.

Anatomical and echocardiographic definitions

	Surgery/necropsy	Echocardiography
Vegetation	Infected mass attached to an endocardial structure or on implanted intracardiac material.	Oscillating or non-oscillating intracardiac mass on valve or other endocardial structures, or on implanted intracardiac material.
Abscess	Perivalvular cavity with necrosis and purulent material not communicating with the cardiovascular lumen.	Thickened, non-homogeneous perivalvular area with echodense or echolucent appearance.
Pseudoaneurysm	Perivalvular cavity communicating with the cardiovascular lumen.	Pulsatile perivalvular echo-free space, with colour-Doppler flow detected.
Perforation	Interruption of endocardial tissue continuity.	Interruption of endocardial tissue continuity traversed by colour-Doppler flow.
Fistula	Communication between two neighbouring cavities through a perforation.	Colour-Doppler communication between two neighbouring cavities through a perforation.
Valve aneurysm	Saccular outpouching of valvular tissue.	Saccular bulging of valvular tissue.
Dehiscence of a prosthetic valve	Dehiscence of the prosthesis.	Paravalvular regurgitation identified by TTE/TOE, with or without rocking motion of the prosthesis.

TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

5.3 Imaging techniques

5.3.1 Echocardiography

- IE must always be suspected in patients with new periprosthetic regurgitation, even in the absence of other echocardiographic findings of 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, or even earlier in the case of S. aureus infection.

5.3 Imaging techniques

5.3.2 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.

5.4 Microbiological diagnosis

5.4.1 Blood culture–positive infective endocarditis

- This is virtually always sufficient to identify the usual causative microorganisms.
- The need for culture before antibiotic administration is self-evident. In IE, bacteraemia is almost constant and has two implications:

(i) there is no rationale for delaying blood sampling with peaks of fever and

(ii) virtually all blood cultures are positive.

5.4 Microbiological diagnosis

5.4.1 Blood culture–positive infective endocarditis

- As a result, a single positive blood culture should be regarded cautiously for establishing the diagnosis of IE.
- The microbiology laboratory should be aware of the clinical suspicion of IE at the time of blood culture sampling.
- When a microorganism has been identified, blood cultures should be repeated after 48–72 h to check the effectiveness of treatment.

5.4 Microbiological diagnosis

5.4.1 Blood culture–positive infective endocarditis

- Automated machines perform continuous monitoring of bacterial growth, which ensures quick provision of reports to physicians.
- When a positive blood culture bottle is identified, presumptive identification is based on Gram staining.
- Complete identification is routinely achieved within 2 days, but may require longer for fastidious or atypical organisms.

5.4 Microbiological diagnosis

5.4.2 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.

5.4 Microbiological diagnosis

5.4.2 Blood culture–negative infective endocarditis

- BCNIE can be caused by fungi or fastidious bacteria, notably obligatory intracellular bacteria.
- Isolation of these microorganisms requires culturing them on specialized media, and their growth is relatively slow.

5.4 Microbiological diagnosis

5.4.2 Blood culture–negative infective endocarditis

- According to local epidemiology, systematic serological testing for Coxiella burnetii, Bartonella spp., Aspergillus spp., Mycoplasma pneumonia, Brucella spp. and Legionella pneumophila should be proposed, followed by specific polymerase chain reaction (PCR) assays for Tropheryma whipplei, Bartonella spp. and fungi (Candida spp., Aspergillus spp.) from the blood.

Investigation of rare causes of blood culture negative infective endocarditis

Pathogen	Diagnostic procedures
Brucella spp.	Blood cultures, serology, culture, immunohistology, and PCR of surgical material.
Coxiella burnetii	Serology (IgG phase I >1:800), tissue culture, immunohistology, and PCR of surgical material.
Bartonella spp.	Blood cultures, serology, culture, immunohistology, and PCR of surgical material.
Tropheryma whipplei	Histology and PCR of surgical material.
Mycoplasma spp.	Serology, culture, immunohistology, and PCR of surgical material.
Legionella spp.	Blood cultures, serology, culture, immunohistology, and PCR of surgical material.
Fungi	Blood cultures, serology, PCR of surgical material.

Ig = immunoglobulin; PCR = polymerase chain reaction.

5.4 Microbiological diagnosis

5.4.3 Histological diagnosis of infective endocarditis

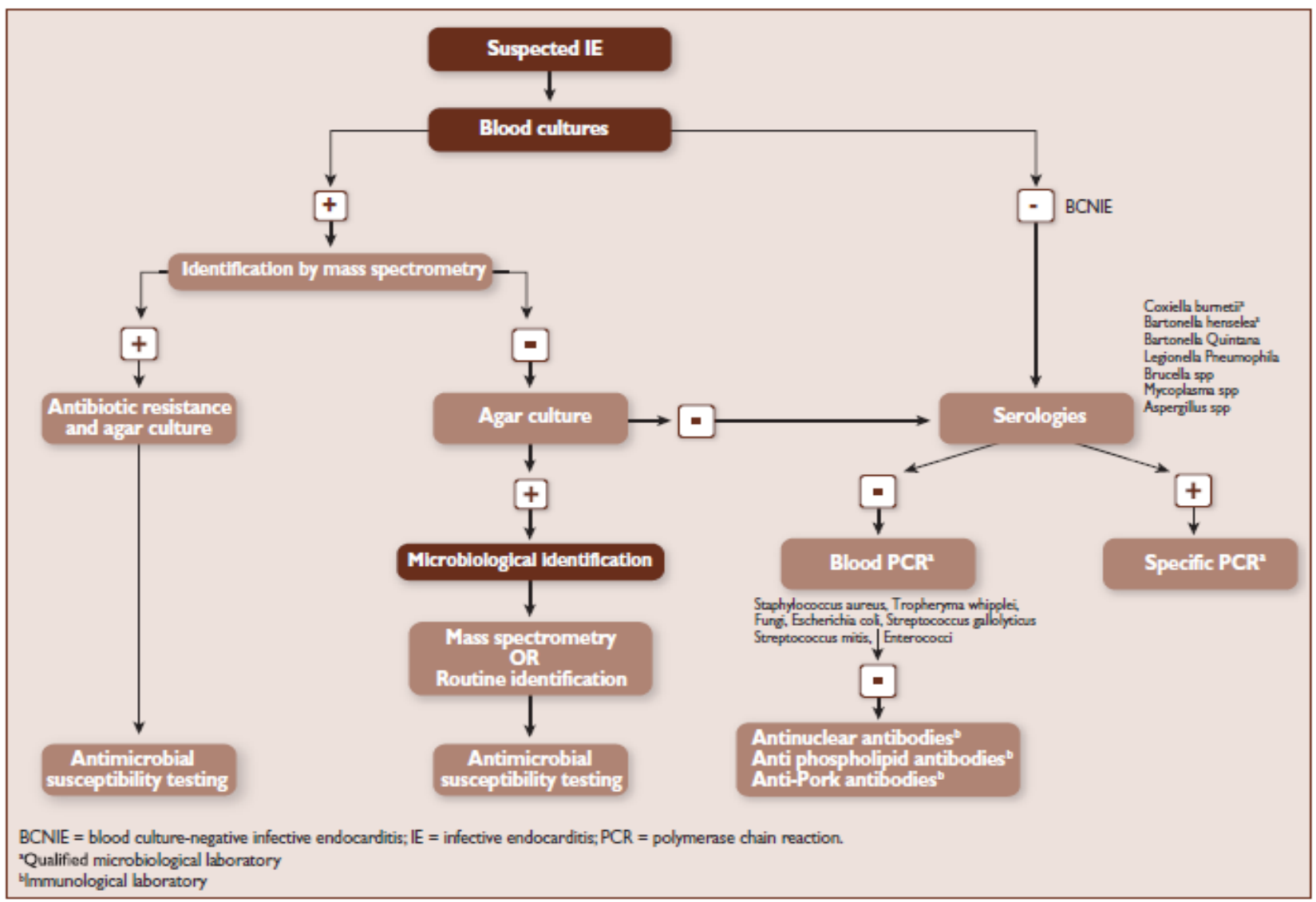
- Pathological examination of resected valvular tissue or embolic fragments remains the gold standard for the diagnosis of IE.
- All tissue samples that are excised during the course of the surgical removal of cardiac valves must be collected in a sterile container without fixative or culture medium.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

5.4 Microbiological diagnosis

5.4.4 Proposed strategy for a microbiological diagnostic algorithm in suspected IE

- When there is clinical suspicion of IE and blood cultures remain negative at 48 h, liaison with the microbiologist is necessary.
- A suggested strategy is the use of a diagnostic kit including blood cultures and systematic serological testing for C. burnetii, Bartonella spp., Aspergillus spp., L. pneumophila, Brucella spp., M. pneumonia, as well as rheumatoid factor, the serological tests for antiphospholipid syndrome [anticardiolipin (IgG) and anti-b2-glycoprotein 1 (IgG and IgM)], antinuclear antibodies and anti-pork antibodies.

Microbiological diagnostic algorithm in culture-positive and culture-negative IE.



BCNIE = blood culture-negative infective endocarditis; IE = infective endocarditis; PCR = polymerase chain reaction.
[a]Qualified microbiological laboratory
[b]Immunological laboratory

Definition of infective endocarditis according to the modified Duke criteria

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 ≤4 days; or
- No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or
- Does not meet criteria for possible IE, as above

5.5 Diagnostic criteria

Given the recent published data, the Task Force proposes the addition of three further points in the diagnostic criteria:

(1) The identification of paravalvular lesions by cardiac CT should be considered a major criterion.

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

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

Definitions of the terms used in the European Society of Cardiology 2015 modified criteria for the diagnosis of infective endocarditis

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:
- ≥2 positive blood cultures of blood samples drawn >12 h apart; or
- All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart); or

c. Single positive blood culture for Coxiella burnetii or phase 1 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}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.

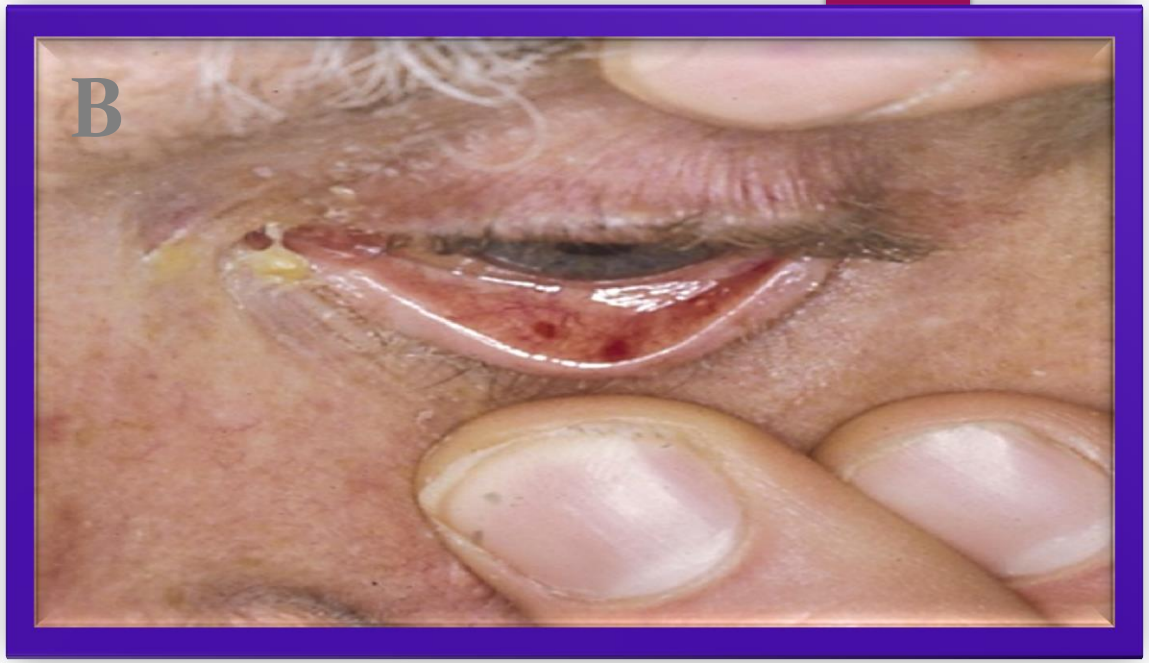
Minor criteria

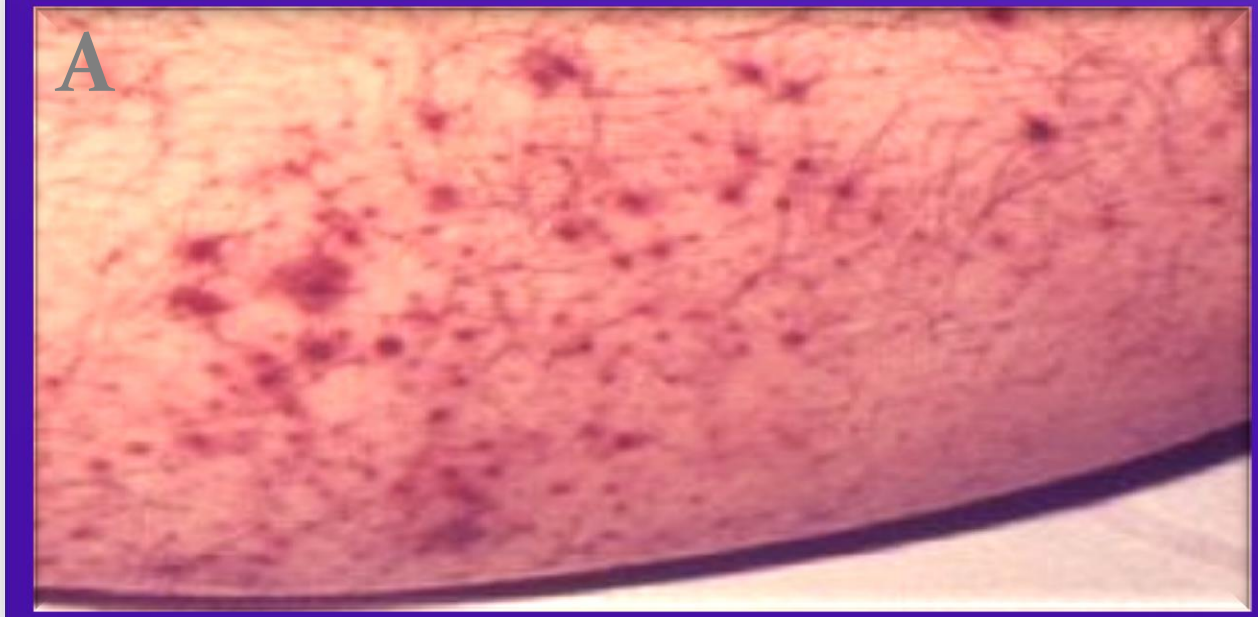
1. Predisposition such as predisposing heart condition, or injection drug use.
2. Fever defined as temperature >38°C.
3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival 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.

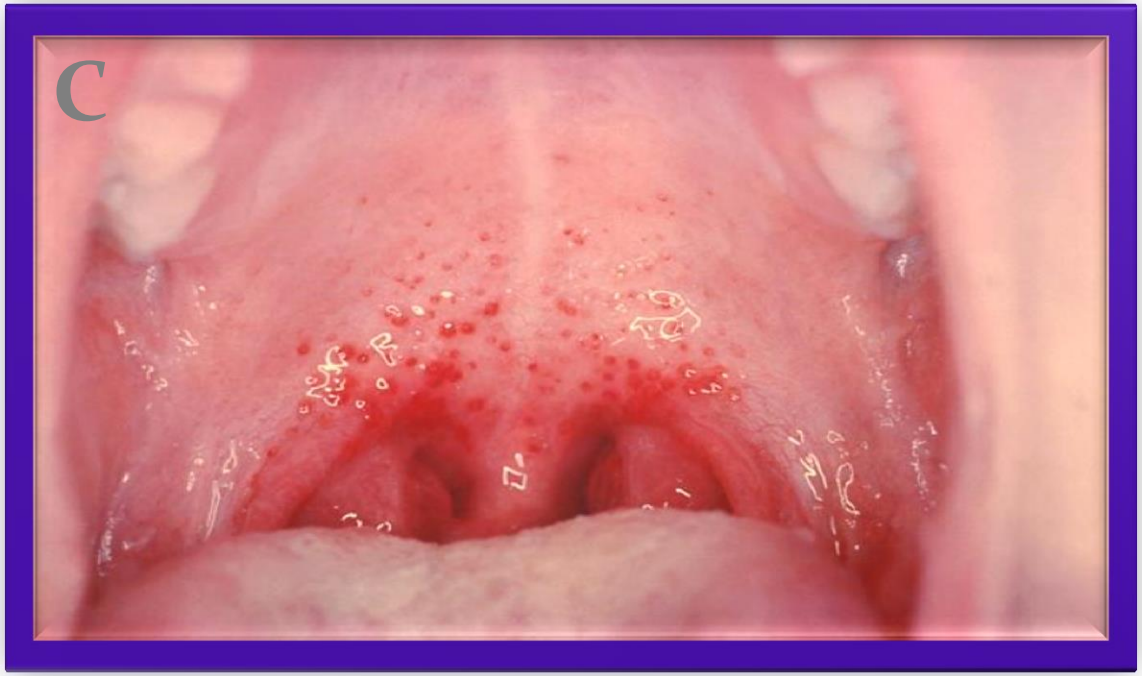
CT = computed tomography; FDG = fluorodeoxyglucose; HACEK = Haemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae, and K. denitrificans; IE = infective endocarditis; Ig = immunoglobulin; PET = positron emission tomography; SPECT = single photon emission computerized tomography. Adapted from Li *et al.*[87]

Eruptions

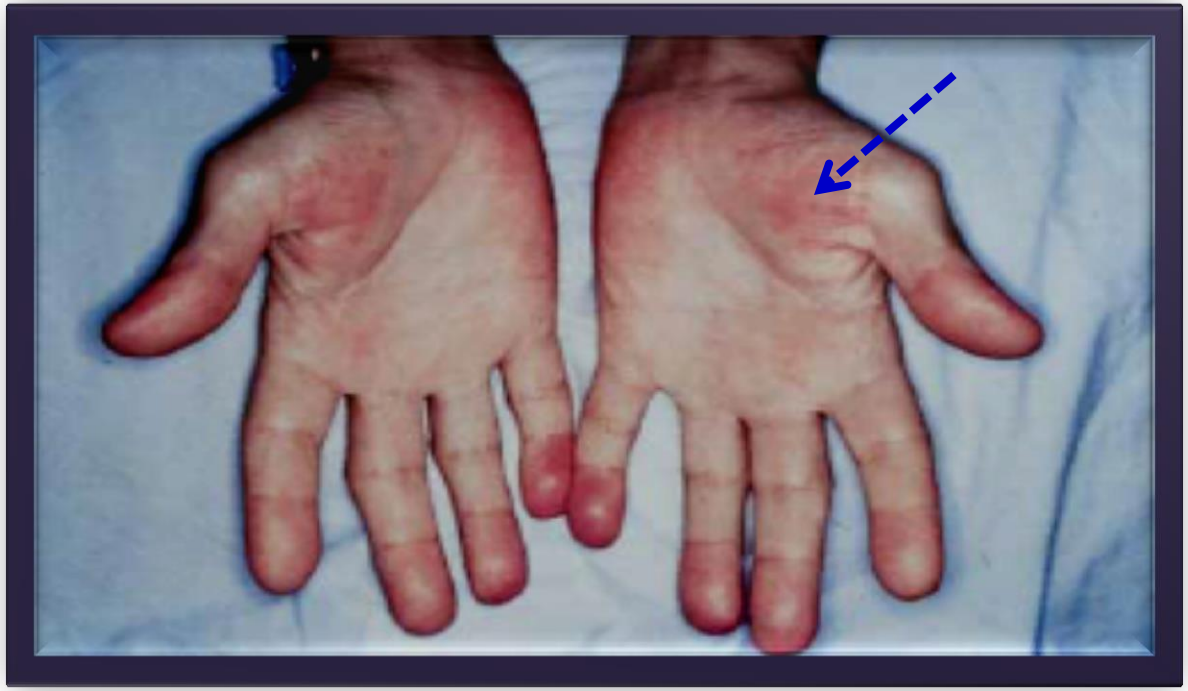
A. skinned
B. conjunctival
C. On lining of the oral cavity

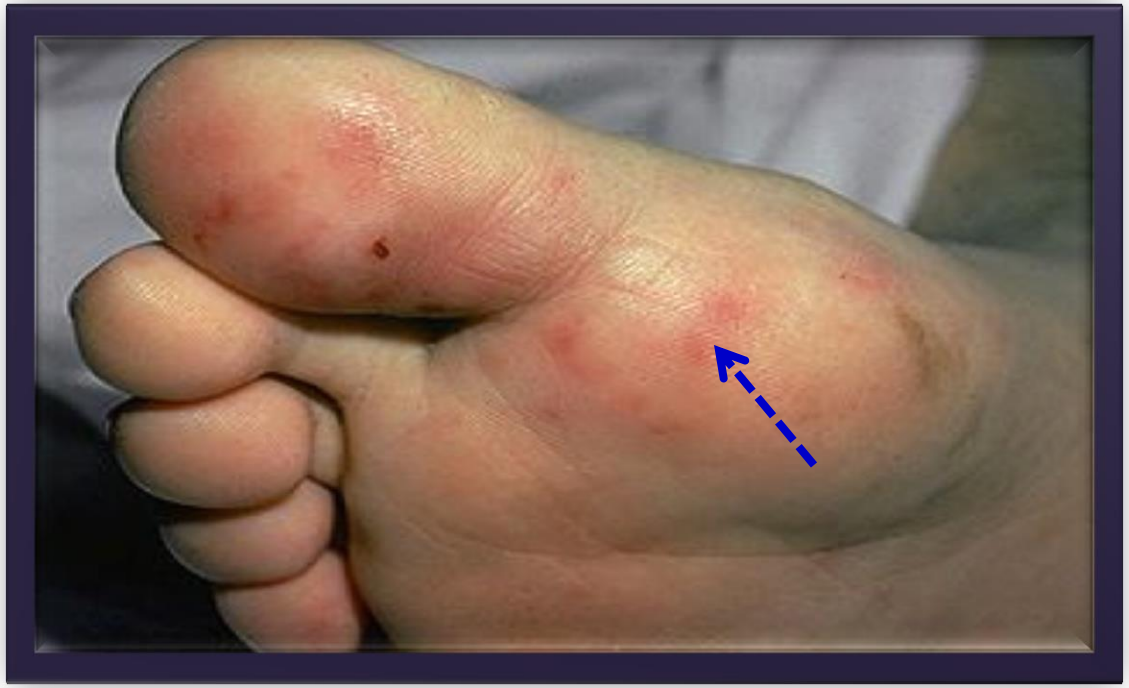






Osler nodules





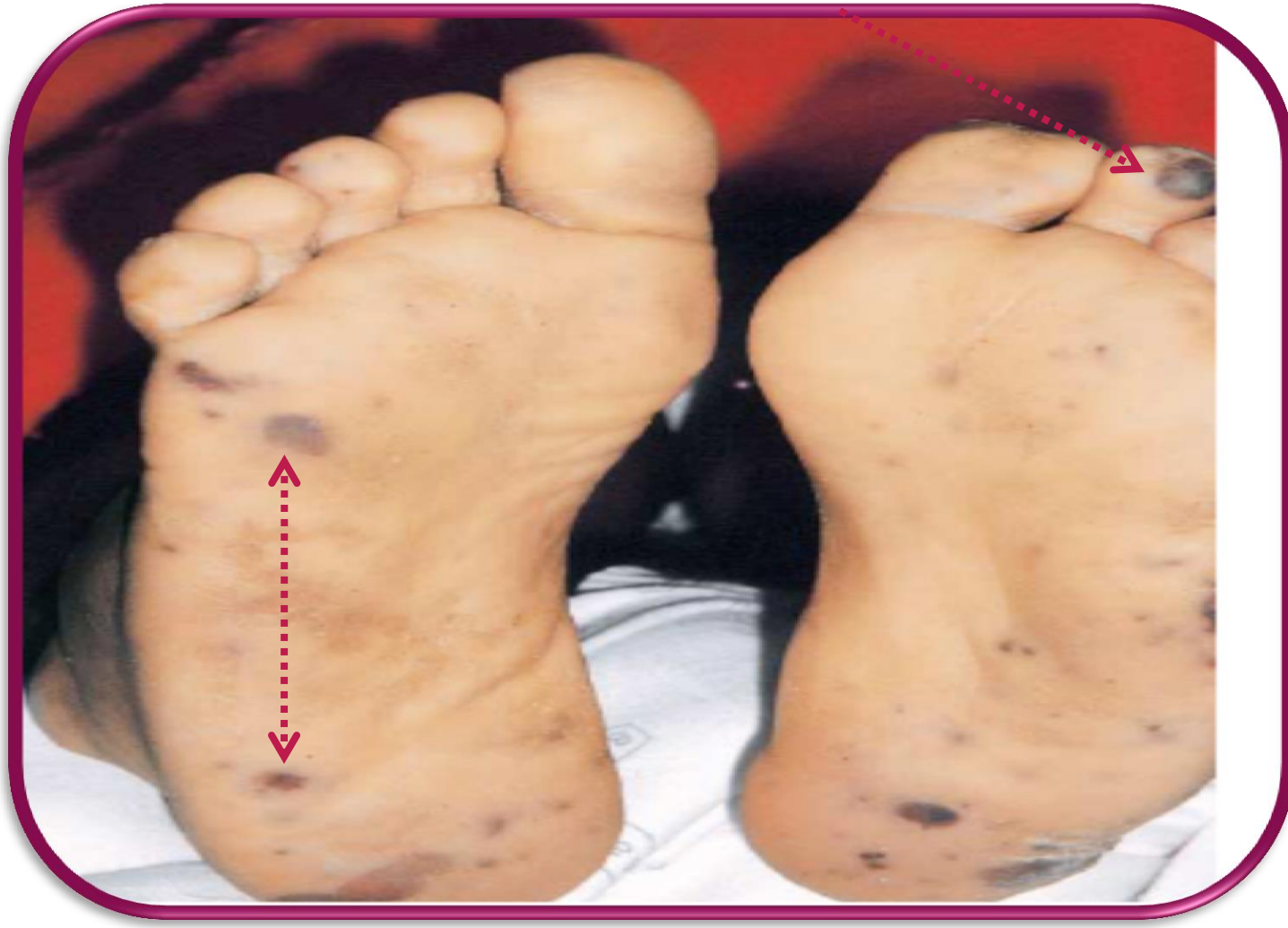
Osler nodules are vasculits
Of small vessels-
mediated imunologically

The pacient T. 46 years,
IE subacute streptococci etiology
with the affectation of VA(Va will bicuspid)

Leziuni Janeway

Janeway injuries :
Septic vasculitis characteristic for acute staphilococcic IE
(Staphylococci. aureus)

Patient L. 42 years
IE of prothesis, acute, staphilococcic etiology



Hemorrhages in splinter

Linear hemorrhages in splinter,

With localization

On the nail bed

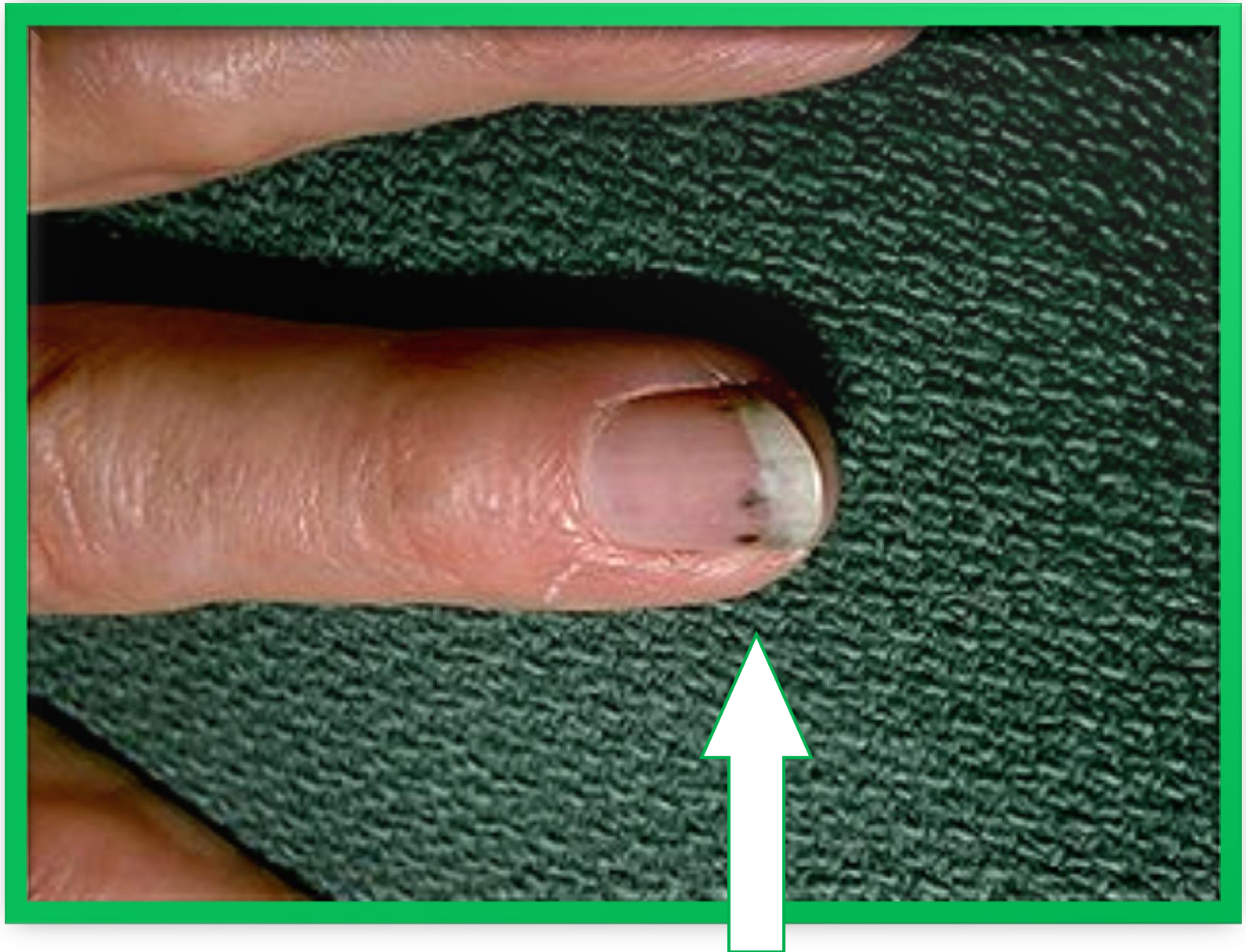
In hands and feet

The patient O. 24 years, IE acute,

Staphilococic etiology, (Stph. aureus) with

Trivalvular affectation, and

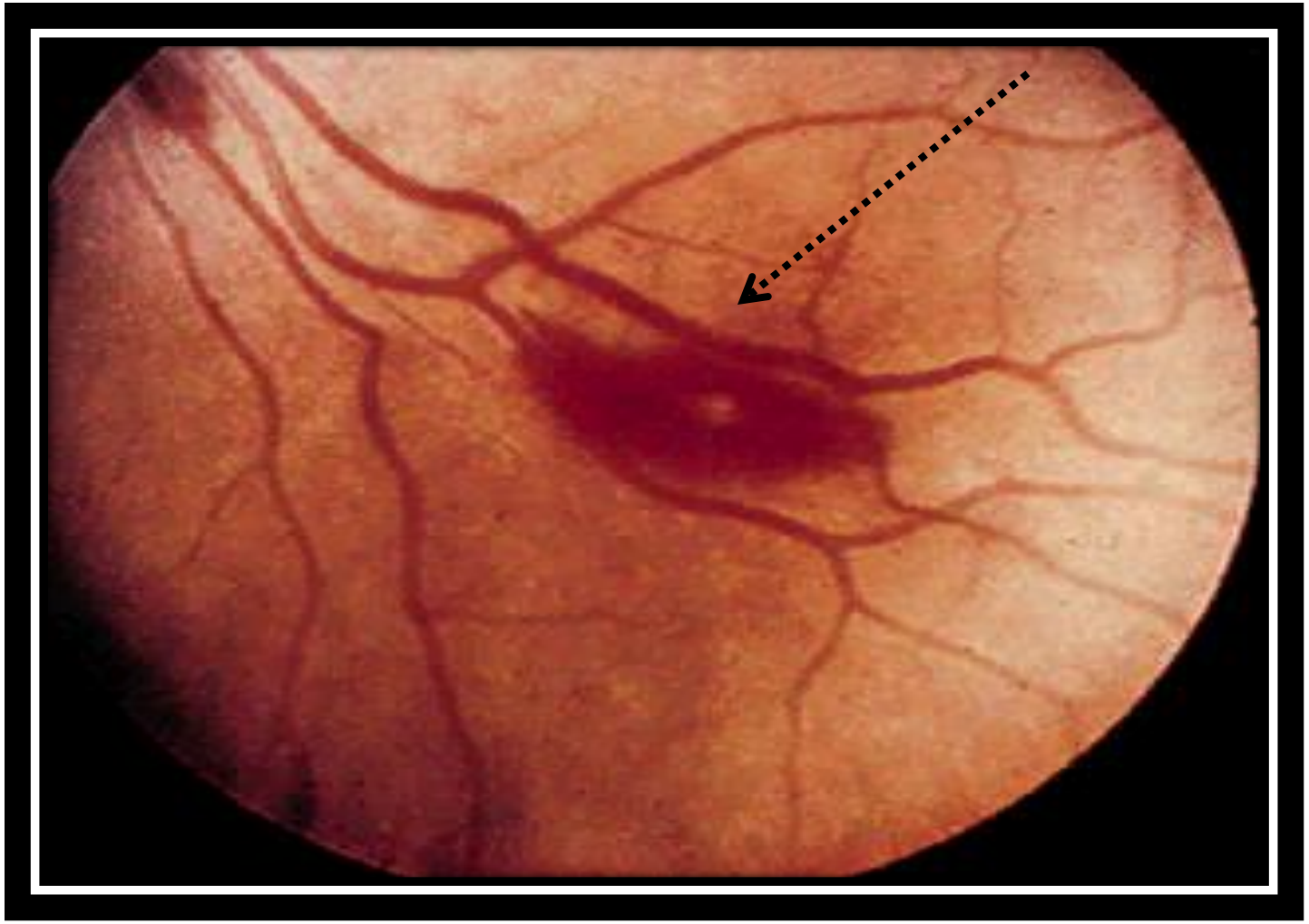
The debut with



Roth spots

Retinal
Hemorrhages -
Dried branches
Localized on the retina

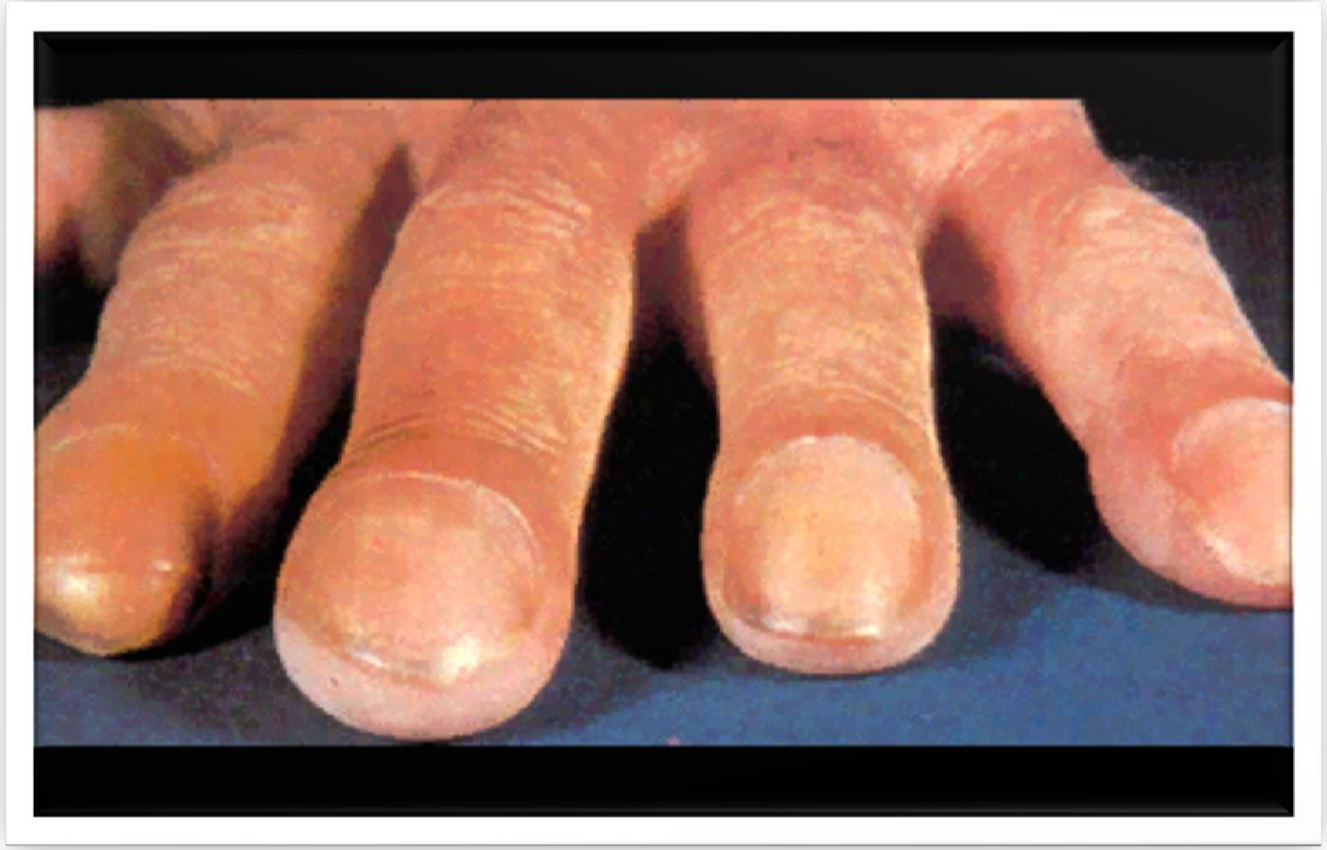
The patient C. 35 y,
IE streptococic etiology
Pyogenes St. , with
The afectation of VA,
Cusp prosthetic rupture,



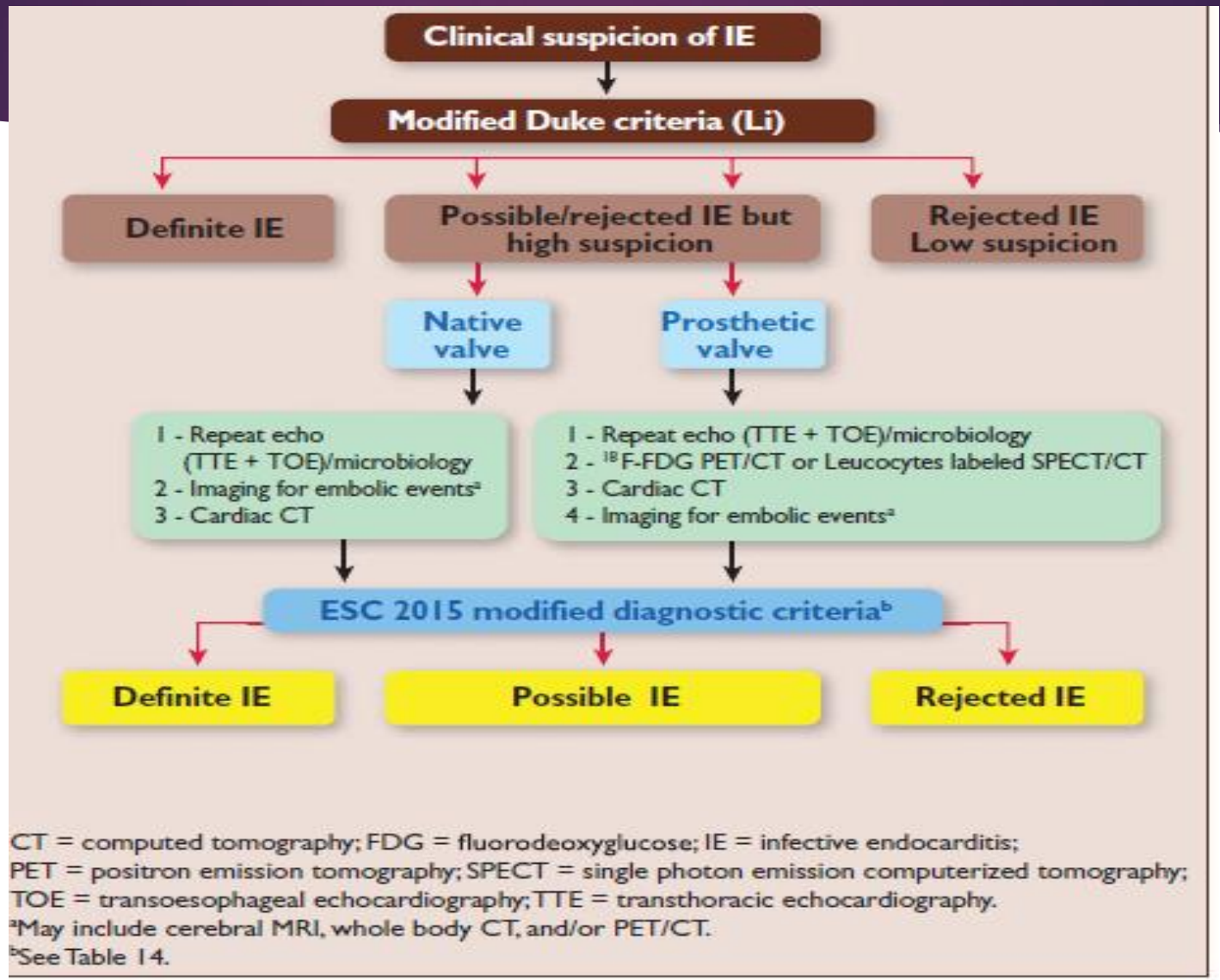
Hipocratic fingers

Fingers of specific form of a chronic process
(in IE
With trenant evolution)

The patient D. 33 years
IE subacute,
Streptococal etiology with
The afection VM și VT.
Diagnosed after
11 months after the debut.



European Society of Cardiology 2015 algorithm for diagnosis of infective endocarditis.



CT = computed tomography; FDG = fluorodeoxyglucose; IE = infective endocarditis; PET = positron emission tomography; SPECT = single photon emission computerized tomography; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

[a]May include cerebral MRI, whole body CT, and/or PET/CT.

[b]See Table 14.

Predictors of poor outcome in patients with infective endocarditis

Patient characteristics • Older age • Prosthetic valve IE • Diabetes mellitus • Comorbidity (e.g., frailty, immunosuppression, renal or pulmonary disease)
Clinical complications of IE • Heart failure • Renal failure • >Moderate area of ischaemic stroke • Brain haemorrhage • Septic shock
Microorganism • *Staphylococcus aureus* • Fungi • Non-HACEK Gram-negative bacilli
Echocardiographic findings • Perianular complications • Severe left-sided valve regurgitation • Low left ventricular ejection fraction • Pulmonary hypertension • Large vegetations • Severe prosthetic valve dysfunction • Premature mitral valve closure and other signs of elevated diastolic pressures

HACEK –

Haemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae,

Actinobacillus actinomycetemcomitans,

Cardiobacterium hominis,

Eikenella corrodens,

Kingella kingae, and K. Denitrificans.

7. Antimicrobial therapy: principles and methods

7.1 General principles

- Successful treatment of IE relies on microbial eradication by antimicrobial drugs. Surgery contributes by removing infected material and draining abscesses. Host defences are of little help. This explains why bactericidal regimens are more effective than bacteriostatic therapy, both in animal experiments and in humans.
- Aminoglycosides synergize with cell-wall inhibitors (i.e. beta-lactams and glycopeptides) for bactericidal activity and are useful for shortening the duration of therapy (e.g. oral streptococci) and eradicating problematic organisms (e.g. Enterococcus spp.).

7. Antimicrobial therapy: principles and methods

7.1 General principles

- Drug treatment of PVE should last longer (at least 6 weeks) than that of native valve endocarditis (NVE) (2–6 weeks), but is otherwise similar, except for staphylococcal PVE, where the regimen should include rifampin whenever the strain is susceptible.
- A new full course of treatment should only start if valve cultures are positive, with the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.

7. Antimicrobial therapy: principles and methods

7.1 General principles

(3) Daptomycin and fosfomycin have been recommended for treating staphylococcal endocarditis and **netilmicin** for treating penicillin-susceptible oral and digestive streptococci, but they are considered alternative therapies in these guidelines because they are not available in all European countries. When **daptomycin** is indicated, it must be given at high doses (≥10 mg/kg once daily132) and combined with a second antibiotic to increase activity and avoid the development of resistance.

7. Antimicrobial therapy: principles and methods

7.2 Penicillin-susceptible oral streptococci and Streptococcus bovis group

- In uncomplicated cases, shortterm 2-week therapy can be administered by combining penicillin or ceftriaxone with gentamicin or netilmicin.
- Gentamicin and netilmicin can be given once daily in patients with IE due to susceptible streptococci and normal renal function.
- Ceftriaxone alone or combined with gentamicin or netilmicin given once a day is particularly convenient for outpatient therapy.

Antibiotic treatment of infective endocarditis due to oral streptococci and Streptococcus bovis group

Antibiotic	Dosage and route	Duration (weeks)	Class[b]	Level[c]	Ref.[d]	Comments
Strains penicillin-susceptible (MIC ≤ 0.125 mg/L) oral and digestive streptococci						
Standard treatment: 4-week duration						
Penicillin G	12–18 million U/day i.v. either in 4–6 doses or continuously	4	I	B	6,8, 135–139	Preferred in patients > 65 years or with impaired renal or VIII (vestibulocochlear) cranial nerve functions. 6-week therapy recommended for patients with PVE
or Amoxicillin[e]	100–200 mg/kg/day i.v. in 4–6 doses	4	I	B		
or Ceftriaxone[f]	2 g/day i.v. or i.m. in 1 dose	4	I	B		
	Paediatric doses:[g] Penicillin G 200,000 U/kg/day i.v. in 4–6 divided doses Amoxicillin 300 mg/kg/day i.v. in 4–6 equally divided doses Ceftriaxone 100 mg/kg/day i.v. or i.m. in 1 dose					

Antibiotic treatment of infective endocarditis due to oral streptococci and Streptococcus bovis group

Standard treatment: 2-week duration						
Penicillin G or	12–18 million U/day i.v. either in 4–6 doses or continuously	2	I	B	6,8, 127, 135–138	Only recommended in patients with non-complicated NVE with normal renal function.
Amoxicillin[e] or	100–200 mg/kg/day i.v. in 4–6 doses	2	I	B		
Ceftriaxone[f] combined with	2 g/day i.v. or i.m. in 1 dose	2	I	B		
Gentamicin[h] or	3 mg/kg/day i.v. or i.m. in 1 dose	2	I	B		
Netilmicin	4–5 mg/kg/day i.v. in 1 dose	2	I	B		Netilmicin is not available in all European countries.
	Paediatric doses:[g] Penicillin G, amoxicillin, and ceftriaxone as above Gentamicin 3 mg/kg/day i.v. or i.m. in 1 dose or 3 equally divided doses					

Antibiotic treatment of infective endocarditis due to oral streptococci and Streptococcus bovis group

In beta-lactam allergic patients[j]						
Vancomycin[j]	30 mg/kg/day i.v. in 2 doses	4	I	C		6-week therapy recommended for patients with PVE
	Paediatric doses[g] Vancomycin 40 mg/kg/day i.v. in 2 or 3 equally divided doses					
Strains relatively resistant to penicillin (MIC 0.250–2 mg/l)[k]						
Standard treatment						
Penicillin G	24 million U/day i.v. either in 4–6 doses or continuously	4	I	B	6,8, 135, 136	6-week therapy recommended for patients with PVE
or Amoxicillin[e]	200 mg/kg/day i.v. in 4–6 doses	4	I	B		
or Ceftriaxone[f]	2 g/day i.v. or i.m. in 1 dose	4	I	B		
combined with Gentamicin[h]	3 mg/kg/day i.v. or i.m. in 1 dose	2	I	B		
In beta-lactam allergic patients[j]						
Vancomycin[j]	30 mg/kg/day i.v. in 2 doses	4	I	C		6-week therapy recommended for patients with PVE
with Gentamicin[k]	3 mg/kg/day i.v. or i.m. in 1 dose	2	I	C		
	Paediatric doses[g] As above					

7. Antimicrobial therapy: principles and methods

7.9 Gram-negative bacteria

HACEK-related species

- If they do not produce beta-lactamase, ampicillin (12 g/day i.v. in four or six doses) plus gentamicin (3 mg/kg/day divided into two or three doses) for 4–6 weeks is an option.
- Ciprofloxacin (400 mg/8–12 h i.v. or 750 mg/12 h orally) is a less well-validated alternative.

7. Antimicrobial therapy: principles and methods

7.10 Fungi

- Antifungal therapy for Candida IE includes liposomal amphotericin B (or other lipid formulations) with or without flucytosine or an echinocandin at high doses; and for Aspergillus IE, voriconazole is the drug of choice and some experts recommend the addition of an echinocandin or amphotericin B.
- Suppressive longterm treatment with oral azoles (fluconazole for Candida and voriconazole for Aspergillus) is recommended, sometimes for life.
- Consultation with an ID specialist from the Endocarditis Team is recommended.

Antibiotic treatment of blood culture-negative infective endocarditis

Pathogens	Proposed therapy[a]	Treatment outcome
Brucella spp.	Doxycycline (200 mg/24 h) plus cotrimoxazole (960 mg/12 h) plus rifampin (300–600/24 h) for ≥3–6 months[b] orally	Treatment success defined as an antibody titre <1:60. Some authors recommend adding gentamicin for the first 3 weeks.
C. burnetii (agent of Q fever)	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h)[c] orally (>18 months of treatment)	Treatment success defined as anti-phase I IgG titre <1:200, and IgA and IgM titres <1:50.
Bartonella spp.[d]	Doxycycline 100 mg/12 h orally for 4 weeks plus gentamicin (3 mg/24 h) i.v. for 2 weeks	Treatment success expected in ≥90%.
Legionella spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 weeks or clarithromycin (500 mg/12 h) i.v. for 2 weeks, then orally for 4 weeks plus rifampin (300–1200 mg/24 h)	Optimal treatment unknown.
Mycoplasma spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 months[e]	Optimal treatment unknown.
T. whipplei (agent of Whipple's disease)[f]	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h)[c] orally for ≥18 months	Long-term treatment, optimal duration unknown.

Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification)

Antibiotic	Dosage and route	Class[b]	Level[c]	Comments
Community-acquired native valves or late prosthetic valves (≥ 12 months post surgery) endocarditis				
Ampicillin with (Flu)cloxacillin *or* oxacillin with Gentamicin[d]	12 g/day i.v. in 4–6 doses 12 g/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 1 dose	IIa	C	Patients with BCNIE should be treated in consultation with an ID specialist.
Vancomycin[d] with Gentamicin[d]	30–60 mg/kg/day i.v. in 2–3 doses 3 mg/kg/day i.v. or i.m. in 1 dose	IIb	C	For penicillin-allergic patients

Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification)

Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis				
Vancomycin[d] with Gentamicin[d] with Rifampin	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 1 dose 900–1200 mg i.v. or orally in 2 or 3 divided doses	IIb	C	Rifampin is only recommended for PVE and it should be started 3–5 days later than vancomycin and gentamicin has been suggested by some experts. In healthcare associated native valve endocarditis, some experts recommend in settings with a prevalence of MRSA infections >5% the combination of cloxacillin plus vancomycin until they have the final S. aureus identification

8. Main complications of left-sided valve infective endocarditis and their management

- Surgical treatment is required in approximately half of the patients with IE because of severe complications.
- Reasons to consider early surgery in the active phase (i.e. while the patient is still receiving antibiotic treatment) are to avoid progressive HF and irreversible structural damage caused by severe infection and to prevent systemic embolism.
- On the other hand, surgical therapy during the active phase of the disease is associated with significant risk.

8. Main complications of left-sided valve infective endocarditis and their management

- In some cases, surgery needs to be performed on an emergency (within 24 h) or urgent (within a few days, < 7 days) basis, irrespective of the duration of antibiotic treatment.
- In other cases, surgery can be postponed to allow 1 or 2 weeks of antibiotic treatment under careful clinical and echocardiographic observation before an elective surgical procedure is performed.
- The three main indications for early surgery in IE are HF, uncontrolled infection and prevention of embolic events

8. Main complications of left-sided valve infective endocarditis and their management

8.1 Heart failure

8.1.1 Heart failure in infective endocarditis

- **HF is the most frequent complication of IE** and represents the most common indication for surgery in IE.
- **HF is observed in 42–60% of cases of NVE** and is more often present when IE affects the aortic rather than the mitral valve.
- HF is mainly **caused by new or worsening severe aortic or mitral regurgitation, although intracardiac fistulae and, more rarely, valve obstruction may also lead to HF.**

8. Main complications of left-sided valve infective endocarditis and their management

8.1 Heart failure

8.1.1 Heart failure in infective endocarditis

- Valvular regurgitation in native IE may occur as a result of mitral chordal rupture, leaflet rupture (flail leaflet), leaflet perforation or interference of the vegetation mass with leaflet closure.
- A particular situation is infection of the anterior mitral leaflet secondary to an infected regurgitant jet of a primary aortic IE.
- Resultant aneurysm formation on the atrial side of the mitral leaflet may later lead to mitral perforation.

8. Main complications of left-sided valve infective endocarditis and their management

8.1 Heart failure

8.1.1 Heart failure in infective endocarditis

- Clinical presentation of HF may include dyspnoea, pulmonary oedema and cardiogenic shock.
- Among the large ICE Prospective Cohort Study patients with HF and IE, 66% were in New York Heart Association class III or IV.
- In addition to clinical findings, TTE is of crucial importance for initial evaluation and follow-up.
- Valve perforation, secondary mitral lesions and aneurysms are best assessed using TOE.

8. Main complications of left-sided valve infective endocarditis and their management

8.3 Prevention of systemic embolism

8.3.2 Predicting the risk of embolism

- Among these, the size and mobility of the vegetations are the most potent independent predictors of a new embolic event.
- Patients with vegetations >10 mm in length are at higher risk of embolism, and this risk is even higher in patients with larger (>15 mm) and mobile vegetations, especially in staphylococcal IE affecting the mitral valve.
- A recent study found that the risk of neurological complications was particularly high in patients with very large (> 30 mm length) vegetations.

9. Other complications of infective endocarditis

9.1 Neurological complications

- Symptomatic neurological complications occur in 15–30% of patients with IE and are mainly the consequence of embolism from vegetations.
- Neurological manifestations occur before or at IE diagnosis in a majority of cases, but new or recurrent events can also take place later in the course of IE.
- Clinical presentation is variable and may include multiple symptoms or signs in the same patient, but focal signs predominate and ischaemic strokes are most commonly diagnosed.

9. Other complications of infective endocarditis

9.1 Neurological complications

- Transient ischaemic attack, intracerebral or subarachnoidal haemorrhage, brain abscess, meningitis and toxic encephalopathy are also seen, and firm evidence supports that additional clinically silent cerebral embolisms **occur in 35–60% of IE patients.**
- **S. aureus IE is more frequently associated with neurological complications** compared with IE caused by other bacteria.
- Vegetation length and mobility also correlate with embolic tendency.

9. Other complications of infective endocarditis

9.2 Infectious aneurysm

- Infectious (mycotic) aneurysms result from septic arterial embolism to the intraluminal space or vasa vasorum or from subsequent spread of infection through the intimal vessels. Infectious aneurysms are typically thin walled and friable and, as such, exhibit a high tendency to rupture and haemorrhage.
- No predictor of rupture has been identified and, in contrast to non-infectious aneurysms, size does not appear to be a reliable predictor of potential rupture.

11. Outcome after discharge: follow-up and long-term prognosis

11.1 Recurrences: relapses and reinfections

- The actual risk of recurrence among survivors of IE varies between 2% and 6%.
- Two main types of recurrence are distinguishable: relapse and reinfection.
- Although not systematically differentiated in the literature, the term 'relapse' refers to a repeat episode of IE caused by the same microorganism, while 'reinfection' describes an infection caused by a different microorganism.
- When the same species is isolated during a subsequent episode of IE, there is often uncertainty as to whether the repeat infection is a relapse of the initial infection or a new infection (reinfection).

11. Outcome after discharge: follow-up and long-term prognosis

11.1 Recurrences: relapses and reinfections

- In these cases, molecular methods including strain-typing techniques should be employed.
- When these techniques or the identity of both isolates is unavailable, the timing of the second episode of IE may be used to distinguish relapse from reinfection.
- Thus, although variable, the time between episodes is usually shorter for relapse than for reinfection.
- Generally speaking, a recurrence caused by the same species within 6 months following the initial infection represents relapse, whereas later events suggest reinfection.
- For these purposes, storage of IE isolates for at least 1 year is recommended.

11. Outcome after discharge: follow-up and long-term prognosis

11.1 Recurrences: relapses and reinfections

- Relapses are most often due to insufficient duration of original treatment, suboptimal choice of initial antibiotics or a persistent focus of infection.

- When the duration of therapy has been insufficient or the choice of antibiotic incorrect, relapse should be treated for a further 4–6 weeks depending on the causative microorganism and its antibiotic susceptibility.

12. Management of specific situations

12.1 Prosthetic valve endocarditis

- PVE is the most severe form of IE and occurs in 1–6% of patients with valve prostheses, with an incidence of 0.3–1.2% per patient-year.
- PVE accounts for 10–30% of all cases of IE and affects mechanical and bioprosthetic valves equally.
- PVE was observed in 16% of cases of IE in a French survey, in 26% of cases in the Euro Heart Survey and in 20% of 2670 patients with definite IE in the ICE Prospective Cohort Study.
- PVE is still associated with difficulties in diagnosis, determination of the optimal therapeutic strategy and poor prognosis.

12. Management of specific situations

12.1 Prosthetic valve endocarditis

12.1.1 Definition and pathophysiology

- Early PVE is defined as IE occurring within 1 year of surgery and late PVE as IE occurring beyond 1 year, because of significant differences between the microbiological profiles observed before and after this time point. However, this is an artificial distinction.
- What is important is not the time from the valve replacement procedure to the onset of IE, but whether IE is acquired perioperatively and which microorganism is involved.

12. Management of specific situations

12.1 Prosthetic valve endocarditis

12.1.1 Definition and pathophysiology

- The pathogenesis of PVE differs according to both the type of contamination and the type of prosthetic valve. In cases with perioperative contamination, the infection usually involves the junction between the sewing ring and the annulus, leading to perivalvular abscess, dehiscence, pseudo-aneurysms and fistulae.

12. Management of specific situations

12.1 Prosthetic valve endocarditis

12.1.3 Prognosis and treatment

- A very high in-hospital mortality rate of 20–40% has been reported in PVE.
- As in NVE, prognostic assessment is of crucial importance in PVE, as it allows identification of high-risk subgroups of patients in whom an aggressive strategy may be necessary.
- Several factors have been associated with poor prognosis in PVE, including older age, diabetes mellitus, healthcareassociated infections, staphylococcal or fungal infection, early PVE, HF, stroke and intracardiac abscess.

12. Management of specific situations

12.1 Prosthetic valve endocarditis

12.1.3 Prognosis and treatment

- Among these, complicated PVE and staphylococcal infection are the most powerful markers.
- These patients need aggressive management, consisting of antibiotic therapy and early radical surgery.
- Antimicrobial therapy for PVE is similar to that for NVE. An exception is S. aureus PVE, which requires a more prolonged (≥6 weeks) antibiotic regimen (particularly in association with aminoglycosides) and frequent use of rifampin.

▶THANK YOU FOR YOUR ATTENTION