2015 ESC Guidelines for the management of infective endocarditis

The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)

Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM)

www.escardio.org/guidelines

The endocarditis team

When to refer a patient with IE to an ‘Endocarditis Team’ in a reference centre?

- Patients with complicated IE (i.e. endocarditis with HF, abscess, or embolic or neurological complication or CHD), should be referred early and managed in a reference centre with immediate surgical facilities
- Patients with non-complicated IE can be initially managed in a nonreference centre, but with regular communication with the reference centre, consultations with the multidisciplinary ‘Endocarditis Team’, and, when needed, with external visit to the reference centre.

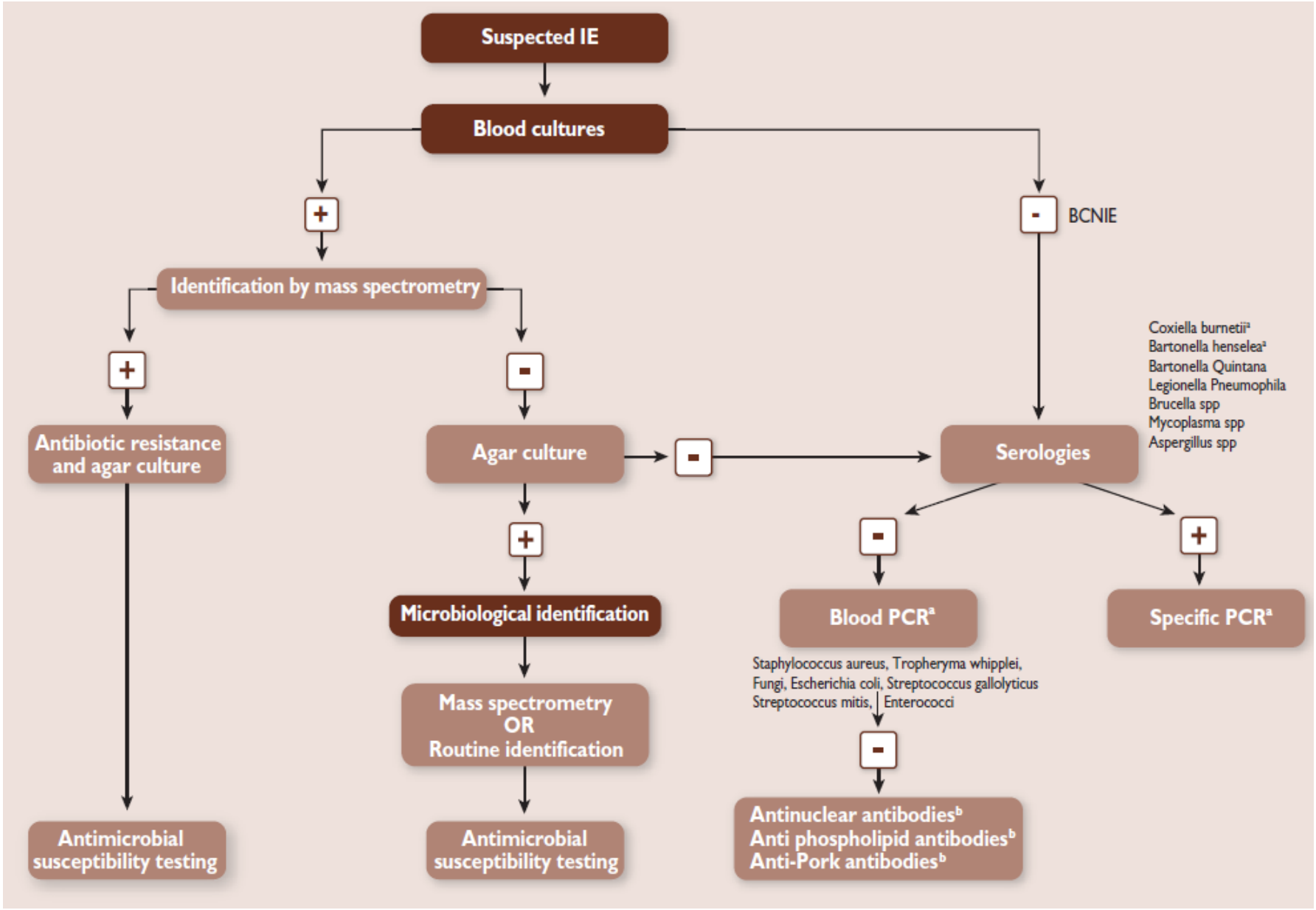
The endocarditis team
Characteristics of the reference centre

- Immediate access to diagnostic procedures should be possible, including TTE, TOE, multislice CT, MRI, and nuclear imaging
- Immediate access to cardiac surgery should be possible during the early stage of the disease, particularly in case of complicated IE (HF, abscess, large vegetation, neurological, and embolic complications)
- Several specialists should be part ot the ‘Endocarditis Team’, including at least cardiac surgeons, cardiologists, anaesthesiologists, ID specialists, microbiologists and, when available, specialists in valve diseases, CHD, pacemaker extraction, echocardiography and other cardiac imaging techniques, neurologists, and facilities for neurosurgery and interventional neuroradiology

The endocarditis team
Role

- The ‘Endocarditis Team’ should have meetings on a regular basis in order to discuss cases, take surgical decisions, and define the type of follow-up
- The ‘Endocarditis Team’ chooses the type, duration, and mode of follow up of antibiotic therapy, according to a standardized protocol, following the current guidelines
- The ‘Endocarditis Team’ should participate in national or international registries, publicly report the mortality and morbidity of their centre, and be involved in a quality improvement programme, as well as in a patient education programme
- The follow-up should be organized on an outpatient visit basis at a frequency depending on the patient’s clinical status (ideally at 1, 3, 6, and 12 months after hospital discharge, since most events occur during this period)

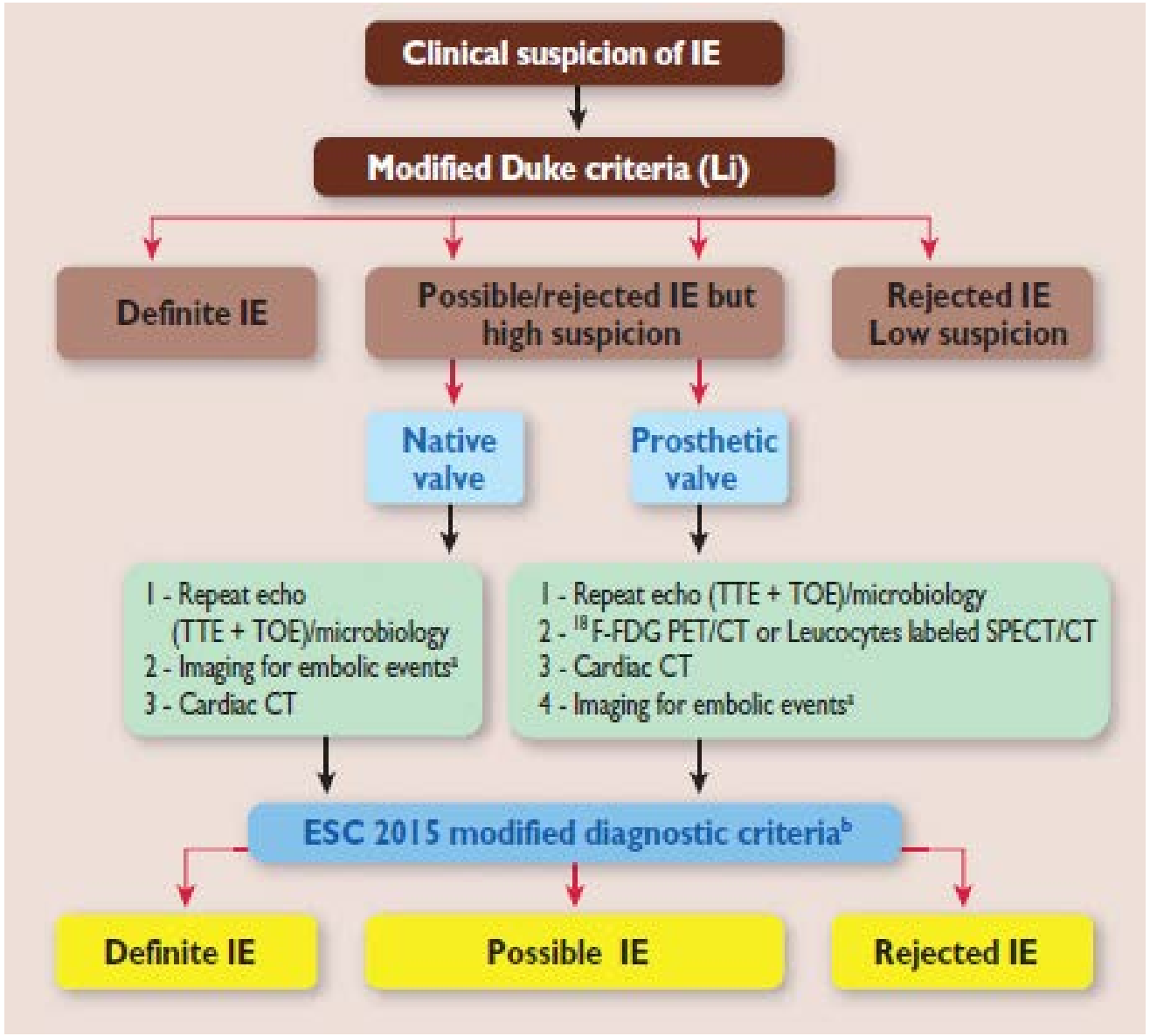
Microbiological diagnostic algorithm in IE



Updated Duke criteria

- **Major criteria**
  - 1. Blood cultures positive for IE
    - a. Typical microorganisms consistent with IE from 2 separate blood cultures: viridans streptococci, S gallolyticus, 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 and last samples drawn ≥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 18F-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 (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

ESC 2015 algorithm for diagnosis of IE



New considerations for Ab Rx of IE in the ESC guidelines

- Aminoglycosides are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated, but they can increase renal toxicity; when they are indicated in other conditions, AG should be given in a single daily dose
- Rifampin should be used only in foreign body infections such as PVE after 3–5 days of effective antibiotic therapy, once the bacteraemia has been cleared
- 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 because they are not available in all European countries. When daptomycin is indicated, it must be given at high doses (≥10 mg/kg, QD) and combined with a 2nd antibiotic to increase activity and avoid the development of resistance
- CLSI instead of EUCAST MIC breakpoints were used…
- The optimal treatment of staphylococcal IE and the empirical treatment are still debated…

Antibiotic treatment of IE due to oral and group D streptococci (1)

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 *or* Amoxicillin[e] *or* Ceftriaxone[f]	12–18 million U/day i.v. either in 4–6 doses or continuously 100–200 mg/kg/day i.v. in 4–6 doses 2 g/day i.v. or i.m. in 1 dose	4 4 4	I I I	B B 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
	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					
Standard treatment: 2-week duration						
Penicillin G *or* Amoxicillin[e] *or* Ceftriaxone[f] combined with Gentamicin[h] *or* Netilmicin	12–18 million U/day i.v. either in 4–6 doses or continuously 100–200 mg/kg/day i.v. in 4–6 doses 2 g/day i.v. or i.m. in 1 dose 3 mg/kg/day i.v. or i.m. in 1 dose 4–5 mg/kg/day i.v. in 1 dose	2 2 2 2 2	I I I I I	B B B B B	6,8, 127, 135–138	Only recommended in patients with non-complicated NVE with normal renal function. 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					
In beta-lactam allergic patients[i]						
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					

Antibiotic treatment of IE due to oral and group D streptococci (2)

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

Antibiotic treatment of IE due to Staphylococcus spp. (1)

Antibiotic	Dosage and route	Duration (weeks)	Class[i]	Level[j]	Ref.[k]	Comments
Native valves						
Methicillin-susceptible staphylococci						
(Flu)cloxacillin *or* oxacillin	12 g/day i.v. in 4–6 doses	4–6	I	B	6,8, 128, 135, 136, 158	Gentamicin addition is not recommended because clinical benefit has not been demonstrated and there is increased renal toxicity
	Paediatric doses:[g] 200–300 mg/kg/day i.v. in 4–6 equally divided doses					
Alternative therapy* Cotrimoxazole[a]	Sulfamethoxazole 4800 mg/day and Trimethoprim 960 mg/day (i.v. in 4–6 doses)	1 i.v. + 5 oral intake	IIb	C		*for *Stahylococcus aureus*
with						
Clindamycin	1800mg/day i.v. in 3 doses	1	IIb	C		
	Paediatric doses:[g] Sulfamethoxazole 60 mg/kg/day and Trimethoprim 12 mg/kg/day (i.v. in 2 doses) Clindamycin 40 mg/kg/day (i.v. in 3 doses)					
Penicillin-allergic patients[h] or methicillin-resistant staphylococci						
Vancomycin[b] **	30–60 mg/kg/day i.v. in 2–3 doses	4–6	I	B	6,8, 135, 136	**Cephalosporins** (cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis
	Paediatric doses:[g] 40 mg/kg/day i.v. in 2–3 equally divided doses					
Alternative therapy**: Daptomycin[c,d]	10 mg/kg/day i.v. once daily	4–6	IIa	C		**Daptomycin** is superior to vancomycin for MSSA and MRSA bacteraemia with vancomycin MIC > 1 mg/L
	Paediatric doses:[g] 10 mg/kg/day i.v. once daily					
Alternative therapy* Cotrimoxazole[a]	Sulfamethoxazole 4800 mg/day and Trimethoprim 960 mg/day (i.v. in 4–6 doses)	1 i.v. + 5 oral intake	IIb	C		*for *Stahylococcus aureus*
with						
Clindamycin	1800mg/day IV in 3 doses	1	IIb	C		

Antibiotic treatment of IE due to Staphylococcus spp. (2)

Antibiotic	Dosage and route	Duration (weeks)	Class[i]	Level[j]	Ref.[k]	Comments
Prosthetic valves						
Methicillin-susceptible staphylococci						
(Flu)cloxacillin *or* oxacillin with Rifampin[e] and Gentamicin[f]	12 g/day i.v. in 4–6 doses	≥ 6	I	B	6,8, 135, 136	Starting rifampin 3–5 days later than vancomycin and gentamicin has been suggested by some experts. Gentamicin can be given in a single daily dose in order to reduce renal toxicity
	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I	B		
	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I	B		
	Paediatric doses:[g] Oxacillin and (flu)cloxacillin as above Rifampin 20 mg/kg/day i.v. or orally in 3 equally divided doses					
Penicillin-allergic patients[h] and methicillin-resistant staphylococci						
Vancomycin[b] with Rifampin[e] and Gentamicin[f]	30–60 mg/kg/day i.v. in 2–3 doses	≥ 6	I	B	6,8, 135, 136	**Cephalosporins** (cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis. Starting rifampin 3–5 days later than vancomycin and gentamicin has been suggested by some experts. Gentamicin can be given in a single daily dose in order to reduce renal toxicity
	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I	B		
	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I	B		
	Paediatric dosing:[g] As above					

Antibiotic treatment of IE due to Enterococcus spp.

Antibiotic	Dosage and route	Duration, weeks	Class[g]	Level[h]	Ref.[i]	Comments
Beta-lactam and gentamicin-susceptible strains (for resistant isolates see [a,b,c])						
Amoxicillin* with Gentamicin[d]	200 mg/kg/day i.v. in 4–6 doses	4–6	I	B	6,8, 129, 135, 136, 186	6-week therapy recommended for patients with >3 months symptoms or PVE
	3 mg/kg/day i.v. or i.m. in 1 dose	2–6**	I	B		
	Paediatric doses:[e] Ampicillin 300 mg/kg/day i.v. in 4–6 equally divided doses Gentamicin 3 mg/kg/day i.v. or i.m. in 3 equally divided doses					
Ampicillin with Ceftriaxone	200 mg/kg/day i.v. in 4–6 doses	6	I	B	183–185	This combination is active against *Enterococcus faecalis* strains with and without HLAR, being the combination of choice in patients with HLAR *E. faecalis* endocarditis. This combination is not active against *E. faecium*
	4 g/day i.v. or i.m. in 2 doses	6	I	B		
	Paediatric doses:[e] Amoxicillin as above Ceftriaxone 100 mg/kg/12 h i.v. or i.m.					
Vancomycin[f] with Gentamicin[d]	30 mg/kg/day i.v. in 2 doses	6	I	C		
	3 mg/kg/day i.v. or i.m. in 1 dose	6	I	C		
	Paediatric doses:[e] Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses. Gentamicin as above					

Antibiotic treatment of IE due to Enterococcus spp.

Antibiotic	Dosage and route	Duration, weeks	Class[g]	Level[h]	Ref.[i]	Comments
Beta-lactam and gentamicin-susceptible strains (for resistant isolates see [a,b,c])						
Amoxicillin* with Gentamicin[d]	200 mg/kg/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 1 dose	4–6 2–6**	I I	B B	6,8, 129, 135, 136, 186	6-week therapy recommended for patients with >3 months symptoms or PVE
	Paediatric doses:[e] Amoxicillin as above Ceftriaxone 100 mg/kg/12 h i.v. or i.m.					This combination is not active against *E. faecium*
Vancomycin[f] with Gentamicin[d]	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 1 dose **Paediatric doses:**[e] Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses. Gentamicin as above	6 6	I I	C C		

HLAR: high-level aminoglycoside resistance; IE: infective endocarditis; MIC: minimum inhibitory concentration; PBP: penicillin binding protein; PVE: prosthetic valve endocarditis.
[a]High-level resistance to gentamicin (MIC >500 mg/L): if susceptible to streptomycin, replace gentamicin with streptomycin 15 mg/kg/day in two equally divided doses.
[b]Beta-lactam resistance: (i) if due to beta-lactamase production, replace ampicillin with ampicillin–sulbactam or amoxicillin with amoxicillin–clavulanate; (ii) if due to PBP5 alteration, use vancomycin-based regimens.
[c]Multiresistance to aminoglycosides, beta-lactams and vancomycin: suggested alternatives are (i) daptomycin 10 mg/kg/day plus ampicillin 200 mg/kg/day i.v. in four to six doses; (ii) linezolid 2 × 600 mg/day i.v. or orally for ≥8 weeks (IIa, C) (monitor haematological toxicity); (iii) quinupristin–dalfopristin 3 × 7.5 mg/kg/day for ≥8 weeks. Quinupristin–dalfopristin is not active against *E. faecalis*; (iv) for other combinations (daptomycin plus ertapenem or ceftaroline), consult infectious diseases specialists.

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

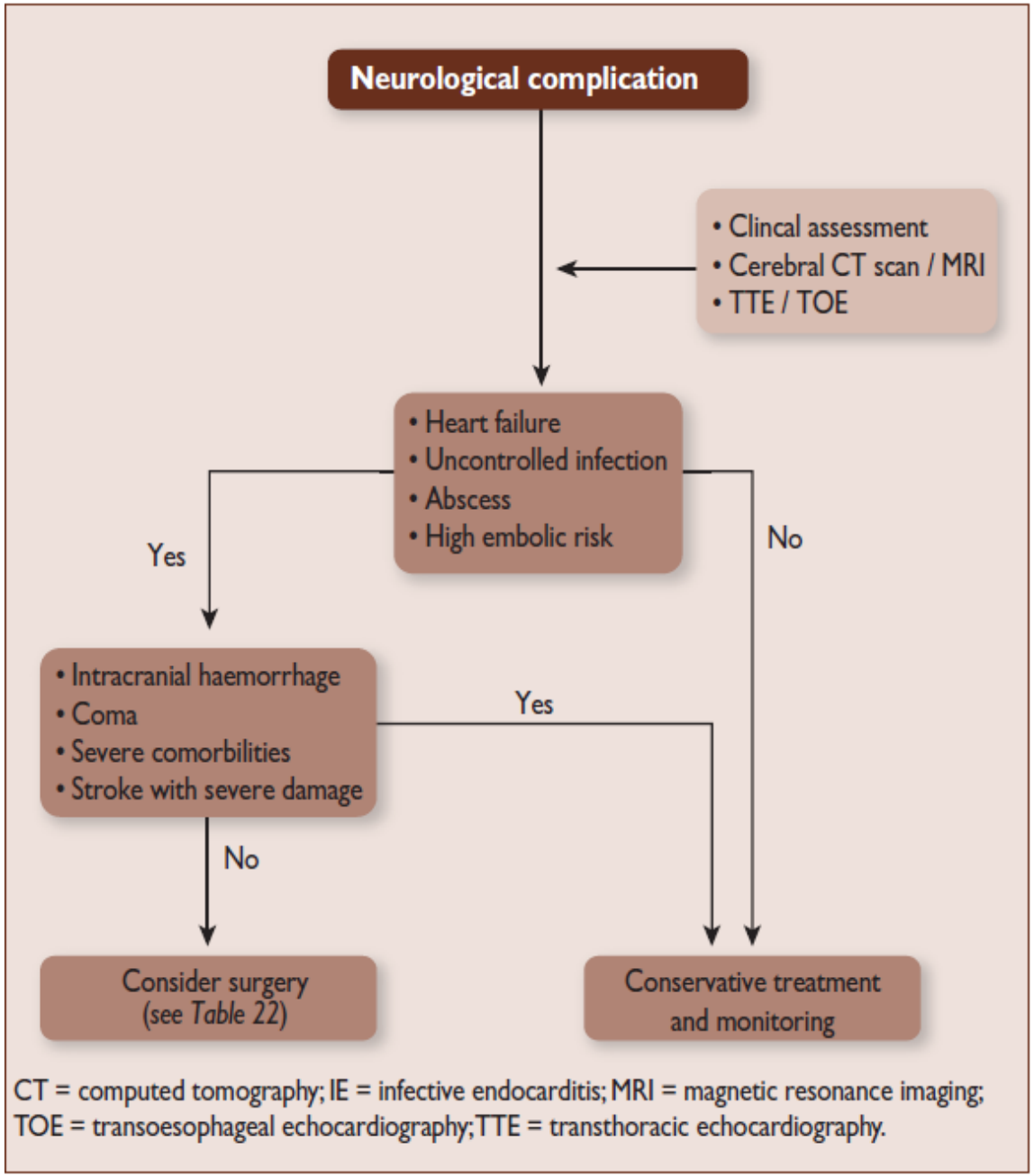
Antibiotic	Dosage and route	Class[b]	Level[c]	Comments
Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis				
Ampicillin with (Flu)cloxacillin *or* oxacillin with Gentamicin[d]	12 g/day i.v. in 4–6 doses 12 g/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. 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
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

Indications and timing of surgery in left-sided NV and PV IE

Indications for surgery	Timing[a]	Class[b]	Level[c]	Ref.[d]
1. Heart failure				
Aortic or mitral NVE or PVE with severe acute regurgitation, obstruction or fistula causing refractory pulmonary oedema or cardiogenic shock	Emergency	I	B	111,115, 213,216
Aortic or mitral NVE or PVE with severe regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor haemodynamic tolerance	Urgent	I	B	37,115, 209,216, 220,221
2. Uncontrolled infection				
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent	I	B	37,209, 216
Infection caused by fungi or multiresistant organisms	Urgent/ elective	I	C	
Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci	Urgent	IIa	B	123
PVE caused by staphylococci or non-HACEK gram-negative bacteria	Urgent/ elective	IIa	C	
3. Prevention of embolism				
Aortic or mitral NVE or PVE with persistent vegetations >10 mm after one or more embolic episode despite appropriate antibiotic therapy	Urgent	I	B	9,58,72, 113,222
Aortic or mitral NVE with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk	Urgent	IIa	B	9
Aortic or mitral NVE or PVE with isolated very large vegetations (>30 mm)	Urgent	IIa	B	113
Aortic or mitral NVE or PVE with isolated large vegetations (>15 mm) and no other indication for surgery[e]	Urgent	IIb	C	

Management of neurological complications of IE

Recommendations	Class[a]	Level[b]	Ref.[c]
After a silent embolism or transient ischaemic attack, cardiac surgery, if indicated, is recommended without delay	I	B	105, 263
Neurosurgery or endovascular therapy is recommended for very large, enlarging or ruptured intracranial infectious aneurysms	I	C	
Following intracranial haemorrhage, surgery should generally be postponed for ≥1 month	IIa	B	264–266
After a stroke, surgery indicated for HF, uncontrolled infection, abscess, or persistent high embolic risk should be considered without any delay as long as coma is absent and the presence of cerebral haemorrhage has been excluded by cranial CT or MRI	IIa	B	9,263
Intracranial infectious aneurysms should be looked for in patients with IE and neurological symptoms. CT or MR angiography should be considered for diagnosis. If non-invasive techniques are negative and the suspicion of intracranial aneurysm remains, conventional angiography should be considered	IIa	B	267, 268



CT = computed tomography; IE = infective endocarditis; MRI = magnetic resonance imaging; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

Cardiac device-related IE: diagnosis

Recommendation	Class	Level
Three or more sets of blood cultures are recommended before prompt initiation of antimicrobial therapy for CIED infection	I	C
Lead-tip culture is indicated when the CIED is explanted	I	C
TOE is recommended in patients with suspected CDRIE with positive or negative blood cultures, independent of the results of TTE, to evaluate lead-related endocarditis and heart valve infection	I	C
Intracardiac echocardiography may be considered in patients with suspected CDRIE, positive blood cultures and negative TTE and TOE results	IIb	C
Radiolabelled leucocyte scintigraphy and 18F-FDG PET/CT scanning may be considered additive tools in patients with suspected CDRIE, positive blood cultures and negative echocardiography	IIb	C

Cardiac device-related IE: treatment

Recommendation	Class	Level
Prolonged (i.e. before and after extraction) antibiotic therapy and complete hardware (device and leads) removal are recommended in definite CDRIE, as well as in presumably isolated pocket infection	I	C
Complete hardware removal should be considered on the basis of occult infection without another apparent source of infection	IIa	C
In patients with NVE or PVE and an intracardiac device with no evidence of associated device infection, complete hardware extraction may be considered	IIb	C
Percutaneous extraction is recommended in most patients with CDRIE, even those with vegetations >10 mm	I	B
Surgical extraction should be considered if percutaneous extraction is incomplete or impossible or when there is associated severe destructive tricuspid IE	IIa	C
Surgical extraction may be considered in patients with large vegetations (>20 mm)	IIb	C

Cardiac device-related IE: reimplantation and prophylaxis

Recommendation	Class	Level
After device extraction, reassessment of the need for reimplantation is recommended	I	C
When indicated, definite reimplantation should be postponed if possible, to allow a few days or weeks of antibiotic therapy	IIa	C
A ‘temporary’ ipsilateral active fixation strategy may be considered in pacemaker-dependent patients requiring antibiotic treatment before reimplantation	IIb	C
Temporary pacing is not routinely recommended	III	B
Routine antibiotic prophylaxis is recommended before device implantation	I	B
Potential sources of sepsis should be eliminated ≥2 weeks before implantation of an intravascular/cardiac foreign material, except in urgent procedures	IIa	C

Recommendations for the use of antithrombotic therapy

Recommendation	Class	Level
Interruption of antiplatelet therapy is recommended in the presence of major bleeding	I	B
In intracranial haemorrhage, interruption of all anticoagulation is recommended	I	C
In ischaemic stroke without haemorrhage, replacement of oral anticoagulant (anti-vitamin K) therapy by unfractionated or low molecular weight heparin for 1–2 weeks should be considered under close monitoring	IIa	C
In patients with intracranial haemorrhage and a mechanical valve, unfractionated or low molecular weight heparin should be reinitiated as soon as possible following multidisciplinary discussion	IIa	C
In the absence of stroke, replacement of oral anticoagulant therapy by unfractionated or low molecular weight heparin for 1–2 weeks should be considered in the case of Staphylococcus aureus IE under close monitoring	IIa	B
Thrombolytic therapy is not recommended in patients with IE	III	C