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Directorate General of Health - DGS
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Proteiform disease with geographical differences

Developing countries
- Rheumatic disease
- Mean age: 30-40 yo
- Streptococcal and blood culture negative
- Often subacute (80%)

Developed countries
- Health care associated: chronic haemodyalisis, diabetes, intravascular devices or IV drug abusers
- Degenerative – elderly
- Mean age: 60 yo
- Usually Staphylococcal
- Increasingly acute (33%)

Unchanged mortality in the last 40 years 20%
## Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTE is recommended as the first-line imaging modality in suspected IE.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>TOE is recommended in all patients with clinical suspicion of IE and a negative or non-diagnostic TTE.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>TOE is recommended in patients with clinical suspicion of IE, when a prosthetic heart valve or an intracardiac device is present.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Repeat TTE and/or TOE within 5–7 days is recommended in case of initially negative examination when clinical suspicion of IE remains high.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Echocardiography should be considered in <em>Staphylococcus aureus</em> bacteraemia.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>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.</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>
Patient characteristics
- Older age
- Prosthetic valve IE
- Diabetes mellitus
- Comorbidity

Clinical complications of IE
- Heart failure
- Renal failure
- More than moderate area of ischaemic stroke
- Brain haemorrhage
- Septic shock

Microorganism
- *Staphylococcus aureus*
- Fungi
- Non-HACEK Gram-negative bacilli

Predictors of poor outcome

Echocardiographic findings
- Periannular 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 pressure
- The sensitivity of the Duke criteria can be improved by **new imaging modalities**:  
  - Cardiac CT scan
  - PET/CT & SPECT/CT
  - Cerebral MRI

that allow the diagnosis of embolic events and cardiac involvement when TTE/TOE findings are negative or doubtful.

*Habib G et al. European Heart Journal; doi:10.1093/eurheartj/ehv319*
Definition of infective endocarditis (modified Duke criteria)

<table>
<thead>
<tr>
<th>Definite IE</th>
<th>Possible IE</th>
<th>Rejected IE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathological criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microorganisms demonstrated by culture or on histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or</td>
<td>1 major criterion and 1 minor criterion; or</td>
<td>Firm alternate diagnosis; or</td>
</tr>
<tr>
<td>Pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis</td>
<td>3 minor criteria</td>
<td>Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days; or</td>
</tr>
<tr>
<td><strong>Clinical criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 major criteria; or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 major criterion and 3 minor criteria; or</td>
<td></td>
<td>No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or</td>
</tr>
<tr>
<td>5 minor criteria</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Major criteria**

1. Blood cultures positive for IE
   a. Typical microorganisms consistent with IE from 2 separate blood cultures:
      • Viridans streptococci, Streptococcus galolyticus (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 18F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT.
   c. Definite paravalvar 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.

Successful treatment relies on microbial eradication by antimicrobial drugs.

Surgery contributes by removing infected material and draining abscesses.

Host defences are of little help.

Early use of bactericidal drugs, according to PK/PD

TDM to guarantee efficacy and avoid toxicity

Aminoglycosides synergize with cell-wall inhibitors (i.e. beta-lactams and glycopeptides) for bactericidal activity and are useful either for shortening the duration of therapy (e.g. oral streptococci) or for eradication of problematic organisms (e.g. Enterococcus spp.).
Initial choice of antibiotics depends on:

1. Whether the patient has received previous antibiotic therapy.
2. Whether the infection affects a native valve or a prosthesis [and if so, when surgery was performed (early vs. late PVE)].
3. The place of acquisition of the infection (community, nosocomial, or nonnosocomial healthcare-associated IE) and knowledge of the local epidemiology, especially for antibiotic resistance and specific “culture-negative pathogens”


Classification and microbiology

- **NVE and late PVE** ( > 1 year after valve surgery) regimens should cover staphylococci, streptococci and enterococci.

- **Early PVE or healthcare-associated IE** regimens should cover methicillin-resistant staphylococci, enterococci and, ideally, non-HACEK Gram-negative pathogens.

- **In HA-IE**, usually associated to IV lines in patients with renal failure, cancer, haemodyalisis, prosthetic valve, pacemaker, MRSA, *Enterococcus* and *Candida* should be covered.

- **Once the pathogen is identified**, the antibiotic treatment must be adapted to its antimicrobial susceptibility pattern.

  
  *Fowler VG et al. Arch Intern Med 2003; 163: 2066-72*  
  *Hsu BB. Infect Control Hosp Epidemiol 2005; 26: 654-7*  
When indicated, aminoglycosides should be given in a single daily dose and with TDM to reduce nephrotoxicity.
Controversies in Antimicrobial Therapy

- **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, because of the likely antagonistic effect of the antibiotic combinations with rifampin against planktonic/replicating bacteria, the synergy seen against dormant bacteria within the biofilms and prevention of rifampin-resistant variants.

- **Cloxacillin/cefazolin** administration is associated with lower mortality rates than other beta-lactams, including amoxicillin/clavulanic acid or ampicillin/sulbactam, and vancomycin for empirically treating MSSA bacteraemia/endocarditis.

Efficacy of nafcillin versus vancomycin in MSSA bacteraemia*

Vancomycin was an independent factor associated with failure (OR: 6.5, \( P = 0.048 \))

*Excludes patients with infective endocarditis

### Vancomycin MIC above 1.5 μg/ml (Etest methodology) is associated with increased mortality

<table>
<thead>
<tr>
<th></th>
<th>Number of MRSA, (MSSA) Isolates</th>
<th>Source</th>
<th>Mortality % (n)</th>
<th>Vancomycin MIC (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≤1</td>
</tr>
<tr>
<td>Bae et al. 2009</td>
<td>65 (0)</td>
<td>IE</td>
<td>39% (11/28)</td>
<td>67% (4/6)</td>
</tr>
<tr>
<td>Haque et al. 2010</td>
<td>158 (0)</td>
<td>HAP</td>
<td>23% (10/43)</td>
<td>52% (15/29)</td>
</tr>
<tr>
<td>Holmes et al. 2011</td>
<td>199 (324)</td>
<td>BSI</td>
<td>12% (7/57)</td>
<td>27% (48/179)</td>
</tr>
<tr>
<td>Musta et al. 2009</td>
<td>242 (0)</td>
<td>BSI</td>
<td>19% (7/36)</td>
<td>48% (10/21)</td>
</tr>
<tr>
<td>Neuner et al. 2012</td>
<td>196 (0)</td>
<td>BSI</td>
<td>10% (1/10)</td>
<td>28% (21/76)</td>
</tr>
</tbody>
</table>

van Hal SJ et al. CID 2012; 54: 755

AUC/MIC > 400 virtually impossible for MRSA with Vancomycin MIC > 1,5 mcg/ml
Daptomycin instead of vancomycin

Daptomycin 10-12 mg/kg

MSSA
Flucloxacillin

MRSA
Vanco MIC ≤1 μg/ml Vancomycin

MRSA
Vanco MIC >1 μg/ml Daptomycin 10-12 mg/kg/d

Daptomycin covers MSSA and MRSA, but:
- high dose needed (10-12 mg/Kg od)
- daptomycin resistance may be creeping up
- still worse than oxacillin

Therefore, never as monotherapy
Mechanism of Vancomycin /Betalactam synergism
“Taking advantage of the backdoor left open”

- not totally clear
- but may include:
  - β-lactam induced potentiation of host defense peptide activity against S. aureus,
  - β-lactam induced alteration of MRSA cell wall which allows for improved VAN binding,
  - a “see-saw” effect whereby reduced vancomycin susceptibility results in reduced transcription of mecA and increased susceptibility to β-lactams.

Retrospective cohort monocentric study of patients with MRSA bacteremia who received vanco + one betalactam (50 pt) versus Vancomycin alone (30 pt).

**TABLE 3 Microbiological eradication in patients with MRSA bacteremia**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Eradication frequency by treatment group&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Combo&lt;sup&gt;b&lt;/sup&gt;</td>
<td>VAN alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>48/50 (96.0)</td>
<td>24/30 (80.0)</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>Patients with IE</td>
<td>11/11 (100.0)</td>
<td>9/11 (81.8)</td>
<td>0.200</td>
<td></td>
</tr>
</tbody>
</table>

Patients with MRSA bacteremia who received Vancomycin+betalactam therapy were more likely to experience microbiological eradication of MRSA than patients who received vancomycin alone.

**TABLE 5 Multivariable analysis of the association between potential predictor variables and microbiological eradication in patients with MRSA bacteremia**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value for the variable&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group (Combo vs VAN alone)</td>
<td>11.24 (1.72–144.34)</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>Vancomycin serum level (mg/liter)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.93 (0.86–0.98)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>0.042 (0.01–0.25)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Dilworth TJ et al. AAC 2014; 58: 102-9*
Combining an anti-staphylococcal β-lactam with vancomycin may shorten the duration of MRSA bacteremia. Further trials with a larger sample size are warranted.

patients with persistent MRSA bacteremia during treatment with daptomycin or “or difficult-to-treat”, appear to quickly clear their bacteremia with the addition of nafcillin or oxacillin, ceftobiprole or ceftaroline.


CORE (Cubicin Outcomes Registry and Experience) study shows that the overall treatment efficacy was slightly enhanced with the addition of a β-lactam (87% vs. 78%; p=0.336), but this trend was most pronounced for bacteraemia associated with endocarditis or bone and joint infection or bacteraemia from an unknown source (90% vs. 57%; p=0.061)


Moreover, daptomycin/β-lactam combination seems to be able to delay in vitro the emergence of daptomycin-resistant strains

When indicated, aminoglycosides should be given in a single daily dose and with TDM to reduce nephrotoxicity.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daptomicin</strong></td>
<td>10-12 mg/Kg od</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gentamicin</strong></td>
<td>3 mg/kg/day i.v. or i.m. in 1 dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rifampin</strong></td>
<td>900–1200 mg i.v. or orally in 2 or 3 divided doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flucloxacillin</strong></td>
<td>12 g/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Strains penicillin-susceptible (MIC < 0.125 mg/L) oral and digestive streptococci

#### Standard treatment: 4-week duration

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration (weeks)</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G or Amoxicillin® or Ceftriaxone</td>
<td>12–18 million U/day i.v. either in 4–6 doses or continuously</td>
<td>4</td>
<td>I</td>
<td>B</td>
<td>6.8, 135–139</td>
<td>Preferred in patients &gt; 65 years or with impaired renal or VIII (vestibulocochlear) cranial nerve functions. 6-week therapy recommended for patients with PVE.</td>
</tr>
<tr>
<td>Paediatric doses: 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</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

#### Standard treatment: 2-week duration

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration (weeks)</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G or Amoxicillin® or Ceftriaxone</td>
<td>12–18 million U/day i.v. either in 4–6 doses or continuously</td>
<td>2</td>
<td>I</td>
<td>B</td>
<td>6.8, 135–138</td>
<td>Only recommended in patients with non-complicated NVE with normal renal function.</td>
</tr>
<tr>
<td>Paediatric doses: Vancomycin 40 mg/kg/day i.v. in 2 or 3 equally divided doses</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### In beta-lactam allergic patients

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration (weeks)</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>30 mg/kg/day i.v. in 2 doses</td>
<td>4</td>
<td>I</td>
<td>C</td>
<td></td>
<td>6-week therapy recommended for patients with PVE.</td>
</tr>
<tr>
<td>Paediatric doses: Vancomycin 40 mg/kg/day i.v. in 2 or 3 equally divided doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Strains relatively resistant to penicillin (MIC 0.250–2 mg/L)

#### Standard treatment

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration (weeks)</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G or Amoxicillin® or Ceftriaxone</td>
<td>24 million U/day i.v. either in 4–6 doses or continuously</td>
<td>4</td>
<td>I</td>
<td>B</td>
<td>6.8, 135, 136</td>
<td>6-week therapy recommended for patients with PVE.</td>
</tr>
<tr>
<td>200 mg/kg/day i.v. in 4–6 doses</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 g/day i.v. or i.m. in 1 dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mg/kg/day i.v. or i.m. in 1 dose</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

#### In beta-lactam allergic patients

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration (weeks)</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin with Gentamicin</td>
<td>30 mg/kg/day i.v. in 2 doses</td>
<td>4</td>
<td>I</td>
<td>C</td>
<td></td>
<td>6-week therapy recommended for patients with PVE.</td>
</tr>
<tr>
<td>3 mg/kg/day i.v. or i.m. in 1 dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric doses: As above</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
IE due to **group A, B, C, or G streptococci**—including Streptococcus anginosus group (S. constellatus, S. anginosus, and S. intermedius) is relatively rare.

- Group A streptococci are uniformly susceptible to beta-lactams whereas other serogroups may display some degree of resistance.
- Group B, C, and G streptococci and S. anginosus produce abscesses and thus may require adjunctive surgery.
- Mortality from group B PVE is very high and cardiac surgery is recommended. **Antibiotic treatment is similar to that of oral streptococci, except that short term therapy is not recommended. Gentamicin should be given for 2 weeks**.

IE due to **S. pneumoniae** is associated with meningitis in up to 30% of cases.

- Treatment of penicillin-susceptible and intermediate strains (MIC ≤0.06 mg/L) is **similar to that of oral streptococci**, except for the use of short-term 2-week therapy, which has not been formally investigated.
- For R strains and in case of meningitis, **cephalosporins HD are recommended**.

Aminoglycosides are no longer recommended in *Staph aureus* NVE: clinical benefits not demonstrated and can increase renal toxicity.
The demonstration, in several cohort studies of E. faecalis IE including hundreds of cases, that ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for non-HLAR E. faecalis IE.

It is also safer, without any nephrotoxicity.

In addition, this is the combination of choice for treating HLAR E. faecalis IE.

The total daily dose of gentamicin can be given in a single daily dose instead of the two or three divided doses recommended up to now.

The length of the treatment for non-HLAR E. faecalis IE may be safely shortened from 4–6 weeks to 2 weeks, reducing the rates of nephrotoxicity to very low levels.
Prosthetic valve IE

- More difficult diagnosis and worse prognosis
- To be managed aggressively, unless non-Staph late PVE
- Surgery for PVE follows the general principles outlined for NVE
- The best therapeutic option in PVE is still debatable but...

- Surgery is recommended for PVE in high-risk subgroups identified by prognostic assessment: PVE complicated by HF, severe prosthetic dysfunction, abscess or persistent fever.
- Emergency surgery is indicated only in cases with refractory congestive HF leading to pulmonary oedema or shock, as in NVE.
- Patients with uncomplicated non-staphylococcal and non-fungal late PVE can be managed conservatively.

Drug treatment of PVE should last longer (at least 6 weeks) than that of NVE (2–6 weeks), but is otherwise similar, except for staphylococcal PVE, where the regimen should include rifampin whenever the strain is susceptible.
<table>
<thead>
<tr>
<th>Indications for surgery</th>
<th>Timing</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic or mitral NVE or PVE with severe acute regurgitation, obstruction or fistula causing refractory pulmonary oedema or cardiogenic shock</td>
<td>Emergency</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Aortic or mitral NVE or PVE with severe regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor haemodynamic tolerance</td>
<td>Urgent</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>2. Uncontrolled infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)</td>
<td>Urgent</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Infection caused by fungi or multiresistant organisms</td>
<td>Urgent/elective</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci</td>
<td>Urgent</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>PVE caused by staphylococci or non-HACEK gram-negative bacteria</td>
<td>Urgent/elective</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>3. Prevention of embolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic or mitral NVE or PVE with persistent vegetation &gt; 10 mm after one or more embolic episode despite appropriate antibiotic therapy</td>
<td>Urgent</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Aortic or mitral NVE with vegetation &gt; 10 mm, associated with severe valve stenosis or regurgitation, and low operative risk</td>
<td>Urgent</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Aortic or mitral NVE or PVE with isolated very large vegetation (&gt; 30 mm)</td>
<td>Urgent</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Aortic or mitral NVE or PVE with isolated large vegetation (&gt; 15 mm) and no other indication for surgery</td>
<td>Urgent</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

Fever and persisting positive cultures after 7–10 days of antibiotic therapy may be related to several factors:

- inadequate antibiotic therapy,
- resistant or difficult to treat organisms,
- infected lines,
- locally uncontrolled infection (perivascular extension),
- embolic complications or extracardiac site of infection,
- adverse reaction to antibiotics.

Management includes:

- antibiotic regimen change
- replacement of i.v. lines
- repeat laboratory tests,
- repeat blood cultures,
- repeat echocardiography,
- search for an intracardiac or extracardiac focus of infection.

Persistent blood cultures 48–72 h after initiation of antibiotics are an independent risk factor for hospital mortality. Surgery should be considered when blood cultures remain positive after 3 days of antibiotic therapy, after the exclusion of other potential causes.
Perivalvular extension of IE

- The most frequent cause of uncontrolled infection
- Associated with a poor prognosis and high likelihood of the need for surgery.
- Includes abscess formation, pseudoaneurysms and fistulae
- Should be suspected in cases with persistent unexplained fever or new atrio-ventricular block.
- TOE, MSCT and PET/CT\textsuperscript{103} are particularly useful for the diagnosis, while the sensitivity of TTE is 50%
- Frequently discovered on a \textbf{systematic TOE}

Systemic embolism
25-50% of cases

- Embolic events may be totally silent in 20–50% of patients with IE, especially those affecting the splenic or cerebral circulation
- Systematic US and rational use of systematic abdominal and cerebral CT scanning
- Higher risk in the first days
- Incidence of stroke in patients receiving appropriate antimicrobial therapy was 4.8/1000 patient-days in the first week of therapy, falling to 1.7/1000 patient-days in the second week, and further thereafter

Complications of IE

- **Neurologic complication** (15-30% of patients and often silent)
- **Infectious aneurysms:** obtain image if any neurological symptom or sign; surgery if growth, rupture or significant symptoms
- **Splenic complications**
- **Myocarditis and pericarditis**
- **Heart rhythm and conduction disturbances**
- **Musculoskeletal complications**
- **Acute Renal Failure** (6-30%, often multifactorial)
In patients without neurological symptoms, MRI shows cerebral lesions in 50% of the patients, most often ischaemic lesions.
The benefit of a collaborative multidisciplinary “endocarditis” team

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
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<tbody>
<tr>
<td>Patients with complicated IE should be evaluated and managed at an early stage in a reference centre, with immediate surgical facilities and the presence of a multidisciplinary ‘Endocarditis Team’, including an ID specialist, a microbiologist, a cardiologist, imaging specialists, a cardiac surgeon and, if needed, a specialist in CHD</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>For patients with uncomplicated IE managed in a non-reference centre, early and regular communication with the reference centre and, when needed, visits to the reference centre should be made</td>
<td>IIa</td>
<td>B</td>
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</table>

Characteristics of the reference centre

1. Immediate access to diagnostic procedures should be possible, including TTE, TOE, multislice CT, MRI, and nuclear imaging.
2. 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).
3. Several specialists should be present on site (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 benefit of a referral system with centers of excellence
Subacute

...the simple being those with few or slight symptoms, and which run a favourable course; the malignant, the cases with severe constitutional disturbance and extensive valve-lesions, whether ulcerative or vegetative, the term being more clinical than anatomical.

The patient has, perhaps, aortic-valve disease, and is under treatment for failing compensation, when he begins to have slight irregular fever, an evening exacerbation of two or three degrees, some increase in cardiac pain, and a sense of restlessness and distress. Embolic phenomena may develop; a sudden hemiplegia; pain in the region of the spleen, and signs of enlargement of the organ; or there is pain in the back, with bloody urine. In other instances, peripheral embolism may take place, with gangrene of the foot or hand. There may be hebetude or a low delirium. Instances such as these are extremely common; and while, in some, the process may be very intense, in others it is essentially chronic, and may last for weeks and months... In very many instances, there is no history of rheumatic fever or of other constitutional disorder; but the endocarditis appears to attack the sclerotic valves as a primary process...

the only one [theory of acute endocarditis] to which I shall refer, is, that it is in all its forms, an essentially mycotic process; the local and constitutional effects being produced by the growth on the valves, and the transference to distant parts of microbes, which vary in character with the disease in which it develops. This very attractive theory can be adjusted to meet every requirement of the case...

Gulstonian Lectures "On Malignant Endocarditis," Royal College of Physicians, London
British Medical Journal, 1885, 1: 467-70, 522-526, 577-579
Conclusions

- A proteiform and evolving disease
- New patients, new forms, new microbiology
- Investigate, culture and treat
- Incorporate modern imagiology for diagnostic work up
- Get it right first time - empirically
- Achieve quick bactericidal activity
- Incorporate PK/PD and TDM concepts
- Do not forget new drugs
- Fine tune your antibiotics according to microbiological results
- Do not forget source control – surgery
- Collaborative multidisciplinary teams and reference centers