My patient has a fever: Is it endocarditis? What should I do?

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Honorary Senior Research Fellow University of Birmingham
Does this patient have endocarditis?

- IVDU
- Murmur, septic emboli to chest, brain, kidneys
- Inflammatory raised, WCC raised
- Blood cultures x3 sets positive for staph aureus
Does this patient have endocarditis?

IVDU

Murmur, septic emboli to chest, brain, kidneys

Inflammatory raised, WCC raised

Blood cultures x3 sets positive for staph aureus
Does this patient have endocarditis?

ESKD. HD line removed.

Inflammatory raised, WCC raised

Blood cultures x3 sets negative

Previous TTEs looked the same
Does this patient have endocarditis?

Valve sparing aortic root replacement 2012

Fever 2/7 presents with stroke to A&E

Inflammatory raised, WCC raised

Blood cultures x3 sets negative (Abx given in A&E)
## Modified Duke Criteria

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Diagnostic</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive BC</td>
<td>2 separate BC</td>
<td>Strep viridans</td>
</tr>
<tr>
<td></td>
<td><em>Persistently positive BC</em></td>
<td>Strep bovis / gallolyticus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HACEK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Staph aureus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enterococci</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coxiella burnetii</td>
</tr>
<tr>
<td>Endocardial involvement</td>
<td></td>
<td>Oscillating mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Path of regurgitant jet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abscess</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dehiscence</td>
</tr>
<tr>
<td>Minor</td>
<td>Predisposition Previous IE, IVDU, vascular lines</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>&gt;38°C</td>
<td></td>
</tr>
<tr>
<td>Vascular phenomena</td>
<td>Aneurysm, arterial emboli, pul infarcts, intracranial haemorrhages, Janeway</td>
<td></td>
</tr>
<tr>
<td>Immune phenomena</td>
<td>GN, Osler’s nodes, Roth spots</td>
<td></td>
</tr>
<tr>
<td>Micro</td>
<td>Single positive BC (not coag neg staph), serology / PCR</td>
<td></td>
</tr>
<tr>
<td>Echo</td>
<td>Other than stated above</td>
<td></td>
</tr>
</tbody>
</table>

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.

**HACEK:**
Haemophilus spp
Aggregatibacter
Cardiobacterium
Eikenella spp
Kingella spp

- **High sensitivity, high specificity**
  - **Definite:** 2 major, 1 major 3 minor, 5 minor
  - **Possible:** 1 major + 1 minor or 3 minor
  - **Rejected:** Not meet criteria, resolution <4 days

Li et al. 2000
Endocarditis is a clinical diagnosis

CASE 1 - YES
2 Major Duke criteria
+ 4 minor

CASE 2 - NO
No Major Duke criteria
+ 2 minor

CASE 3 - YES
1 Major Duke criteria
+ 3 minor
How do you get IE?

- Abnormal cardiac tissue: nonbacterial thrombotic endocarditis (NBTE)
- Undamaged cardiac tissue: pro-inflammatory endothelial lesion (staph)

**TRANSIENT BACTEREAEMIA**
- Chewing
- Tooth brushing
- Invasive procedure
- IVDU
- Malignancy

Very dependent on magnitude of bacteraemia and pathogen

Werden 2013 Nat. Rev. Cardiol
Table 2  Levels of evidence

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Data derived from multiple randomized clinical trials or meta-analyses.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of evidence B</td>
<td>Data derived from a single randomized clinical trial or large non-randomized studies.</td>
</tr>
<tr>
<td>Level of evidence C</td>
<td>Consensus of opinion of the experts and/or small studies, retrospective studies, registries.</td>
</tr>
</tbody>
</table>
Changing trends

The incidence of IE is increasing

- Increasing prevalence
- Increasing native valve disease
- Devices / prosthetic material (approx. 30% IE cases)
- In hospital mortality static 15-30%
- Bugs are changing:
  - Staph aureus 32%
  - Coag neg staph 11%
  - Oral strep 17%
  - Enterococci 10%
  - Strep Bovis / galloyticus 6%

Still rare: Incidence 3-7 per 100,000 person years
But 3rd-4th most life threatening infection
Profile of IE Past & Present

<table>
<thead>
<tr>
<th>PAST</th>
<th>PRESENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic valves</td>
<td>Prosthetic valves</td>
</tr>
<tr>
<td>Young</td>
<td>Aging</td>
</tr>
<tr>
<td></td>
<td>Intra-cardiac devices</td>
</tr>
<tr>
<td></td>
<td>Dialysis</td>
</tr>
<tr>
<td>Oral Streptococci</td>
<td>Staphylococci</td>
</tr>
<tr>
<td>Estimated mortality 20%</td>
<td>Estimated mortality 20%</td>
</tr>
<tr>
<td>Minimal evidence base</td>
<td>Minimal evidence base</td>
</tr>
</tbody>
</table>

Relevance to NHS:
- Median 4-6 week in-patient stay,
- Approx. 50% require cardiac surgery,
- In-hospital mortality still around 20%

Huge Financial Costs

Outcomes improved by prompt diagnosis, Abx, early surgery (if indicated)
Making a diagnosis of IE:

“Clues” Typical presentation
- 90% fever
- Murmur 85% (new 48%)
- Emboli 30%
- “High risk”: VHD, congenital HD, previous IE, HCM, ICED

Atypical presentation:
- Elderly
- Abx pre treatment
- Immunocompromised
- Less virulent organism

Hugely variable clinical presentation

J Antimicro Chemother 2011
Microbiology

- Pivotal in ALL guidelines
- Duration of therapy starts on 1\textsuperscript{st} day cultures are negative
- If tissue culture + or bacterial PCR + $\rightarrow$ restart entire course

If acute: 2 sets, >1hr apart
If subacute: 3 sets, >6hr apart. Pragmatic
Avoid sampling from lines unless paired
Repeat cultures if still febrile > 7 days of Tx
Culture negative IE ~ 5-20% cases

Usually due to prior Abx administration

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Diagnostic procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Brucella</em> spp.</td>
<td>Blood cultures; serology; culture, immunohistology and PCR of surgical material</td>
</tr>
<tr>
<td><em>Coxiella burnetii</em></td>
<td>Serology (IgG phase 1 &gt; 1:800); tissue culture, immunohistology and PCR of surgical material</td>
</tr>
<tr>
<td><em>Bartonella</em> spp.</td>
<td>Blood cultures; serology; culture, immunohistology and PCR of surgical material</td>
</tr>
<tr>
<td><em>Treponema whipplei</em></td>
<td>Histology and PCR of surgical material</td>
</tr>
<tr>
<td><em>Mycoplasma</em> spp.</td>
<td>Serology; culture, immunohistology and PCR of surgical material</td>
</tr>
<tr>
<td><em>Legionella</em> spp.</td>
<td>Blood cultures; serology; culture, immunohistology and PCR of surgical material</td>
</tr>
</tbody>
</table>

HACEK organisms – fastidious GN bacilli
Fungal - (candida), aspergillus

Techniques:
Histological / Immunological
Molecular / 16S PCR
Imaging in IE

JAC 2012 – “in all cases of suspected IE” (ideally in 24 hours)
JAC 2012 – “routine echo in all” Staph aureus / candidaemia
ESC 2015 – TTE in all with high clinical suspicion no time interval
ACC 2016 – in all cases of suspected IE (<12 hours)
Who gets an echo / who *should* have an echo

- TTE has low diagnostic yield in all comers BUT remains in all guidelines!

- **Greaves criteria**: 500 consecutive patients referred for TTE:
  
  48% patients referred had none of Duke clinical criteria + negative TTE: high cost / poor use of resources

**Table 2** Clinical criteria that are significant independent predictors by multivariate analysis of evidence of endocarditis on transthoracic echocardiography

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolism</td>
<td>414 (57 to 3028)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Central venous access</td>
<td>87 (9 to 837)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Injected drug use</td>
<td>22 (3 to 159)</td>
<td>0.002</td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>14 (1.3 to 157)</td>
<td>0.03</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>7.4 (1.6 to 34)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.

**Table 4** Numbers of patients with positive transthoracic echocardiography according to the number of risk factors present*

<table>
<thead>
<tr>
<th>Number of risk factors present</th>
<th>Number of patients in each group</th>
<th>Proportion with positive TTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>239 (48%)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>192 (38%)</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>2</td>
<td>49 (10%)</td>
<td>17 (40%)</td>
</tr>
<tr>
<td>3-5</td>
<td>20 (4%)</td>
<td>20 (46%)</td>
</tr>
</tbody>
</table>

*Vascular embolic phenomena, the presence of central venous access, a recent history of injected drug use, presence of a prosthetic valve, and positive blood cultures.

Pick up with TTE at best ~ 50%: *“Endocarditis remains a clinical diagnosis”*  
Greaves et al. Heart 2003
## Treatment: Abx vs. Surgery

<table>
<thead>
<tr>
<th>Type IE</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVE PVE, CDRIE</td>
<td>4 weeks</td>
</tr>
<tr>
<td></td>
<td>Prolonged (6 weeks)</td>
</tr>
<tr>
<td>Severe MV or AV regurg + no HF</td>
<td>Elective surgery</td>
</tr>
<tr>
<td>AV, MV NVE or PVE with severe regurg / obstruction causing refractory HF</td>
<td>Emergency surgery</td>
</tr>
<tr>
<td>Uncontrolled infection (abscess, aneurysm)</td>
<td>Urgent surgery</td>
</tr>
<tr>
<td>Fungi, drug resistant IE</td>
<td>Urgent surgery</td>
</tr>
<tr>
<td>Vegetation &gt;10mm + ≥1 embolic episode. Large vegetation &gt;15mm</td>
<td>Urgent surgery</td>
</tr>
</tbody>
</table>

### Very Early Surgery to Prevent Embolism and Death

**Recommendations: Indications for surgery**

**A. HEART FAILURE**
- Aortic or mitral IE with severe acute regurgitation or valve obstruction causing refractory pulmonary oedema or cardiogenic shock
- Aortic or mitral IE with fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema or cardiogenic shock
- Aortic or mitral IE with severe acute regurgitation and persisting HF or echocardiographic signs of poor hemodynamic tolerance (early mitral closure or pulmonary hypertension)
- Aortic or mitral IE with severe acute regurgitation and no HF

**Timing**
- Emergency
- Urgent
- Elective

**Level of evidence**
- B
- C

**B. UNCONTROLLED INFECTION**
- Locally uncontrolled infection
- Persisting fever and positive blood culture > 7-10 days
- Infection caused by fungi or multiresistant organisms

**Timing**
- Urgent/elective

**Level of evidence**
- B

**C. PREVENTION of EMBOLISM**
- Aortic or mitral IE with large vegetations (>10 mm) following one or more embolic episodes, despite appropriate antibiotic treatment
- Aortic or mitral IE with large vegetations (10 mm) and other predictors of complicated course (HF, persistent infection, abscess)
- Isolated very large vegetations (>16 mm)

**Timing**
- Urgent
- Urgent

**Level of evidence**
- B
- C

*(ESC 2009)*
Outcomes

Static mortality

Thuny F Lancet 2012

Thuny F Am Heart J 2012
Early Surgery versus Conventional Treatment for Infective Endocarditis

Duk-Hyun Kang, M.D., Ph.D., Yong-Jin Kim, M.D., Ph.D., Sung-Han Kim, M.D., Ph.D., Byung Joo Sun, M.D., Dae-Hee Kim M.D., Ph.D., Sung-Cheol Yun, Ph.D., Jong-Min Song, M.D., Ph.D., Suk Jung Choo, M.D., Ph.D., Cheol-Hyun Chung, M.D., Ph.D., Jae-Kwan Song, M.D., Ph.D., Jae-Won Lee, M.D., Ph.D., and Dae-Won Sohn, M.D., Ph.D.
Early surgery vs. completed Abx therapy?

But

- exclusion of patients with high comorbidities
- Vegetation length is not the only predictor of embolism

No difference in all cause mortality at 6/12

Significant difference in composite: death any cause, embolic event, HF, recurrent IE at 6/12: 3% vs. 28%

Other take home points!

• Prevention: NICE vs. the world

• New imaging developments: may accelerate diagnosis & risk stratification

• Endocarditis Team: collaborative approach to a complex illness
No distinction between high and low risk patients

Active dental infection at site of treatment – personal choice

Antibiotic prophylaxis against infective endocarditis is not recommended routinely:
- for people undergoing dental procedures
- for people undergoing non-dental procedures at the following sites:
  - upper and lower gastrointestinal tract
  - genitourinary tract; this includes urological, gynaecological and obstetric procedures, and childbirth
  - upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy. [2015]
New developments: 18F FDG PET-CT

- Silent peripheral emboli
- Infectious mets

- PVE
- Aortic root abscess
- Pacing system infections – negative / equivocal echo (20% IE related to devices/ PV)
PET-CT

Pacemaker pocket infection

CT suspicious

PET avid uptake

Peri-aortic abscess

Pizzi Circ 2015
Endocarditis Team

• Cardiologist interest in valves
• ID / Microbiologist
• Surgeon expertise in complex valves

+- EP expert in device extraction
+- ortho opinion
+- neuro-surgery opinion
Early transfer to reference centre

Box 1  Indications for transfer to a surgical centre

- Prosthetic valve or implantable cardiac electronic device infection
- Severe regurgitation even if currently stable haemodynamically
- Abscess
- Invasive organism, for example, *Staphylococcus aureus* *
- Organisms that are hard to manage medically, for example, fungi
- Failure to respond to antibiotics
- Stroke (or other embolism) and large residual vegetation
- Recurrent emboli
- Renal failure

*Cases of *S aureus* infective endocarditis (IE) may be respond to antibiotics therapy alone, but should trigger a discussion.

†Renal failure in IE has many and sometimes multiple origins including glomerulonephritis, renal emboli, aminoglycoside therapy and low cardiac output. It can contribute to the decision for early surgery when associated with severe valve destruction or failure to control sepsis and should therefore trigger a discussion with the surgical centre.

Approx 50% require surgery

Follow-up: 1, 3, 6, 12 month: 8% relapse and 15% recurrence at 2 years (10% need surgery)
IE Team Results (Leeds data)

• **Improved diagnosis:** 155 referrals – 91 IE (59%)

• **IE excluded:** earlier D/C (29/7 vs. 47/7)

• **Bed days saved:** 1152

• **Reduction in 1 year mortality:** 18.5 to 12%

Courtesy of Dr Sandoe - Leeds
### Summary

#### DIAGNOSIS

**Clinical suspicion of IE**
- Modified Duke criteria (Li)
  - Definite IE
  - Possible/rejected IE but high suspicion
  - Rejected IE Low suspicion
    - Native valve
    - Prosthetic valve

1. Repeat echo (TTE + TOE)/microbiology
2. Imaging for embolic events
3. Cardiac CT

**ESC 2015 modified diagnostic criteria**
- Definite IE
- Possible IE
- Rejected IE

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#### TREATMENT

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<th>Treatment</th>
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- **AV, MV NVE or PVE with severe regurg / obstruction causing refractory HF**
  - Emergency surgery

- **Uncontrolled infection (abscess, aneurysm)**
  - Urgent surgery

- **Fungi, drug resistant IE**
  - Urgent surgery

- **Vegetation >10mm + ≥1 embolic episode. Large vegetation >15mm**
  - Urgent surgery

---

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

*May include cerebral MRI, whole body CT, and/or PET/CT.

*See Table 14.
Summary

• IE prevalence is increasing: devices, prosthetic material

• Rare disease but huge financial burden to NHS

• Mortality remains high and static

• MDT approach required
What do these two have in common?
Thank you & Questions