If you don’t take a temperature

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Case 1

- 63 yo Retired female swimming coach
- 2 year history of
- Malaise, lassitude, sweats, mouth ulcers, deranged LFT’s (seen by 2 hepatologists) and Weight loss ≥ 2 stone
- 6/52 history of ↑SOB and malaise
- Referred - ?endocarditis
PMH

- DVT aged 24 when on OCP
- Adult onset type 1 diabetes mellitus
- Vasculitic rash on legs 2/12 previously
- No miscarriage, No raynauds, No arthritis
Examination

- Thin
- Marked palmer erythema
- Pulse 80 bpm reg
- BP 150/80
- No peripheral stigmata of IE
- Temp 37.4
- Ejection systolic and early diastolic murmur
Investigations

- ESR - 121
- CRP - 10
- Blood cultures x 7 - (CoNS in one bottle of 7 sets)
- Na 135, K 4.6, Urea 8.7, Creat 124
- GGT 81, ALP 221, ALT 30, Alb 38, Bili 9
- Hb 10.7, WCC 3.4, NØ 1.92, Plt 158
- IgG 32.9, IgA 6.47, IgM 5.75 (polyclonal)
- Urine dipstick – Protein 2+, Blood 4+, RCC 20, WCC 0, NG
- 1.5g proteinuria
What are the possible causes?
What are the possible causes?

- Autoimmune (Libman Sachs) (2.5%)
- Bacterial endocarditis – e.g. negative cultures due previous treatment (10.4%)
- *Coxiella burnetii* (37%)
- *Bartonella* (12.4%)
- *Legionella pneumophila* (0.3%)
- HACEK (0.4%)
- Fungal (1%)
- Nutritionally variant streptococci
- *Brucella mellitensis* (0%)
- *Mycoplasma pneumoniae* (0%)
- Chlamydia (0%)
- *Tropheryma whipplei* (2.6%)
- Figures in brackets from reference 1
What other history is required?
What other history is required?

- Previous antibiotic treatment – none
- Dental disease / dental work – Dental review – apical infection of rear bottom right molar
- Pets - none
- Travel history – see next slide
- Family history – nil relevant
Travel History

• 2000 – India, Nepal, Egypt, Greece
• 2006 – China, Lapland, Spain, Cyprus
• 2009 – Sardinia
What further investigations are required?
What further investigations are required?

- Echo ± TOE
- USS abdo
- *Coxiella burnetii* serology
- *Bartonella* serology
- Auto-antibody screen
- ??prolonged culture discuss
- ?Brucella given travel history
BSAC guidelines

- Incubate blood cultures for 7 days without extension / subculture
- Serology for *Coxiella* and *Bartonella*
- Consider serology for *Brucella* in patients at risk of exposure
- Serology for *Chlamydia, Legionella* and *Mycoplasma* not recommended
- Broad range PCR on valve tissue (+histology)
- Real time PCR on blood – insufficient data to recommend use
Further results

- Rh. Factor - 35
- ENA, ANA, ANCA, cardiolipin, Anti DS DNA, GBM ab and complement screen all negative
- USS – Marked Splenomegaly 17cm, Hydronephrosis L kidney
- Liver biopsy – reactive, consistent with but not diagnostic of autoimmune hepatitis
- Ca 19-9 – 56 (<35)
Echo

- TTE
- Severe AR, thickened leaflets particularly LCC, regions of nodular thickening / calcification. R & LCC fused. Possible strands on AV/LVOT. Suggest TOE.
- TOE
- Severe central AR
- Thickened leaflets, nodules of calcium on leaflets and at bases of LCC and RC
- No obvious mobile vegetations
- Mild MR
Further review

- Rheumatology review – Autoimmune hepatitis, low grade LN, ↑ESR, Normal CRP, ↑IgG, Proteinuria and haematuria, vasculitic rash, leucopaenia / neutropaenia = probable lupus. Recommend renal biopsy and PET scan for aortitis.
- IV methylprednisolone started day 26
- Haematology review – “pancytopenia” + low ferritin -> iron replacement followed by BM if no response
- Microbiology – serology for culture negative endocarditis
Day 29

- Q fever serology CFT: 1:512
- Microimmunofluorescence results CAMR
  - Phase 2 IgG 1:81920, Phase 2 IgM 1:2560,
  - Phase 1 IgG 1:81920, Phase 1 IgA 1:40960
- PCR on EDTA blood - negative
- Consistent with Chronic Q fever
Does negative PCR exclude disease?

• No
• Positive PCR is helpful
• Negative PCR does not exclude disease and is unlikely to be positive in a patient with very elevated phase 1 IgG (≥25,600)
Further management

- Started on doxycycline 200mg od and hydroxychloroquine 200mg bd
- Rapid clinical response (felt better)
- Developed vasculitic rash on arms - ?Jarisch - Herrxheimer type response
Diagnosis and Management

- Chronic Q fever endocarditis
- Phase 1 IgG > 800 compatible with diagnosis (UK titres higher than French titres)
- Doxycycline 200mg od adjusted according to levels – target ≥ 5 μg/l
- Hydroxychloroquine as per BNF (normally 200mg bd) adjusted according to levels – target 0.8-1.2 μg/ml
- Advise re sun exposure + eye symptoms (bulls eye retinopathy)
- Screen for eye problems regularly
- Sun cream
- Minimum 18 months treatment or until phase 1 IgG <400 for 6 months (French titres which are often lower than CAMR titres)
- Specialist advice available through CAMR
Day 50

- Aortic Valve Replacement
- Aortic valve thickened with focal calcification at base of leaflets
- Areas of intimal hyperplasia similar to rheumatoid valves
- Calcified cardiac valve with patchy dense chronic inflammatory cell infiltrate consistent with chronic endocarditis
- *Coxiella burnetii* PCR positive on valve
18 months into treatment

- Phase 1 IgG antibodies 1:10240
- Phase 1 IgA antibodies 1:2560
- Phase 2 IgG antibodies 1:40960
- ESR 14
- CRP 1
Case 2

- 31 yo Iranian illegal immigrant
- Living in UK for 2 years
- Chest pain, flu like illness
- 6kg weight loss in 6 months
- Dental work 6 months ago
- Rheumatic fever (10 years)
- On penicillin V prophylaxis
Examination

- Fever 38.5
- Pan systolic and Ejection systolic murmur
- No peripheral stigmata of Infective Endocarditis
TTE

• Rheumatic valvular heart disease
• MS, AR, AS
• Mobile mass on aortic valve
Results

- Hb 10.9, WCC 3.9, Plt 169
- Na 135, K 3.8, Urea 4.0, Creat 102
- LFT - normal
- CRP 59 (1 in 2006)
- ASOT - 40
Microbiology review

- 3 sets of blood cultures over 72 hours
- Start benzylpenicillin + gentamicin
- Serology for culture negative endocarditis
- Blood cultures x 8 negative
Further management

- Ceftriaxone and gentamicin
- Brucella abortus CFT- 1 in 256
- Brucella mellitensis CFT - 1 in 256
- *Chlamydia psittaci* – 1 in 16
- Blood cultures flagged positive – No organisms seen, no growth
Thoughts?
Thoughts?

- Choice of empirical treatment – initially thought to be related to dental work
- Check history of unpasteurised milk – Patient reports he has never drunk unpasteurised milk
- *C. Psittaci* – low level titre – doubtful significance
- Brucella serology significance - ?cross reactivity
- Blood culture - ?Extend culture, ?how long for
- Doxycycline added
Further information

• Bartonella serology
• *Bartonella henselae* IgM < 40
• *Bartonella henselae* IgG ≥ 2056
• *Bartonella quintana* IgM = 40
• *Bartonella quintana* IgG ≥ 2056
• Brucella serology negative at reference laboratory
Thoughts?

- Brucella probably false positive
- Bartonella IgG not specific to one species
- Bartonella IgM more consistent with quintana - ?human louse contact
- Further history – arrived in UK 2 years ago in the back of a lorry, No shower for 10 days, itching +++ at the time
- Tissue => PCR at surgery = Positive for bartonella spp => sequencing = \textit{B. quintana}
Conclusion of case

- Surgery
- Post op – Ceftriaxone, gent, cefuroxime, teicoplanin (no doxycycline) !!!
- Gent, cefuroxime and teic stopped
- Ceftriaxone given for 2 weeks post op
- Doxycycline restarted
- Rifampicin added
- Doxycycline and rifampicin given for 3 months
Culture Negative endocarditis

- 819 patients with BCNE, 60 excluded => 759 patients
- Serology for *Coxiella burnetii, Bartonella quintana, Bartonella henselae, Legionella pneumophila, Brucella melitensis, Mycoplasma pneumoniae*
- PCR on heart valves
- Cell culture – human endothelial cells in shell vials
- Histopathological analysis on valves
- Auto-antibody screen – Rheumatoid factor, ANA, anti-DNA.
- Western blot for bartonella on negatives
<table>
<thead>
<tr>
<th></th>
<th>Histopathology (%)</th>
<th>Auto-antibody (%)</th>
<th>Serology (%)</th>
<th>PCR blood n=257 (%)</th>
<th>PCR tissue n=227 (%)</th>
<th>Western blot (%)</th>
<th>Total n=495 of 759 (%)</th>
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</thead>
<tbody>
<tr>
<td>Non-infective</td>
<td>12 (1.6)</td>
<td>7 (0.9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>19 (2.5)</td>
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<tr>
<td>Q fever</td>
<td>NA</td>
<td>NA</td>
<td><strong>274 (36)</strong></td>
<td>16 (2.1)</td>
<td>30 (4)</td>
<td>NA</td>
<td><strong>274 (37)</strong></td>
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<tr>
<td>Bartonella</td>
<td>NA</td>
<td>NA</td>
<td><strong>80 (10.5)</strong></td>
<td>12 (1.6)</td>
<td>19 (2.5)</td>
<td>4 (0.5)</td>
<td><strong>92 (12.3)</strong></td>
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<tr>
<td>Legionella</td>
<td>NA</td>
<td>NA</td>
<td>2 (0.3)</td>
<td>0</td>
<td>1 (0.1)</td>
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<td>2 (0.3)</td>
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<tr>
<td>Whipples</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5 (0.7)</td>
<td>17 (2.2)</td>
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<td><strong>19 (2.5)</strong></td>
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<td>18sDNA</td>
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<td>NA</td>
<td>1 (0.1)</td>
<td>7 (0.9)</td>
<td>NA</td>
<td>8 (1)</td>
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<tr>
<td>16sDNA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2 (0.3)</td>
<td><strong>79 (10.4)</strong></td>
<td>NA</td>
<td><strong>81 (10.6)</strong></td>
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<tr>
<td>Total (not dx by serology)</td>
<td>12 (1.6)</td>
<td>7 (0.9)</td>
<td><strong>356 (46.9)</strong></td>
<td>36 (4.7) (8)</td>
<td><strong>153 (20) (108)</strong></td>
<td>4 (0.5)</td>
<td>495 (65.3)</td>
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<tr>
<td>Bartonella species</td>
<td>12.4</td>
<td>28.4</td>
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<td>Brucella melitensis</td>
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<tr>
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<tr>
<td>Corynebacterium species</td>
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<td>Coxiella burnetii</td>
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<td>7.9</td>
<td>12.7</td>
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<td>HACEK bacteria</td>
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<td>Staphylococcus species</td>
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<td>3.4</td>
<td>11.1</td>
<td>6.4</td>
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<tr>
<td>Streptococcus species</td>
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<td>1.1</td>
<td>6.3</td>
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<tr>
<td>Tropheryma whippelii</td>
<td>2.6</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
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<td>Other bacteria</td>
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<tr>
<td>Fungi</td>
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<td>0</td>
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<td>No etiology</td>
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<td>82.9</td>
<td>50.8</td>
<td>54.8</td>
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</tbody>
</table>

**NOTE.** Data are percentages. HACEK, Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella.

\(^a\) Patients classified as excluded were not included in this analysis.
Conclusions

- Serology for *Coxiella burnetii* and *Bartonella* spp. has high yield (74.8% (356/478))
- Autoantibody screens for non infective causes similarly useful
- PCR on heart valve tissue is diagnostically useful (Yield = 69% (157/227) and makes diagnosis in 23% (109/478 not diagnosed by other test)
- Other tests have low yield and should be applied if above tests are negative or if history suggests specific test may be worthwhile
Suggested Diagnostic hierarchy

First line: Routine diagnostics

Second Line: Serology for *C. burnettii and Bartonella spp* + Rheumatoid factor and autoantibodies

Third line: Bartonella, Whipples & 18sRNA PCR

Fourth line (all low yield): Serology – mycoplasma, legionella, brucella, chlamydia. PCR - 16S RNA (if previous antibiotic therapy), Bartonella (Western blot), ?Mycobacterial blood culture.

Tissue available – Histology, PCR and culture on tissue
If negative - Primer extension enrichment reaction, autoimmunohistochemistry.
Figure 2. Diagnostic tests applied to clinical specimens for identification of causative agents of blood culture–negative endocarditis. Agents include Tropheuma whipplei. AIHC, autoimmunohistochemistry; PCR, polymerase chain reaction; PEER, primer extension enrichment reaction; rRNA, ribosomal RNA.
However...

- Case reports of cases of Q fever endocarditis in patients with other bacterial causes (3)
- “Dual pathogen endocarditis”
PCR on valve tissue

- 127 patients (105 examined by PCR) (4)
- 16S rRNA and 18s rRNA
- Specific PCR for *staph, strep, entec, enterobacteriaceae*, *Mycoplasma, Coxiella, Bartonella, Aspergillus*
- Sensitivity 61% Specificity 64%
- False positives (contamination) 18.7% cf valve culture (1.7%)
- Etiological diagnosis in 23% of endocarditis unknown aetiology
IF YOU DON’T TAKE A TEMPERATURE - YOU WON’T FIND A FEVER
Learning points

• Causes of culture negative endocarditis can be elucidated in the majority of cases with appropriate testing
• Serology for *Coxiella burnetii* and *Bartonella spp.* should be carried out in cases of ?CNE
• These infections don’t cause typical lesions of endocarditis and can present very indolently
• CRP can be normal
• Presentation can be subtle / confusing
• Echo’s do not always give typical findings
• PCR on valve tissue also useful
• All serological and PCR results must be interpreted cautiously