A familiar foe, an unfamiliar ally

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Infectious Diseases AT
Westmead Hospital
Acknowledgements

• case and slides courtesy of Dr Tim Gilbey
Case: Mr PJ, presenting complaint

• Malaise, fatigue
  • Unwell 1/52
  • Progressively reduced exercise tolerance -> SOBOE 5m (previously unlimited)
  • Visitor from Hobart; arrived 3 days ago

• Chest pain
  • Intermittent for 1/52; minimal relief from Panadeine Forte
  • 8/10, radiates to arm & neck, pleuritic

• Diarrhoea
  • Black, uncontrollable at times; few episodes of large volume
PHx

1. Mechanical AVR 1980s
   • Unclear indication; possible rheumatic heart disease

2. MV Infective Endocarditis 2000
   • *Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus*)
   • Medically managed in Hobart

3. Previous UGI bleed secondary to angiodysplasia

4. Colonic polyps
Medications

• warfarin 6mg daily
• simvastatin 20mg daily
• telmisartan 40mg daily
• escitalopram 40mg daily
Initial Examination (ED)

• A – dry, coated tongue
• B – decreased breath sounds both bases, RR 25, sats 95%RA
• C – systolic murmur with S2 click, all areas, no radio-radial delay, BP equal bilat, HR 105, BP 108/57, no peripheral oedema
• D – alert and oriented
• E – abdomen SNT, normal bowel sounds, no masses palpated
• dried dark/black stool on legs
Baseline Bloods

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Level</td>
<td>133 mmol/L</td>
</tr>
<tr>
<td>Potassium Level</td>
<td>3.7 mmol/L</td>
</tr>
<tr>
<td>Chloride Level</td>
<td>97 mmol/L</td>
</tr>
<tr>
<td>Bicarbonate Level</td>
<td>25 mmol/L</td>
</tr>
<tr>
<td>Anion gap</td>
<td>1.5 mmol/L</td>
</tr>
<tr>
<td>Urea Level</td>
<td>9.6 mmol/L</td>
</tr>
<tr>
<td>Creatinine Level</td>
<td>94 mmol/L</td>
</tr>
<tr>
<td>eGFR</td>
<td>73 mL/min/1.73m²</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>39 umol/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>67 g/L</td>
</tr>
<tr>
<td>Total Globulin</td>
<td>41 g/L</td>
</tr>
<tr>
<td>ALT</td>
<td>60 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>67 U/L</td>
</tr>
<tr>
<td>GGT</td>
<td>14.2 U/L</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>330 U/L</td>
</tr>
<tr>
<td>hs Troponin I</td>
<td>388 ng/mL/L</td>
</tr>
<tr>
<td>Random Glucose Level</td>
<td>9.8 mmol/L</td>
</tr>
<tr>
<td>C Reactive Protein</td>
<td>231 mg/L</td>
</tr>
<tr>
<td>Inspired Oxygen</td>
<td>21.0 %</td>
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<tr>
<td>Blood pH</td>
<td>7.47</td>
</tr>
<tr>
<td>Blood pO2</td>
<td>24 mmHg</td>
</tr>
<tr>
<td>Blood pCO2</td>
<td>33 mmHg</td>
</tr>
<tr>
<td>Blood O2 Saturation</td>
<td>43 %</td>
</tr>
<tr>
<td>Blood HCO3</td>
<td>23 mmol/L</td>
</tr>
<tr>
<td>Blood Base Excess</td>
<td>132 mmol/L</td>
</tr>
<tr>
<td>Blood Standard Base Excess</td>
<td>0 mmol/L</td>
</tr>
<tr>
<td>Blood Sodium</td>
<td>132 mmol/L</td>
</tr>
<tr>
<td>Blood Potassium</td>
<td>3.9 mmol/L</td>
</tr>
<tr>
<td>Blood Chloride</td>
<td>99 mmol/L</td>
</tr>
<tr>
<td>Blood Creatinine</td>
<td>64 umol/L</td>
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<tr>
<td>Blood Glucose</td>
<td>10.0 mmol/L</td>
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<tr>
<td>Blood Lactate</td>
<td>3.5 mmol/L</td>
</tr>
<tr>
<td>Blood Calcium Ioniised</td>
<td>1.12 mmol/L</td>
</tr>
<tr>
<td>Blood Bilirubin</td>
<td>130 g/L</td>
</tr>
<tr>
<td>Blood Total Haemoglobin</td>
<td>130 g/L</td>
</tr>
<tr>
<td>Blood Oxygenhaemoglobin</td>
<td>42.0 %</td>
</tr>
<tr>
<td>Blood Carboxyhaemoglobin</td>
<td>0.6 %</td>
</tr>
<tr>
<td>Blood Deoxyhaemoglobin</td>
<td>56.6 %</td>
</tr>
<tr>
<td>Blood Methaemoglobin</td>
<td>0.6 %</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>132 g/L</td>
</tr>
<tr>
<td>White Cell Count</td>
<td>18.9 x 10^9/L</td>
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<tr>
<td>Platelets</td>
<td>141 x 10^9/L</td>
</tr>
<tr>
<td>RCC</td>
<td>4.5 x 10^12/L</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6.0 %</td>
</tr>
<tr>
<td>MCV</td>
<td>88 fl</td>
</tr>
<tr>
<td>MCH</td>
<td>30 pg</td>
</tr>
<tr>
<td>MCHC</td>
<td>354 g/L</td>
</tr>
<tr>
<td>RDW</td>
<td>14.5 %</td>
</tr>
<tr>
<td>Absolute Neutrophils</td>
<td>16.5 x 10^9/L</td>
</tr>
<tr>
<td>Absolute Lymphocytes</td>
<td>1.2 x 10^9/L</td>
</tr>
<tr>
<td>Absolute Monocytes</td>
<td>1.2 x 10^9/L</td>
</tr>
<tr>
<td>Absolute Basophils</td>
<td>0.6 x 10^9/L</td>
</tr>
<tr>
<td>Absolute Eosinophils</td>
<td>0.6 x 10^9/L</td>
</tr>
</tbody>
</table>

Obstructive LFTs with elevated bilirubin
Elevated troponin
Elevated CRP and WCC with neutrophilia
Slightly subtherapeutic INR
Elevated lactate
Initial Management (ED)

- IVC and bloods
- SBP 110, anginine avoided – morphine administered
- empiric antibiotics - ceftriaxone IV 1g and azithromycin 500mg stat
- flu POC swabs
- NBM
- PPI infusion
- telemetry
- urine MCS
- group and screen taken
Thoughts? Any other plans? Ix?
Progress

- Admitted under ID; Abx changed to Flucloxacillin 2g QID and Ceftriaxone 1g BD
- S/B Gastro; nil evidence of ongoing bleed; continue PPI
- MSU +ve Staphylococcus aureus
- BC +ve Staphylococcus aureus
- TTE:
  - Difficult to exclude prosthetic aortic valve endocarditis or root abscess
  - At least moderate eccentric MR
Progress

• TTE: mobile echodense lesion on MV
  • -> Abx changed to Fluclox 2g q4h + Ciprofloxacin 400mg IV b.d
• TOE:
  • Prosthetic AV:
    • Well seated, functions normally
    • Small linear echodensity (0.7cm) noted prolapsing into LVOT
    • Aortic root is slightly thickened with no evidence of an apparent root abscess
  • MV:
    • Independently mobile echodensity (1.5 x 0.9cm), prolapsing into LV cavity
    • At least moderate eccentric MR
Progress – D3

• Ongoing fevers
• Multiple sets blood cultures now positive *S. aureus*
• PACE: reduced GCS
  • CT Brain:
Progress – D3

• CT Brain:
  • 5mm hyperdense focus at the right frontal lobe is non-specific, and could represent a focus of intraparenchymal haemorrhage, or alternatively a hyperdense small mass lesion
• INR: 5.1
• -> warfarin ceased & reversed with vitamin K
• Heparin infusion commenced to cover mechanical valve, aiming apt 60-70
Temperature

WCC

Day 0  Day 1  Day 2  Day 3  Day 4  Day 5  Day 6  Day 7  Day 8  Day 9  Day 10  Day 11  Day 12  Day 13  Day 14  Day 15  Day 16  Day 17  Day 18

T 37.7

WCC 11
Progress – D4

• Ongoing fevers
• Acute onset chest pain at rest; left sided, non pleuritic, non-radiating
• New TWI inferolateral ECG leads
• Initial trop 987 -> serial 19,970
• -> aspirin commenced. Already on heparin. Symptomatic measures.
• Ongoing culture-positivity: what now?
• Added rifampicin
Progress – D6

• Ongoing fevers
• Persisting bacteraemia
• Cardiothoracics consulted re: AVR + MVR
Progress

- D8: PACE for reduced GCS
- New dysarthria, left hemiparesis
- -> repeat CT Brain:
Progress

• All anticoagulation ceased
• Impending cardiac valvular surgery cancelled

• Persisting fevers
• Rising WCC
• Culture-positive to day 6
Progress summary

• Previously well, independent 50M
• Staph aureus endocarditis, both prosthetic & native valves involved
• Prolonged bacteraemia
• On three-drug therapy
• Persisting fevers & elevated inflammatory markers
• Unfit for surgical source control due to ICH
Plans at this stage?
Bacteriophage

• Viruses that infect bacteria (infect prokaryotic rather than eukaryotic cells)

• Ubiquitous in nature. Part of the normal human gut microbiome; outnumber gut bacteria 10:1
Bacteriophage therapy

• Bacteriophage therapy pre-dates antibiotics – first discovered and used in the early 1900’s (penicillin mass production began 1942)
• Fell out of favour in the Western world for a variety of reasons, including the advent of antibiotics
• Increasing interest in the role of bacteriophage therapy in recent years, in the context of increasing antibiotic resistance
Phage therapy – How does it work

• Phage = Virus
  • -> trophic for specific host organism
  • -> Narrow spectrum
  • E.g. particular phages may infect Pseudomonas aeruginosa only

• Phage infection of target bacteria leads to:
  • Transcription of viral DNA -> phage replication
  • -> replicated phage escape via lysis of host bacteria

• Phage ≠ Drug
  • Administered phage then replicates within host bacteria
  • -> increased phage proportional to bacterial population
Lytic phage vs Temperate (Lysogenic) phage

bacteriophage
bacterium
bacterial DNA
phage DNA

lytic

stress

temperate
Phage Therapy – Who Fits the Bill?

- Invasive monomicrobial infections
  - Staph aureus
  - Pseudomonas aeruginosa
- Particularly:
  - Blood stream infections
  - Prosthesis infections
  - Patients deteriorating despite conventional therapy
- Best outcomes are likely to be had in those treated early
Progress

• Commenced staphylococcal bacteriophage (AB-SA01) b.d. for 14 days
• Other therapies continued
Day 0
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day 9
Day 10
Day 11
Day 12
Day 13
Day 14
Day 15
Day 16
Day 17
Day 18

Temperature

WCC

Bacteriophage AB-SA01

Ceft
Azith
Gent
Vanc
Rifampicin
Cipro IV bd
Cipro PO bd
Cipro 400mg IV tds
Fluclox 2g q4h
Fluclox 14g infusion

Temperature

WCC

T 37.7
WCC 11
Progress – D12

• Acute abdo pain
  • Generalised tenderness. Nil peritonism
• Acute peak in inflammatory markers
• -> CT Abdo / Pelvis:
Progress

• Clinically stabilised
• Defervesced
• Cultures remained clear
• Fluctuating neurological deficit. Short stay in stroke ward with minimal participation.
• Nil further infective / embolic events
• Ultimately discharged to Royal Hobart Hospital day 37 for completion of antimicrobials and rehabilitation
Thank you

• Questions / Comments?