Haematological Emergencies

Dr Cameron Curley
Haematologist
Royal Brisbane & Women’s Hospital
Case 1

• Mr PW 67yr old man

• Presents to their local practice GP being “unwell” since waking this am

• He describes he had been “watching his temp closely over the last 3 hours given he is on chemotherapy for lymphoma” and Temps had been 37C, 37.8C, 37.4C on the last 3 readings.

• On reviewing your colleagues notes and patient correspondence in the medical record you see he has recently been diagnosed with DLBCL and is receiving RCHOP chemotherapy. The patient states he received his last dose 9 days ago.
Case 1

- On inspection he is flushed with warm peripheries.
- HR 105, BP 110/60, RR 20, Sat 98%. Temp is 38.5°C.
- He has no central venous access device visible. Cardiovascular and respiratory examination are unremarkable.
- Abdomen is soft and non-tender.
Case 1

- He hands you a book of his latest blood results from clinic yesterday

- They show: Hb 105, WCC 0.5, Neut 0.05, PLT 98.

- As he sits up to put his shirt back on after being examined he collapses back on the bed.

- He is conscious, orientated and has the following obs: HR 120, BP 90/50, RR 22, Sat 98%
Case 1 - Question

• What would you do next?

a. Direct the practice nurse to call for an ambulance and continue on with the next patient?

b. Call an ambulance and whilst waiting put in a cannula and give fluids

C. Direct his wife whom is present to take him to his specialists hospital for urgent specialist care (40mins away)

d. Take blood cultures and give IV antibiotics (assuming available)

e. Both b and d
Definitions

- Neutropenia = ANC < 1.00 x 10⁹/L
- Severe neutropenia = ANC < 0.5 x 10⁹/L
- Profound neutropenia = ANC < 0.1 x 10⁹/L
Febrile Neutropenia

1. ANC < 1.00 x 10^9/L

2. Temp ≥ 38.3°C x 1 or > 38°C sustained

Risk of infection is linked to degree, duration and cause of neutropenia
Neutropenia - Causes

1. Decreased production
   - Bone marrow infiltration (ALL/lymphoma/non-haem malignancy etc) - pancytopenia
   - Agranulocytosis/bone marrow aplasia (Chemotherapy; drugs – clozapine, Methotrexate, azathioprine, mercaptopurine; immune- Aplastic anaemia)
   - Inherited
Neutropenia – Causes:

2. Peripheral destruction/sequestration
   - Hypersplenism including Felty’s syndrome
   - Autoimmune neutropenia – including lupus etc
   - Drug induced – maturation arrest (beta lactam antibiotics etc)
   - Viral infections
Initial Mx FN (ED)

1. Identify FN patient at triage – ie. patient receiving chemotherapy in last 6 weeks whom presents with a fever or unwell

2. Assessed with Hx, examination & FBC, ELFT, Lactate within 15mins of triage (if stable) - ? Source ? prior MRO

3. Culture – >2 sets of Blood cultures, msu, sputum, NPS if indicated

4. EARLY (<60mins), appropriate antibiotics and IV fluids

5. Imaging - CXR, (+/- CT chest/abdomen)

6. Discuss with treating Haematologist/ Oncologist
## ASID guidelines

### Table 3  Initial antibiotic selection (doses for normal renal function).

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Recommendation (grading and level of evidence)</th>
</tr>
</thead>
</table>
| **Patients without features of systemic compromise** (beta-lactam monotherapy is recommended unless allergy to the recommended agent(s)) | No penicillin allergy:  
Piperacillin-tazobactam 4.5 g IV six- to eight-hourly (grade A) OR  
Cefepime 2 g IV eight-hourly  
Other reasonable choice for monotherapy is ceftazidime 2 g IV eight-hourly (grade A) |
| Non-life-threatening penicillin allergy (rash):  
Cefepime 2 g IV eight-hourly (grade C)  
Other reasonable choices for monotherapy are ceftazidime 2 g IV eight-hourly or meropenem  
1 g IV eight-hourly (grade C) |
| Life-threatening (immediate) penicillin allergy or beta-lactam allergy:  
Austenam 1–2 g IV eight-hourly OR ciprofloxacin 400 mg IV 12-hourly (expert opinion)  
+vancomycin 1.5 g IV 12-hourly (if CrCl >90 mL/min) OR  
1 g IV 12-hourly (if CrCl 60–90 mL/min)†† |
| **Patients with systemic compromise** (The combination of a beta-lactam antibiotic with an aminoglycoside is the regimen of choice) | As for patients without features of systemic compromise (expert opinion):  
+gentamicin 5–7 mg/kg ideal body weight IV once daily, adjusted to level  
+vancomycin 1.5 g IV 12-hourly (if CrCl >90 mL/min) OR  
1 g IV 12-hourly (if CrCl 60–90 mL/min)‡‡ |
| **Patients with cellulitis, obviously infected vascular devices, or MRSA carriers with extensive skin breaks/desquamation** | As for patients without features of systemic compromise:  
+vancomycin 1.5 g IV 12-hourly (if CrCl >90 mL/min) OR  
1 g IV 12-hourly (if CrCl 60–90 mL/min)‡‡ |
| **Patients with features of abdominal or perineal infection** | As for patients without features of systemic compromise:  
+metronidazole 500 mg IV/oral 12-hourly if receiving cefepime, ceftazidime or ciprofloxacin first-line (grade D)  
Alternatively, piperacillin-tazobactam or meropenem will provide adequate anaerobic cover, if required (grade B), other than for suspected or proven *Clostridium difficile-*associated diarrhoea or colitis |

Tam CS et al, IMJ 2001;40:90-101
Time to antibiotics (TTA)

Prospective cohort study of 307 inpatients treated for FN.

TTA for first fever or any fever was associated with survival (28 day mortality) in MV analysis
RR = 1.18 (1.10-1.26).

28 day mortality increased by 18% for every hour delay in TTA.

Case 1 - Question

What would you do next?

a. Direct the practice nurse to call for an ambulance and continue on with the next patient?

b. Call an ambulance and whilst waiting put in a cannula and give fluids

C. Direct his wife whom is present to take him to his specialists hospital for urgent specialist care (40mins away)

d. Take blood cultures and give IV antibiotics (assuming available)

e. Both b and d
Case 2

• Ms TL, 19yr old woman

• Presents to her GP with a 3 week history of fevers, headaches, sore throat, arthralgias and 10 days of heavy menorrhagia. She has recently completed a course of amoxicillin for presumed strep throat.

• Previously fit and well. No travel.

• O/E: HR 100, BP 100/60, RR 18, SaO2 98%, Temp = 37C
Case 2

O/E:

- Pale, no lymphadenopathy, no tonsillar erythema or enlargement. Otoscopic examination is normal
- Ecchymoses – legs, back
- Heart sounds normal, chest clear
- No hepatosplenomegaly
Case 2

- You request blood tests including:
  
  FBC, ELFT, Coags, Iron studies
  
  CRP, EBV, CMV, Ross River, Barmah Forest, Dengue serology
Case 2

Urgent lab results are called through that PM:

PT 28 sec (11-16); aPTT 52 sec (23-38);

Fib 0.5ug/L (2-4); D-Dimer 27ug/ml (0-0.5)

Hb 90g/L, MCV 82fL, WCC 8.8, Neut 1.4  PLT 28

Alb 37g/L, Bili 8, GGT 150u/L, ALP 128 u/L ALT 45u/L, AST 39 u/L, LDH 250u/L
Case 2 - Question

• What is the most likely diagnosis?

a. Vitamin K deficiency due to antibiotics with poor dietary intake

b. Coagulopathy of liver disease

c. DIC secondary to malignancy

d. Dengue Haemorrhagic Fever

C. DIC secondary to malignancy
DDx

- Vitamin K defy
  - Prolonged PT > aPTT, normal Fib level

- Coagulopathy of liver disease
  - Prolonged PT > aPTT, low Fib, PLT rarely <50-80, D Dimer usually not marked elevated

- Dengue Haemorrhagic Fever
  - Usually prolonged aPTT, and low Fib but normal PT. usually have very low Alb
Disseminated Intravascular Coagulation (DIC)

• Acquired syndrome characterized by systemic intravascular activation of coagulation leading to microthrombi formation and a coagulopathy due to consumption.
DIC – Lab findings

Prolonged PT and aPTT
Low Fibrinogen
High D-Dimer levels
Low PLT
Possible red cell fragmentation (MAHA)

ISTH scoring system for DIC

<table>
<thead>
<tr>
<th></th>
<th>PLT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>50-100</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>2</td>
</tr>
<tr>
<td>Elevated D Dimer</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Strong</td>
<td>3</td>
</tr>
<tr>
<td>Prolonged PT</td>
<td>&lt;3 sec</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3-6 sec</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;6 sec</td>
<td>2</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>&gt;1.0ug/L</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt;1.0ug/L</td>
<td>1</td>
</tr>
</tbody>
</table>

Sens = 93% Spec = 98%

DIC - Causes

1. Malignancy – Metastatic Prostate, pancreatic, ovarian cancer or APML (Acute Promyelocytic leukaemia)
2. Sepsis
3. Trauma
4. Burns
5. Pancreatitis
6. Obstetric complications – PET, IUFD, Abruptio Placentae
7. ABO incompatible transfusion reaction
DIC - Treatment

If bleeding or acute DIC

1. PLT transfusions to keep count > 50
2. Fresh Frozen Plasma (FFP) x 4 if prolonged PT/aPTT
3. Cryoprecipitate x10 if Fib <1.0ug/L
4. TREAT THE CAUSE

Prothrombinex and heparin have no role
Case 2

- Lab haematologist calls to inform you there are circulating abnormal promyelocytes and faggott cells
- Consistent with a diagnosis of Acute Promyelocytic Leukaemia (APML)
APML

- Clear haematological emergency
- Highly curable in 90-95% of patients
- Associated with a high mortality at presentation (10%+) – due to bleeding and thrombosis
- Early: ATRA, arsenic and correction of coagulopathy are the key
- Need rapid communication and admission with a specialised haematology unit immediately
Case 3

- Mrs P.M 47yr old woman
- Presents with 4 day history of recurrent epistaxis, and a new rash on her legs.
- No past medical history.
Case 3

- O/E: Alert, orientated.
- HR 70, BP 120/65,
- RR 16, SaO2 = 98% RA
- Temp = 36 C,
True or False:

1. The diagnosis is suggestive of meningococcal sepsis and blood cultures followed by IV ceftriaxone is recommended.

2. The picture suggests marked thrombocytopenia and a FBC should be taken and the patient reviewed the following day to confirm a diagnosis of ITP.

3. The presentation is suggestive of acquired haemophilia and blood tests for factor 8 levels are indicated.

4. The patient should proceed directly to the nearest hospital for inpatient therapy.

5. A detailed medication history may reveal a causative agent.
Case 3

True or False:

1. The diagnosis is suggestive of meningococcal sepsis and blood cultures followed by IV ceftriaxone is recommended.  **False**

2. The picture suggests marked thrombocytopenia and a FBC should be taken and the patient reviewed the following day to confirm a diagnosis of ITP.  **False**

3. The presentation is suggestive of acquired haemophilia and blood tests for factor 8 levels are indicated.  **False**

4. The patient should proceed directly to the nearest hospital for inpatient therapy.  **True**

5. A detailed medication history may reveal a causative agent.  **True**
Case 3

- Hb 128g/L,
- WCC 5.0; Neut 3.8
- PLT 2 x 10E9/L
- PT 16 sec; aPTT 34 sec
- Fib 2.5 ug/L
- Cr 67umol/L
- LDH 221 U/L; LFT’s normal
Case 3

- Consistent with newly diagnosed ITP
  - With marked thrombocytopenia
  - & non-life threatening bleeding (mucosal)

Treated with prednisolone 1mg/kg
Immune Thrombocytopenic Purpura (ITP)

• Acquired, non-malignant bleeding disorder, where patients develop thrombocytopenia due to excessive peripheral destruction of PLT (usually in the spleen) due to most commonly the development of cross reacting auto-anti-PLT antibodies.

• Presentation depends on the degree of thrombocytopenia and the specificity of the anti-PLT ab.

• May be primary or secondary (underlying causative condition – APLS, SLE etc) and newly diagnosed (<3mths since dx), persistent (3 to 12 mths since dx) or chronic (>12mths since dx)
Diagnosing ITP

- **A diagnosis of exclusion:**
  1. Isolated thrombocytopenia (no anaemia, no neutropenia)
  2. No features suggestive of a primary BM disorder (no circulating blasts, no nucleated red blood cells)
  3. Normal LDH (unless co-existing haemolysis – Evan syd)
  4. Normal coagulation prolife (Not DIC)
  5. No splenomegaly/portal HTN
  6. Not drug related – Quinine, heparin etc
  7. Excluded infection causes (HIV, HCV)
ITP – Bleeding risk

- PLT count <10 (RR 46 x c/w >10)
- Age – risk of bleeding increases with age:
  - ICH risk 0.4% in children vs 1.4% in adults
  - Risk of fatal haem 0.4%/yr <40yrs vs 13%/yr age >60yr
- Duration – more common serious bleeding in chronic ITP
- Rapidity of fall (most notable with drug induced)

Note: PLT <30 indication for therapy in absence of bleeding (adult)
Treatment ITP

- In absence of active bleeding:
  - Prednisolone 1mg/kg (weaned over 3-6mths)
  - (or Dexamethasone 40mg/D by 4)
  - No PLT transfusions
Case 3

- Day 2 post admission – patient developed large volume GI bleed
- Hb dropped to 84g/L with haemodynamic instability
Case 3

- Treated with:
  1. Methylprednisolone 1g IV
  2. Intravenous immunoglobulin (1g/kg x 2 days)
  3. PLT transfusions
Treatment ITP – life threatening bleeding

- Life threatening bleeding:
  - Intracranial haemorrhage
  - Bleeding with haemodynamic instability

- Pulse methylprednisolone, IVIG and PLT transfusion

- If refractory – splenectomy/thrombopoietin analogues (Romiplostim/Eltrombopag)

Figure 1. Approach to emergency management of severe bleeding in patients with immune thrombocytopenia using combination therapy.

Arnold D. Hematology 2015
Haem Emergency Summary

- **Febrile neutropenia** (<1.0 + temp >38C)
  - Risk relates to degree, duration and cause
  - Time to antibiotics is the key to outcome
  - Specific AB – PIPTAZ, Cefepime +/- Gentamicin /Vancomycin

- **DIC**
  - high PT, aPTT and low Fib and high D-Dimer
  - Causes: Malignancy, sepsis, obstetric, pancreatitis
  - Treat the cause, remember APML and early ATRA, PLT and cryo
Haem Emergency Summary

- **ITP**

  - Bleed Risk depends on degree (<10), age, duration and rapidity of fall
  
  - Diagnosis of exclusion (isolated, normal coags, normal LDH, no drugs, no infection)
  
  - PLT <30 needs therapy (discuss by phone)
  
  - If bleeding need urgent inpatient care
Thank you


