THE NORTHERN HOSPITAL

PANCYTOPENIA (ACUTE SEVERE)

Introduction

Unlike severe cytopenias affecting one blood cell lineage (isolated anaemia, neutropenia or thrombocytopenia), the cause of a unexpected **marked pancytopenia** is frequently a **primary bone marrow disorder.**

These cases will require close consultation with the Haematology Unit

Note that in early presentations of bone marrow failure there may be relative sparing of one or more lineages initially.

Patients with mild pancytopenia will usually require only a more limited selection of investigations.

Marked pancytopenia is defined as:

Haemoglobin	< 80g/L
AND	
White Cell Count	$<1.0 \times 10^9$
(AND/ OR Neutrophil Count)	$<0.5 \times 10^9$ (if numerous blasts or lymphoma cells)
AND	
Platelets	$<50 \times 10^9$

The most important differential to exclude is **Acute Leukaemia** presenting without a leukocytosis (in particular APML - Acute Promyelocytic Leukaemia). **Rapid recognition and management of this rare condition can be life-saving.**

The combination of moderate to severe anaemia and thrombocytopenia (bicytopenia) with an **elevated white cell count** is a common presentation of acute leukaemias and some myeloproliferative disorders.

This guideline is **not** intended to cover the management of patients receiving chemotherapy or radiotherapy for malignancy who present with pancytopenia, where the pancytopenia is most likely therapy-related but some of the management principles may be still helpful for such cases.

Pathology

The causes of pancytopenia may be broadly divided into three main categories:

1. **Failure of production:**

   - Primary bone marrow failure:
     - ♥ Congenital syndromes (very rare)
     - ♥ Acquired aplastic anaemias
   - Secondary bone marrow failure:
     - ♥ Drugs
     - ♥ Haematinic deficiency (B12/folate)
     - ♥ Toxins
     - ♥ Radiation
     - ♥ Viral infection, (including HIV, hepatitis B & C, parvovirus).
     - ♥ Marrow infiltration (eg: leukaemia, lymphoma, myeloma, myelofibrosis, metastatic non-haematological malignancy)

2. **Splenic sequestration:**

   From splenomegaly / hypersplenism due to:

   - End-stage liver disease / cirrhosis.
   - Extramedullary haemopoiesis in myelofibrosis and/or massive splenic enlargement due to infiltration by malignancy, storage disorders or amyloidosis.

   The degree of hypersplenism correlates poorly with splenic size.

3. **Peripheral destruction:**

   - This is through autoimmune mechanisms.

     There may be concurrent autoimmune haemolytic anemia (AIHA), autoimmune neutropenia and immune thrombocytopenia (ITP).

     It may also be due to a manifestation of a generalized connective tissue disorder such as SLE.

Clinical assessment

Important points of history:

Drug and toxin exposure history, including:

1. Medications
2. Recent Cytotoxic therapy (chemotherapy, radiotherapy)
3. Non-prescription / herbal / complementary medicine use may provide valuable clues to the possible aetiology.

Important points of examination:

1. Vital signs, especially fever (febrile neutropenia)
2. Lymphadenopathy:

   This may be found in:

   - Systemic viral infection
   - Haematological malignancy
   - Drug reactions
   - Connective tissue disorders.

3. Splenomegaly:

   - This is suggestive of either portal hypertension / cirrhosis

   Or

   - In the absence of signs of chronic liver disease, an underlying haematological disorder, systemic infection or connective tissue disorder.

Differential diagnoses:

Important differential diagnoses can include:

1. Acute leukaemia (including Acute Promyelocytic Leukaemia)
2. Myelodysplasia
3. Lymphoma (with extensive bone marrow infiltration)

4. Myeloma (with extensive bone marrow infiltration)

5. Myelofibrosis and other myeloproliferative disorders

6. Extensive metastatic bone marrow infiltration by non-haematological cancer

7. Marrow infiltration by storage disorders or amyloidosis

8. Aplastic anaemia (primary or secondary to drugs / toxins / radiotherapy), PNH

9. Megaloblastic anaemia (B12/folate deficiency)

10. End-stage liver disease / cirrhosis with hypersplenism / portal hypertension

11. Acute HIV or other viral infection, including haemophagocytosis

12. Overwhelming sepsis

13. Connective tissue disease

Investigations

Blood tests:

The following blood tests are mandatory for the initial assessment and supportive management of the markedly pancytopenic patient until a definite diagnosis can be made (usually by bone marrow biopsy once the patient has been stabilised).

1. **FBE including blood film review** (preferably by an experienced senior scientist or Haematologist)

    - **This is the single most important diagnostic and prognostic test.**

    - Assessment of a good quality blood film by an experienced morphologist will provide a working diagnosis and help guide subsequent definitive therapy in the majority of cases based on the presence or absence of concerning features and the MCV.

      Unfortunately, the absence of blasts on the initial film does not completely exclude acute leukaemia and other bone marrow disorders can present with circulating blasts (marrow infiltration, myelodysplasia, myelofibrosis, sepsis), so bone marrow biopsy is often required for a definitive diagnosis.

    - An FBE result from the last 3-6 months to compare with the current results may help assess the chronicity and temporal onset of the pancytopenia and provide clues to the diagnosis.

- **Reticulocyte count:**
    - ♥ An elevated reticulocyte count is suggestive of occult bleeding or concurrent haemolysis
    - ♥ A low reticulocyte count is consistent with bone marrow failure

2. Blood Group and screen

3. U&Es/ glucose

4. Biochemical assessment for tumour lysis:

    - Ca / PO_4
    - Mg
    - LDH
    - Uric acid

5. LFTs (including total protein):

    - Severe liver dysfunction can contribute to cytopenias either through the underlying liver dysfunction or through sequestration from portal hypertension and hypersplenism.
    - A markedly elevated total protein level and low albumin level may suggest myeloma.

6. Coagulation studies:

    These are to assess for significant coagulopathy / DIC secondary to the underlying disease process (most commonly acute myeloid leukaemia, (ie APML) or high-grade lymphoma) or concurrent sepsis

    - APTT
    - PT/INR
    - Fibrinogen

7. D-dimers:

    Pancytopenia with grossly elevated D-dimer levels is highly suggestive of **APML** (Acute Promyelocytic Leukaemia)

The associated coagulopathy is a life threatening condition (even if platelet count and other coagulation studies are only mildly affected) and this complication may respond to prompt treatment with **ATRA (all-*trans* retinoic acid)**

8. CRP

9. Blood Cultures, (intercurrent bacterial infection).

10. B12 and folate levels:

    - To rule out readily treatable B12 deficiency either as the primary cause or as contributor, particularly in elderly patients presenting without any other worrying features.

11. Iron studies:

    - Iron deficiency rarely causes a pancytopenia, but the presence of iron deficiency may point to occult bleeding from gastrointestinal tract cancer

    - Grossly elevated ferritin levels > 10,000 are highly suggestive of a haemophagocytic syndrome.

12. TFTs:

    - Severe hyperthyroidism and hypothyroidism (particularly autoimmune thyroid disease) are very rare, but readily treatable causes of pancytopenia

13. Further serological testing may also be ordered by the specialist Haematologist Unit, (see Appendix 1)

CXR

A baseline CXR assessment is required to rule out intercurrent infection, fluid overload secondary to severe anaemia, old tuberculosis scarring and to assess for mediastinal masses / lymph nodes which may give clues to the udnerlying aetiology.

Urine M&C

Looking for intercurrent infection

Ultrasound

An ultrasound of the Liver, Portal Vein and Spleen is useful.

Even in the absence of clinically palpable splenomegaly, assessment for portal hypertension may provide a clue to the presence of occult liver disease as a contributor to the low blood counts and detect metastatic deposits or evidence of infiltration.

CT Scan

A CT scan of the Abdomen /Pelvis / Neck/Chest is indicated for patients presenting with peripheral lymphadenopathy, splenomegaly, mediastinal widening on CXR, and/or constitutional symptoms of weight loss, fevers and drenching night sweats to assess for underlying malignancy (particularly lymphoma) and occult deep infection.

Bone Marrow Biopsy

In many cases, a working diagnosis can be made from the blood film but **bone marrow biopsy** may be needed to further define the diagnosis and obtain samples for special testing that allows prognostication and tailoring of definitive therapy.

Initial results from bone marrow biopsies may take up to 1-3 days depending on the underlying disorder.

In an elderly patient with significant co-morbidities or poor functional status who is likely to be unfit for aggressive therapy, a bone marrow biopsy may be deferred initially if otherwise stable and/or performed in the context of a clinical trial or prognostic assessment at a later stage.

Management

The initial priority in the ED will be supportive care and stabilisation to allow further assessment and diagnosis by the Medical team and Clinical Haematology.

Reduction in early mortality will mainly be dependent on:

- Prompt management of severe anemia
- Neutropenic fever
- Coagulopathy
- Tumour lysis prophylaxis, (see also tumour lysis syndrome guidelines).

Red cell transfusion therapy:

Support anaemia with leukodepleted ABO matched red cell products.

Depending on the patient's symptoms and underlying cardiorespitratory reserve, the usual NHMRC red cell transfusion guidelines apply.

For patients < 60 years old - CMV negative, irradiated red cell products should be used at least until CMV status is determined as such patients are potential candidates for allogeneic stem cell transplantation.

Standard leukodepleted blood products do provide a reasonable measure of protection against the rare (but real) late complications of less than ideal blood products if CMV negative irradiated products are not available.

Life saving blood product support should not be delayed if CMV negative and/or irradiated blood products are not readily available.

Remember: a patient must first live to develop late transfusion complications!

Patients who refuse blood product support (for example Jehovah's Witnesses) should be discussed with the Laboratory Haematologist on call. Management of such patients is challenging but not impossible and requires specialist Transfusion Medicine input.

Treatment of Febrile Neutropenia

See separate specific guidelines for Febrile Neutropenia

Treatment of Coagulopathy

Aspects of management will include:

1. **Platelets:**

    - These should be kept above 10 x 10^9 if clinically stable.
    - If there is concomitant fever, infection or other high-risk features, a more liberal threshold of 20 x 10^9 is recommended.
    - Patients with active bleeding may require platelet support at higher platelet count levels.

    Note that all Victorian platelet products are leukodepleted and irradiated. Although CMV negative platelet products are theoretically preferable for transplant eligible patients (< 60 years old), short supply and clinical necessity overrule this and platelet support should not be withheld if CMV negative products are not readily available.

2. **FFP:**

    - **At doses of 15ml/kg** (4 units of 300mL for an "average" 80 kg patient) is suggested for patients with an APTT or PT/INR > 1.5 times the upper limit of normal initially.
    - They should be given even in patients without clinical bleeding to prevent any delays in diagnostic procedures (eg: marrow biopsy, lumbar puncture, lymph node biopsy)

3. **Cryoprecipitate:**

At doses of 1 unit per 10kg body weight should be considered for patients with absolute fibrinogen levels < 1.5 in the presence of clinical bleeding or upcoming procedures as above.

Patients with suspected APML should have platelet counts kept > 50 x 10^9 and have their coagulopathy aggressively treated in an attempt to normalise their parameters, even in the absence of clinically significant bleeding.

4. **Vitamin K 10mg**

   Should be given intravenously if there is suspicion of concomitant Vitamin K deficiency, liver dysfucntion or in patients presenting on warfarin therapy to help optimise their coagulation status.

5. **Prothrombinex-VF** should be **avoided** in pancytopenic patients presenting with a coagulopathy as it is potentially thrombogenic and may precipitate progressive DIC in susceptible patients.

   It is relatively contraindicated in patients with pre-existing DIC, severe liver disease and recent thromboses.

   It is indicated only for correction of excess anticoagulation due to warfarin and other coumarin anticoagulants.

6. **Aspirin and/or Clopidogrel** should be withheld if platelet counts are < 100 x 10^9 and/or there is clinical bleeding **unless there is an absolute contraindication to stopping** due to recent insertion of a bare-metal or drug-eluting coronary stent.

   Such patients should be discussed urgently with Cardiology.

Tumour Lysis Prophylaxis

All suspected cases of acute leukaemia or undiagnosed pancytopenia should be given routine basic tumour lysis prophylaxis at least until a high-grade haematological malignancy is excluded as early prophylaxis may prevent biochemical and metabolic complications of spontaneous tumour lysis:

Treatment includes:

1. Hydration:

   Intravenous rehydration and **ongoing hydration with normal saline**, with attention to the use of diuretics to prevent fluid overload in elderly patients or patients with a significant history of cardiac compromise.

2. **Allopurinol 300mg (100mg if renal impairment) STAT**

Then further allopurinol should be given up to twice daily at a dose appropriate for the patient's renal function.

Even if fasting for a procedure, allopurinol should be given with a few sips of water whenever possible.

3. **Rasburicase**

This is given as a single dose and should be considered in patients with high-risk features (elevated LDH, elevated uric acid, pre-existing renal impairment) or evidence of active tumour lysis / renal failure.

Appendix 1

Further serological testing:

Although not central to the management of the pancytopenic patient in the ED, the following testing may be important to the early phases of management and diagnosis if sent promptly or added onto the initial screening bloods.

1. Infectious diseases:

    - HIV, CMV, EBV, HSV, Hepatitis B, Hepatitis C, Parvovirus serology

    Acute viral infection can present with marked pancytopenia.

    Parvovirus B19 infection classically causes pure red cell aplasia but can cause pancytopenia, particularly in immunocompromised individuals

2. Connective tissue diseases:

    - ANA, RhF

    Systemic autoimmune disease can present with pancytopenia with associated immune destruction of red cells, neutrophils and platelets

3. Multiple myeloma:

    - EPG, immunoglobulin levels, B2-microglobulin, urine Bence-Jones protein

    Plasma cell disorders may rarely present with marked pancytopenia, often in conjunction with renal failure, hypercalcaemia and bone pain. Light chain myeloma may present without a markedly elevated total protein and/or protein: albumin gap.

Dr Lachlan Hayes, Staff Clinical Haematologist.
Dr J. Hayes
November 2010