Aplastic Anaemia

Aplastic anaemia is a rare, potentially life-threatening failure of haemopoiesis characterised by pancytopenia and hypocellular bone marrow.\(^1\) Aplastic anaemia is defined as pancytopenia with a hypocellular bone marrow in the absence of an abnormal infiltrate and with no increase in reticulin.\(^2\)

Epidemiology\(^3\)

- The annual incidence of aplastic anaemia is about two cases per million population.
- Aplastic anaemia is 2-3 times more common in Asia than in the West.
- Acquired aplastic anaemia most commonly presents between the ages of 15 years and 25 years but there is a second smaller peak in incidence after age 60 years.
- Certain histocompatibility locus specificities, especially HLA DR2, are associated with an underlying predisposition to acquired aplastic anaemia.

Causes\(^1\)

Most cases are acquired and immune-mediated but there are also inherited forms.\(^2\) Environmental triggers include drugs, viruses and toxins.\(^4\)

- Congenital or inherited - eg, Fanconi’s anaemia, Diamond-Blackfan syndrome: congenital aplastic anaemia is very rare, the most common type being Fanconi’s anaemia (inherited as an autosomal recessive disorder).
- Acquired:
  - Idiopathic.
  - Infection: 5-10% of severe acquired cases are preceded by seronegative hepatitis.\(^2\)
  - EBV, HIV, parvovirus and mycobacteria.
  - Toxic exposure: radiation, chemicals (eg, benzene).
  - Drugs - eg, chloramphenicol, sulfonamides, gold, penicillamine, indometacin, diclofenac, naproxen, piroxicam, phenytoin, carbamazepine, carbimazole, thiouracil, dosulepin, phenothiazines, chlorpropamide, chloroquine.
  - Transfusional graft-versus-host disease.
  - Pregnancy.
  - Sickle cell anaemia: aplastic crisis associated with parvovirus infection.
  - Genetic factors influencing the capacity for bone marrow to regenerate have been identified.\(^2\)

Presentation\(^1\)

- A family history of cytopenias should raise suspicion of an inherited disorder even when no physical abnormalities are present.\(^5\) In children and young adults, short stature, café au lait spots and skeletal anomalies suggest the possibility of a congenital form of aplastic anaemia.\(^6\)
- A preceding history of jaundice, usually 2-3 months before, may indicate a post-hepatitic aplastic anaemia.
- The history should include drug exposure and occupation (exposure to chemicals or pesticides).
- Aplastic anaemia can present abruptly over, or insidiously over, weeks to months. Clinical manifestations are proportional to the peripheral-blood cytopenias and include:
  - Patients with aplastic anaemia most commonly present with symptoms of anaemia (pallor, headache, palpitations, dyspnoea, fatigue, or ankle oedema) and thrombocytopenia (skin or mucosal haemorrhage, visual disturbance due to retinal haemorrhage, petechial rashes).
  - Infection - a less common presentation.
  - There is no lymphadenopathy or hepatosplenomegaly (in the absence of infection).

Differential diagnosis
Investigations

- FBC, reticulocyte count, blood film.
- HbF estimation in children.
- Bone marrow aspirate and trephine biopsy, including cytogenetics.
- Peripheral blood cytogenetics to exclude Fanconi's anaemia if under 35 years old.
- Flow cytometry has to a large extent replaced Ham's test to exclude paroxysmal nocturnal haemoglobinuria (PNH) clones (50% of patients with aplastic anaemia have small PNH clones).
- Urine haemosiderin if Ham's test is positive or there is phosphatidylinositol glycan-anchored protein deficiency.
- Vitamin B12 and folate.
- LFTs.
- Viral studies: hepatitis A, B and C, Epstein-Barr virus, cytomegalovirus (CMV).
- Antinuclear antibody and anti-dsDNA.
- CXR: to exclude infection.
- Abdominal ultrasound scan: an enlarged spleen and/or enlarged lymph nodes raise the possibility of a malignant haematological disorder as the cause of the pancytopenia. In younger patients, abnormal or anatomically displaced kidneys are features of Fanconi's anaemia.

Associated diseases

There is high incidence of concomitant myelodysplastic syndrome and paroxysmal nocturnal haemoglobinuria.

Classification of acquired aplastic anaemia

- A wide range of disease activity from very mild to severe.
- The risk of morbidity and mortality from aplastic anaemia correlates better with the severity of the cytopenias than with bone marrow cellularity.
- To define aplastic anaemia based on FBC and bone marrow findings, at least two of the following must be present:
  - Haemoglobin <10 g/dL
  - Platelet count < 50 x 10^9/L
  - Neutrophil count <1.5 x 10^9/L

- Acquired aplastic anaemia is classified as non-severe, severe, or very severe on the basis of the degree of peripheral-blood pancytopenia:
  - Non-severe:
    - Hypocellular bone marrow but the cytopenias do not meet the criteria for severe disease.
  - Severe:
    - Bone marrow cellularity <25%, or 25-50% with <30% residual haemopoietic cells.
    - Two out of three of the following:
      - Neutrophils <0.5 x 10^9/L
      - Platelets <20 x 10^9/L
      - Reticulocytes <20 x 10^9/L
  - Very severe:
    - As for severe but neutrophils <0.2 x 10^9/L.
Management

The course of non-severe aplastic anaemia is variable. The majority of cases have a relatively indolent and mild course requiring no treatment. However, in one study 18.8% of patients with non-severe disease progressed to severe disease. 

- Treatment should be based on the degree of cytopenia, not the marrow cellularity. Patients with asymptomatic cytopenias probably need no treatment.
- Whether treatment of non-severe aplastic anaemia affects survival is not clear.
- The effective treatments for acquired severe aplastic anaemia are as follows:
  - Allogeneic bone marrow stem cell transplantation is the initial treatment of choice for newly diagnosed patients if an HLA-compatible identical sibling donor is available, if they are young and have severe or very severe aplastic anaemia.
  - Immunosuppressive therapy: the British Committee for Standards in Haematology (BCSH) recommends antithymocyte globulin (ATG) although the British National Formulary (BNF) refers to a similar preparation, antilymphocyte globulin. The response rate to either drug may be improved when ciclosporin is given as well. The combination is indicated for:
    - Patients with non-severe aplastic anaemia who are transfusion-dependent
    - Patients with severe or very severe aplastic anaemia, aged >40 years
    - Younger patients with severe or very severe disease where an HLA-identical sibling donor is not available
  - Oxymetholone tablets are listed in the BNF as an alternative to immunosuppressive therapy but the BCSH guidelines advise caution in women (risk of masculinisation) and the elderly (risk of cardiac failure, high serum cholesterol, impaired glucose tolerance and prostatism).
  - High-dose cyclophosphamide without transplantation of bone marrow is no longer recommended in view of the high incidence of toxicity.

Supportive care

- Transfusions:
  - Platelet transfusions should be considered when the platelet count is <10 x 10^9/L (or <20 x 10^9/L in the presence of fever).
  - Risks and benefits also need careful evaluation in view of potential complications - eg, CMV infection.
  - For patients in whom marrow transplantation may be attempted or who are immunosuppressed, irradiated blood components should be given.
  - For patients with life-threatening neutropenic sepsis, consider transfusion of irradiated granulocytes.
  - Iron overload can cause significant problems in heavily transfused patients. Consider iron chelation therapy if the serum ferritin is >1000 μg/L.

- There have been anecdotal reports of vaccination producing bone marrow failure or triggering relapse of aplastic anaemia, so vaccinations, including influenza vaccinations, should only be given when absolutely necessary.
- Growth factors: erythropoetin is no longer recommended but granulocyte colony-stimulating factor (G-CSF) should be considered in patients with overwhelming infection who have not responded to the appropriate intravenous antibacterial or antifungal treatment. This should be stopped after one week if there is no demonstrable increase in neutrophil count. One study reported the successful use of granulocyte transfusions combined with G-CSF in patients with severe aplastic anaemia who had contracted severe infections.
Antibiotics:

- Overwhelming sepsis caused by bacteria or fungi (especially aspergillus) is the most frequent cause of death from aplastic anaemia.
- In most circumstances, prophylactic antibiotics are unnecessary.
- Patients with a high risk of infection should be managed in isolation when in hospital and should receive prophylactic antibiotics and antifungals, regular mouth care including an antiseptic mouthwash such as chlorhexidine and food of low bacterial content.\(^1\)
- For patients with absolute neutrophil counts consistently lower than $0.5 \times 10^9/L$, oral prophylaxis with an antibiotic should be given.
- Patients with febrile neutropenia should be treated promptly with broad-range antibiotics; in those with persistent fever after the initiation of antibacterial drugs, intravenous amphotericin should be added.
- Prophylaxis for Pneumocystis jirovecii pneumonia should be given to all patients for at least six months after bone marrow transplantation but is not routinely given after ATG in Europe.

Complications

- The major causes of morbidity and mortality from aplastic anaemia include infection and bleeding.
- Complications of bone marrow transplantation - eg, graft-versus-host disease, graft failure.
- Paroxysmal nocturnal haemoglobinuria and myelodysplastic syndrome commonly arise in patients with aplastic anaemia.

Prognosis

- Aplastic anaemia has a varied clinical course; some patients have mild symptoms that necessitate little or no therapy, whereas others present with life-threatening pancytopenia representing a medical emergency.\(^8\)
- Non-severe aplastic anaemia is seldom life-threatening and in most cases no therapy is necessary.
- The two-year mortality rate with supportive care alone for patients with severe or very severe aplastic anaemia is about 80%; invasive fungal infections and overwhelming bacterial sepsis are the most common causes of death.\(^7\)
- Improvements in bone marrow transplantation and immunosuppression have increased the number of long-term survivors of patients with aplastic anaemia.\(^{11}\)
- One review reported that, in general, elderly patients have an inferior outcome following immunosuppressive therapy and stem cell transplantation.\(^{12}\)

Prevention

If a drug trigger can be identified, the patient should be advised never to take the drug again. If a drug is linked with the development of aplastic anaemia this should be reported through the Yellow Card Scheme. An electronic version is also available online at www.mhra.gov.uk/yellow card.

Further reading & references

1. Guidelines for the diagnosis and management of aplastic anaemia; British Committee for Standards in Haematology (April 2009)
9. British National Formulary

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