A Canadian commentary on the British guidelines for the management of adult patients with aplastic anemia

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Background

- Aplastic anemia is defined as pancytopenia with hypocellular bone marrow, in the absence of an abnormal infiltrate or marrow fibrosis.
- This is a rare disease, with an incidence of ~2 cases per million population per year, and has a bimodal distribution, with peaks at 10–25 years and older than 60 years.
- Although the great majority (70–80% of cases) is idiopathic, examination of drug, occupational exposure and family history may be helpful in discerning an underlying etiology.
- Without appropriate investigation and treatment, aplastic anemia is fatal within months of diagnosis—the most common cause of death is infection.

Here we summarize evidence-based guidelines for management of adults with aplastic anemia recently published by The British Society for Standards in Haematology.1

Diagnosis and initial workup

The diagnosis of aplastic anemia requires demonstration, on a good quality bone marrow aspirate and core biopsy, of marrow hypoplasia (bone marrow cellularity < 25%) and the absence of diagnostic features of myelodysplastic syndrome. It is important to note that the presence of clonal cytogenetic abnormalities does not rule out the possibility of AA.

In addition to the bone marrow examination, the following investigations are essential in the initial workup of AA:

- **Complete blood count:** Patients usually present with pancytopenia although, in the early stages, isolated cytopenia, particularly thrombocytopenia, may occur. The reticulocyte count is low (<20 × 10^9/L by manual count or <60 × 10^9/L by automated technologies). The blood film must be examined to exclude presence of dysplastic neutrophils, abnormal platelets, blasts and other abnormal cells.
- **Flow cytometry to detect PNH cells:** GPI-deficient cells can be identified by peripheral blood high-sensitivity flow cytometry in ~50% of patients with AA. Although the PNH cell population is almost always small (<10% of peripheral leukocytes), in about 1/3 of cases the clone grows over time and can necessitate specific treatment.
- **Viral studies:** Hepatitis A/B/C, EBV, CMV, HIV and Parvovirus B19. Liver function tests should also be performed in all AA cases at the time of diagnosis to detect ongoing hepatitis. AA due to hepatitis is rare, it usually occurs 2–3 months after an acute episode of hepatitis and is more common in young males. In post-hepatic AA, the serology is often negative for the known hepatitis viruses. CMV should be assessed if SCT is being considered. HIV more commonly causes isolated cytopenias, but is a very rare cause of AA. Likewise, parvovirus B19 is more usually associated with pure red aplasia, but has been reported with AA.
- **Tests to exclude rare causes of AA:** Peripheral blood chromosomal breakage analysis (diepoxybutane test) to exclude Fanconi anemia should be performed in younger patients (<50 years), or those who have a family history, and all patients who are candidates for allogeneic stem cell transplant. Vitamin B12 deficiency very rarely causes marrow aplasia, but is easily treated and should be excluded. Pancytopenia in systemic lupus erythematosus may rarely be associated with a hypocellular marrow, and so patients should be screened for anti-nuclear antibody and anti-double stranded DNA.
- **Imaging:** Chest x-ray is useful at presentation to exclude infection and for comparison with subsequent films. X-rays of the hands, forearms and feet may be indicated if an inherited bone marrow failure syndrome is suspected. If abdominal ultrasound reveals an enlarged spleen and/or lymph nodes, the possibility of a malignant hematological disorder should be considered as the cause of the pancytopenia. In younger patients, abnormal or anatomically displaced kidneys are features of Fanconi anemia.

Other emerging diagnostic tests—peripheral blood leukocyte telomere length, next-generation gene sequencing panels, and single-nucleotide polymorphism array karyotyping—require special technology and are neither routinely available nor considered to be standard of care, but where available may provide useful information in diagnosis and management of AA patients.

Grading the severity of aplastic anemia

- **Severity of aplastic anemia should be according to Camitta criteria (Grade 1C):**
  - **Severe (SAA):** marrow cellularity <25%, plus at least 2 of neutrophil <0.5 × 10^9/L, platelets <20 × 10^9/L. Reticulocyte <20 × 10^9/L.
  - **Very severe (VSAA):** same as severe, except neutrophil <0.2 × 10^9/L.
  - **Cases of AA not meeting criteria for severe or very severe disease are referred to as non-severe AA (NSAA).**

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AA and PNH
- Small PNH clones can be detected in up to 50% of patients with AA.
- All patients with AA should be tested for PNH at the time of diagnosis.
- Patients who test negative should be retested every six months for two years, then annually unless signs and symptoms appear.
- Patients in whom a PNH clone is detected should be retested every three months for two years, after which the monitoring frequency may be reduced only if the clone size is stable.

Treatment of aplastic anemia
All patients with AA require supportive care to ameliorate symptoms and complications caused by cytopenias. However, in all cases of SAA and VSAA, as well as in NSAA associated with significant symptoms or need for blood transfusions, disease-modifying treatment with immunosuppressive therapy (IST) or allogeneic stem cell transplantation (SCT) should be considered.

Supportive care:
- Anemia
  - Transfusions should be given to improve quality of life (Grade 1A).
  - Transfusion threshold should be individualized according to co-morbidities (Grade 1A).
- Thrombocytopenia
  - Only one adult platelet dose is routinely required (Grade 1A).
- Prophylactic platelet transfusions should be given to stable aplastic anemia patients on active treatment, with a transfusion threshold of 10 x 10^9/L (Grade 1B).
- If additional risk factors for bleeding exist, a higher prophylactic transfusion threshold 20 x 10^9/L is recommended (Grade 2C).
- Prophylactic platelet transfusions are not recommended for patients not on active treatment (Grade 2B).
- Neutropenia
  - Prophylactic antibiotics and antifungal therapy are recommended per local policies (Grade 2B).
  - Patients receiving immunosuppressive therapy should receive prophylactic anti-viral agents, but routine prophylaxis against Pneumocystis jirovecii is not necessary (Grade 2C).
  - Irradiated blood products are recommended for patients undergoing immunosuppressive therapy (Grade 1C) and hematopoietic stem cell transplantation (Grade 1A).

Immunosuppressive therapy (IST):
- Current standard first line IST is horse antithymocyte globulin (ATG) combined with cyclosporin (Grade 1A).
  - ATG must be given as an in-patient.
  - ATG is a powerful immunosuppressive agent; it should only be used in centres that are familiar with using the drug and its side effects.
  - Cyclosporine therapy is started two weeks after ATG administration and is continued as long as blood counts continue to improve; after a further 12 months of treatment the dose is slowly tapered.
  - IST is the recommended first-line treatment for the following groups (Grade 1A):
    - NSAA patients who are transfusion dependent, bleeding, encountering infections or for lifestyle (activities).
    - SAA/VSAA patients in the absence of an HLA-matched sibling.
    - SAA/VSAA patients >35–50 years of age.
  - The six-month response rate to a first course of horse ATG is around 70%.
  - Five-year OS is age-dependent: 100% for age <20 years, 92% for 20–40 years, 71% for 40–60 years and 56% for >60 years.
  - Vaccinations in AA patients
    - There is a risk of relapse of AA following vaccinations in patients who have responded to IST.
    - Vaccination, including influenza, should be avoided in AA patients.
    - An exception is AA patients who have received SCT, who should receive all routine vaccinations.

Hematopoietic stem cell transplantation:
- HLA identical sibling donor HST is the treatment of choice for severe disease in young adult patients, but co-morbidities need to be carefully reassessed in patients aged 35–50 (Grade 1B).
- For adult MSD HSCT, the survival is age-dependent, but OS is 70–85% between the ages of 30 and 50 years.
- Matched unrelated donor transplant in adults should be considered as second-line therapy after lack of response to one course of immunosuppressive therapy.
- In patients without response to IST for whom no matched sibling or unrelated donor can be identified, alternative donor HSCT using either cord blood, a haploidentical family donor or a 9/10-matched UD may be considered.

Treatment of AA in elderly patients:
- Treatment of AA in elderly patients (older than 60 years) is more complex than in younger patients and has worse outcomes due to poorer tolerability of treatment.
- Although older age per se is not a reason to withhold treatment, there is no place for SCT as first-line therapy in patients older than 60 years.
- IST with ATG/cyclosporine or cyclosporine is an option for first-line therapy.
- Patients who are intolerant of, or decline IST should be offered best supportive care.

REFERENCE