Aplastic anaemia: continued cause for concern

Aplastic anaemia is a rare disorder of haemopoiesis characterised by blood pancytopenia and bone marrow hypoplasia, with an overall incidence in the general population of 3-6 per million, and affecting 2-4 per million children under 15 years. The age distribution is bimodal with peaks under 20 and over 40 years, and the incidence is higher in the Orient than the West, probably reflecting greater exposure to environmental toxins and hepatitis. In most series there is a male preponderance.

Aetiology
The failure of haemopoiesis may be constitutional or acquired. Viruses (particularly non-A, non-B hepatitis and Epstein-Barr), drugs (chloramphenicol, non-steroidal anti-inflammatory, gold), and environmental toxins have been implicated but over 70% of acquired cases are idiopathic.

The mechanism of bone marrow failure is unclear in most cases. Haemopoietic precursors from index patients grow poorly in culture, and data for an immune mediated disorder are conflicting, although a proportion of patients respond to immune suppression. In several series, up to 50% of adults treated with immune suppression by antilymphocyte globulin have subsequently developed a clonal disorder of haemopoiesis including acute myeloid leukaemia, paroxysmal nocturnal haemoglobinuria or myelodysplasia, and this argues for an underlying defect in haemopoiesis in many cases. With viruses or drugs possibly acting as a trigger in already abnormal marrow.

Constitutional causes of aplastic anaemia include Fanconi's anaemia (autosomal recessive trait, low birth weight, poor growth, and skeletal, cardiac, and urogenital anomalies) and dyskeratosis congenita (sex linked, nail atrophy, mucosal leucoplasia), and although Swachman's syndrome is typified by neutropenia and exocrine dysfunction of the pancreas, pancytopenia occurs in a minority of children.

Diagnosis
At diagnosis, the history should include specific inquiry regarding drug exposure, possible toxins, and recent infections, particularly hepatitis. Examination may reveal stigmata of Fanconi's anaemia or dyskeratosis congenita. The blood film shows a variable degree of pancytopenia, and one or more cell lines may be disproportionately affected. Although pallor and bruising are usual at presentation, infection and haemorrhage are less common, and indicate a poor prognosis. A trephine biopsy to assess marrow cellularity is essential, and typically shows pronounced hypocellularity with replacement of haemopoietic tissue by fat cells. Marrow involvement may be patchy with residual islands of normal or increased cellularity, which may cause diagnostic uncertainty. Inflammatory cells may be prominent, and residual haemopoietic cells may be mildly dysplastic, but there is no increase in blasts and malignant cells are not seen.

Initial investigation should exclude constitutional causes of marrow failure. In Fanconi's anaemia culture of blood lymphocytes with diepoxybutane or mitomycin C reveals an increase in chromosomal breaks, gaps, rings, and translocations, a manifestation of the underlying defect of DNA repair in this disorder. Imaging may show skeletal, cardiac, or renal abnormalities. A Ham's (acidified serum lysis) test is required to exclude paroxysmal nocturnal haemoglobinuria, a disorder of haemopoiesis characterised by increased sensitivity of erythrocytes to lysis by complement, which may precede or evolve from aplastic anaemia. Viral serology and liver function tests may show evidence of hepatitis, Epstein-Barr virus, or parvovirus infection.

Disease severity is assessed by the modified criteria of Camitta et al (table), which primarily reflect the severity of blood pancytopenia and have considerable prognostic importance. Patients with neutrophils less than 2 x 10^9/L neutrophils fare particularly poorly and are identified as having very severe aplastic anaemia, whereas more mildly affected individuals have non-severe aplasia.

Treatment
Children with severe aplastic anaemia have a poor prognosis with supportive care alone, with only 20% surviving one year from diagnosis. Broad spectrum antibiotics are essential for infections, with blood and platelet transfusions as clinically indicated, and blood products should be leucocyte depleted to reduce sensitisation to HLA antigens; this is most conveniently achieved by in line filters at the bedside. Refactoriness to platelet transfusion develops in 50% of those who have had several transfusions, but is not dose dependent, and prophylactic platelet support may be indicated in severe cases.

Ideally patients with negative serology for cytomegalovirus should receive cytomegalovirus negative blood products, but the use of leucocyte depleting filters may reduce the risk of its transmission from unscreened blood products.

In acquired aplastic anaemia, the options for curative treatment lie between allogenic bone marrow transplantation for those with an HLA full match family donor, and immune suppressive treatment. Children with severe or very severe aplastic anaemia are best treated by bone marrow transplantation, and recent experience indicates an 80% five year disease free survival in such cases. Graft rejection, once a major barrier to success, has been reduced by modern preparative schedules incorporating cyclophosphamide and cyclosporin, and graft versus host disease is generally mild and responsive to treatment in paediatric series. Similarly, infection with cytomegalovirus, a major cause of death in adult transplants, is a less common complication of bone marrow transplantation in childhood. Survival is improved by early compared with delayed transplantation, and all families should be tissue typed at presentation. Unfortunately, 70% of patients have no family donor, and treatment for these cases is by immune suppression in the first instance.

Antilymphocyte globulin (or antithymocyte globulin) is the standard method of immune suppression in aplastic anaemia, and is administered as a five day course via a

Criteria for severe aplastic anaemia

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<td>Blood (at least two of three must be present):</td>
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<td>(1) Neutrophils &lt;0.5 x 10^9/L</td>
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<td>(2) Platelets &lt;20 x 10^9/L</td>
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<td>(3) Corrected reticulocytes &lt;1%</td>
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Bone marrow:
- Either: cellularity <25% normal
- Or: cellularity <50% normal, with residual haemopoietic cells <30%
central venous catheter. A test dose is necessary as a precaution against anaphylaxis, platelet transfusion is indicated because antilymphocyte globulin exacerbates thrombocytopenia, and methylprednisolone cover is necessary to reduce the otherwise high incidence of serum sickness. The response to antilymphocyte globulin may be delayed, and observation for three to four months is necessary to detect improvement. A second course may prove effective if the initial response is unsatisfactory. The overall response rate is 50–60%, and is greater in non-severe compared with severe aplastic anaemia, but in many cases antilymphocyte globulin results in improvement rather than normalisation of the blood count.  

An unsatisfactory response to antilymphocyte globulin is most likely in patients with a neutrophil count of <0.2 x 10^9/l, sepsis, or haemorrhage, in young children, and females. In the few paediatric series survival rates have ranged from 40–70%, but patient numbers were small, and follow up short. Subsequent relapse of aplastic anaemia occurs in 30% of cases. Several series have described the evolution of acute myeloid leukaemia, paroxysmal nocturnal haemoglobinuria, or myelodysplasia in 30–50% adults treated with antilymphocyte globulin, although these complications have not been described in children. These reservations notwithstanding, at present antilymphocyte globulin remains the treatment of choice for cases with non-severe aplastic anaemia. Although of no proved benefit when used alone, androgens may be synergistic in combination with antilymphocyte globulin, and controlled studies are underway to resolve this question.

For patients who have failed first line treatment, responses have been described after immune suppression with cyclosporin or high doses of methylprednisolone. Of these cyclosporin is the more promising, and has proved useful in patients who have relapsed after or failed to respond to antilymphocyte globulin. Controlled studies of cyclosporin alone and in combination with antilymphocyte globulin are in progress. Improvements in neutrophil counts during treatment with the recombinant haemopoietic growth factor granulocyte macrophage colony stimulating factor are of interest, but this treatment had no effect in patients with very low neutrophil counts, or sepsis at the time of treatment. Finally some patients have received transplants from matched unrelated donors, or family donors with some degree of mismatch, and although this approach is experimental it may offer the best hope of cure for patients unresponsive to first line treatment.

The pancytopenia of Fanconi’s anaemia responds to oral androgens, but an increased risk of leukaemia in these children and the potential toxicity of androgen treatment indicate bone marrow transplantation as the treatment of choice whenever possible. Due to the defect in DNA repair, these children are particularly sensitive to standard preparative regimens, but good results are now obtained with reduced dose treatment. Treatment for dyskeratosis congenita is unsatisfactory as there is an increased risk of epithelial neoplasia in these patients.

In conclusion, despite progress in the management of aplastic anaemia, this condition remains a major challenge for the future. Accurate diagnosis, early referral, and support with antibiotics and blood products as indicated remain essential to maximise the prognosis for children affected by this often devastating disease.