Paul Ehrlich, who won the Nobel Prize in 1908 was the first to describe the entity that we know today as Aplastic Anaemia: he described the first case in 1888, in a young woman who died of an abrupt illness with severe anaemia, haemorrhage, hyperpyrexia, and a hypocellular bone marrow. One hundred and twenty six years later we still have a diagnosis of “Idiopathic Aplastic Anaemia” where we are unable to tell a young adult who presents with catastrophic bone marrow failure as to why this has happened and speculate that there could have been some insult (drug/infection) on an underlying genetic defect which triggered an immune response against the hematopoietic stem cell. Since our understanding of the aetiology in the individual patient is uncertain the management algorithm is also empiric. The severity of the disease process based on the presenting blood counts and marrow cellularity is defined by International Aplastic Anaemia Study Group Criteria but the tempo of the disease varies with some patients presenting with mild chronic cytopenia and others with a rapidly fatal disease.

It is believed that the incidence of Aplastic anaemia is around 2-3/million population from studies in the Western world. The incidence of aplastic anaemia is higher in Asia than in the West. A large study from Thailand, conducted with the same methodology and some of the same personnel as the IAAAS, found a rate of 3.9/million for the Bangkok metropolitan area and 5/million in the northeast region of Khonkaen. There is no epidemiological data on the true incidence of Aplastic Anaemia from India and we have to depend on hospital based statistics. If we extrapolate the data from Aoki then there would be 7200 new cases of Aplastic Anaemia every year in India. However many of these would probably never be even diagnosed because of the lack of facilities in peripheral hospitals.

There have been rapid advances in our understanding of the molecular biology of the inherited bone marrow failure syndromes with Fanconi anaemia being the prototype of a disorder where there is failure of the DNA repair processes in the cell. Our ability to diagnose forme fruste’s of this disease by new molecular techniques is important when a patient with Fanconi anaemia is being taken for stem cell transplantation. The recent understanding of the telomere and its abnormalities which result in a variety of genetic disorders called “telomeropathies” has allowed us to understand the molecular basis of Dyskeratosis congenita; the other genetic disorder which causes aplastic anaemia. Telomere shortening is present even in patients with “idiopathic” aplastic anaemia and this may be the underlying problem increasing the likelihood that an environmental insult can trigger the immune response against the haematopoietic stem cell.

The exact cause of haematopoietic failure in Aplastic anaemia in the individual patient remains obscure and we are still left with the dilemma of whether it is a problem with the seed (the haematopoietic stem cell) or the soil (the microenvironment). Drugs and exposure to chemical agents are implicated and there is a long list of agents capable of damaging the marrow. In about 10% of patients previous viral hepatitis is linked to the development of marrow failure. There is considerable evidence to suggest that in many patients immune mediated mechanisms are responsible for marrow failure: these include the association with HLA, in vitro co-culture studies of stem cells with T lymphocytes, failure of engraftment in syngeneic stem cell transplants without prior conditioning, autologous recovery after allogeneic stem cell transplantation and the successful outcome after administration of anti lymphocyte globulin to patients. Figure 1 illustrates the possible sequence of events in immune mediated marrow failure.

Aplastic anaemia is considered in any patient with pancytopenia and a bone marrow aspirate and trephine biopsy are essential to confirm the diagnosis.
Stress testing to exclude FA is essential in all children: tests for PNH and cytogenetic examination of the bone marrow to exclude hypoplastic MDS is useful. Screen for blood borne viruses is mandatory both for the aetiology and since most patients have been transfused.

Once a diagnosis has been established the following treatment options are available today:

- Haematopoietic stem cell transplantation
- Therapy with Anti-lymphocyte (ALG) and Anti-thymocyte (ATG) immunoglobulin
- Cyclosporine
- Androgens and Danazol

The choice of the optimal therapy for the individual patient remains empiric.

Haematopoietic stem cell transplantation if there is a stem cell donor remains the treatment of choice for young patient with very severe aplastic anaemia and it is possible achieve disease free survival in the region of 85% in young patients.12,13 However many patients with SAA in India present late, having received multiple transfusions and are often septic: waiting for these patients to stabilise when there are no neutrophils is often of no use and the transplant should be performed as quickly as possible under appropriate antimicrobial cover.14 Logistics and resources are the most important constraints. The use of fludarabine along with cyclophosphamide has reduced rejection but graft versus host disease remains a problem.15,16 ALG or ATG would be the first line of treatment for older adults with SAA who are not septic. The choice of the product is important with data suggesting that horse ATG is more effective than rabbit ATG.17 Some studies suggest that ATGAM produced in India is comparable to the Pfizer product but larger studies need to be done to confirm this.18 The exact mechanism by which ALG and ATG work to restore haematopoiesis is unclear since destruction of T-cells alone with monoclonal anti T-cell antibodies is not effective.19 Administration of ALG/ATG to a sick aplastic anaemia patient requires experience and adequate transfusion support and management of infection. Response rates in the region of 60% can be expected but some patients will have clonal evolution to PNH and myelodysplastic (MDS) syndrome. Cyclosporine is always administered for 3 to 6 months after ATG: however the drug can be used as a single agent in patients with no severe aplastic anaemia with responses in the region of 30-40%.20 Preventing gingival hyperplasia and proper control of drug induce hypertension is essential in the patient with a low platelet count. The drug must be tapered slowly if there is a response. There is an association between HLA and cyclosporine response and dependence.21

There is a place for androgens in the management of patients with non severe aplastic anaemia when resources are limited and an occasional patient who has failed other therapies responds to treatment.22 Virilisation, hepatic dysfunction and premature closure of the epiphyses in children are important side effects. Danazol should be used in preference to oxymethalone or stanozolol in females. There is data that danazol may be useful in patients with Dyskeratosis congenita.23,24

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Aplastic anaemia remains a challenging clinical
problem and early diagnosis and prompt institution of the appropriate treatment for the individual patients should be the goals for physicians in India. The data and publications on Aplastic Anaemia from India is limited and this issue of JAPI is an attempt to bring together perspectives and data from different haematologists from India.

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