

# Aplastic anemia- a quick review

## Abstract

Aplastic anemia is a rare bone marrow disorder characterized by pancytopenia. It can be congenital but is usually idiopathic but rarely certain drugs, chemicals and infections can cause aplastic anemia. It is diagnosed with hypocellular bone marrow. The definitive treatment is allogeneic hematopoietic stem cell transplant, however supportive care with transfusion and immunosuppressive therapy can provide symptomatic relief and improved quality of life. Patients should always be encouraged to enroll into clinical trials.

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## Introduction

Aplastic anemia (AA) is a rare hematologic disease and a distinctive example of bone marrow failure syndromes. AA is characterized by diminished or absent hematopoietic precursors in the bone marrow, most often due to injury to the pluripotent stem cell. The designation “aplastic anemia” is a misnomer, because the disorder is characterized by pancytopenia rather than anemia. The disease is estimated to occur in two to four individuals per million populations every year.<sup>1-6</sup>

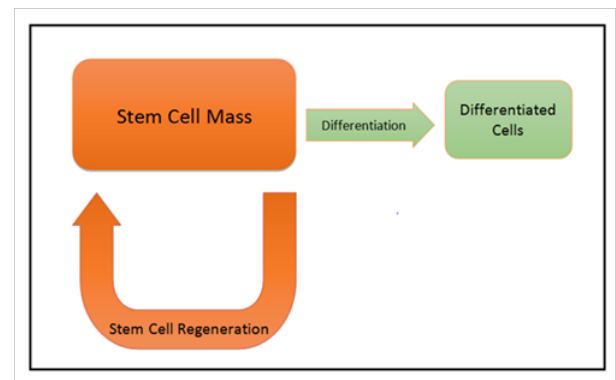
Paul Ehrlich introduced the concept of aplastic anemia in 1888 when he studied a case of a pregnant woman who died of bone marrow failure.<sup>7</sup> However; it was not until 1904 that Anatole Chauffard named this disorder aplastic anemia.

## Etiology

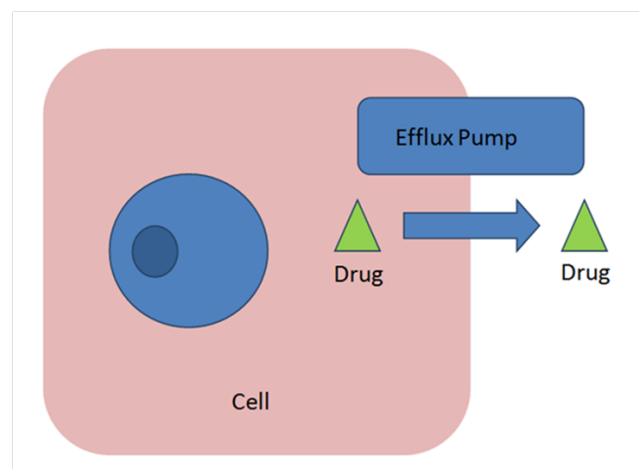
AA results secondary to a reduction in the pluripotent stem cell number below a critical mass. This is due to a conflict between self-renewal versus differentiation (Figure 1). The ultimate effect is stem cell or bone marrow failure. Usually AA is idiopathic, however it can be attributable to cytotoxic drugs (chloramphenicol, gold),<sup>8</sup> radiation, toxic chemicals (like Benzene, solvents and glue vapors), viral infections (Epstein- Virus Infection, Seronegative Non A-G hepatitis),<sup>9,10</sup> immune related disorders (Eosinophilic fasciitis, SLE, Graft versus host disease),<sup>11</sup> thymoma, anorexia nervosa and paroxysmal nocturnal hemoglobinuria(PNH).

## Drug induced AA

Majority of patients exposed to the implicated drugs do not develop AA, and the exact mechanism for the idiosyncratic reaction is unknown. The P-glycoprotein, Multi-Drug Resistance Gene, (MDR-1) gene product, and the multidrug resistance-associated protein, are energy-dependent transmembrane efflux pumps for a variety of lipophilic drugs.<sup>12,13</sup> They are responsible for keeping the drugs out of the cells (Figure 2). An overexpression of these proteins confers the multidrug resistance phenotype to cancer cells, whereas an under-expression in normal cells allows cytoplasmic accumulation of drugs and enhances their toxic effects.<sup>14</sup>



**Figure 1** Depicting the delicate balance between stem cell differentiation and regeneration in the etiology of aplastic anemia.



**Figure 2** Depicting the mechanism of drug efflux from the cell.

## Viral infections

Certain viruses are implicated in causing aplasia.

## Parvovirus B19

This virus more commonly attacks pro-erythroblasts and causes transient red cell aplasia, as seen in patients with chronic hemolytic anemia. However, pancytopenia can also occur, particularly in patients who are immune compromised.<sup>15</sup>

## Hepatitis virus and human immunodeficiency virus (HIV)

These viruses may involve T cell activation with release of cytokines or activation of a cytotoxic T cell clones which recognize similar target antigens on both liver and bone marrow cells.<sup>16</sup>

## Autoimmune AA

Autoimmune bone marrow inhibition may be mediated by the release of interferon gamma (IFN-gamma) due to its marrow suppressing effect, under the influence of the transcription factor T-bet and/or cytokines such as TNF-alpha and various interleukins.<sup>17</sup>

Unregulated lymphocyte activation, like mutations of perforin in hemophagocytic lymphohistiocytosis, or an autoimmune state due to impaired numbers or function of cluster of differentiation (CD4+/CD25+)/ transcription factor fork-head box P3 positive (FOXP3+) T regulatory cells, secondary to the actions of T helper 17 (Th17) cells results in a hematopoietic inhibitory response. This inhibition may be mediated by IFN-gamma or the cytokine cascade released by IFN-gamma ultimately leading to apoptotic death of hematopoietic stem cells in the bone marrow.<sup>18-22</sup>

## Clinical manifestations

Patients with AA are usually well, prior to the diagnosis. AA occasionally comes to medical attention because of fatigue and other symptoms associated with progressive anemia. More common presentations include recurrent infections due to profound neutropenia

or mucosal hemorrhage due to thrombocytopenia. Infections are typically bacterial. Invasive fungal infection is a common cause of death; especially in subjects with prolonged and severe neutropenia.<sup>23</sup> Increased menstrual flow is also a common complaint in premenopausal women.

## Diagnosis

Patients with AA, have clinical findings consistent with pancytopenia, especially pallor and petechiae. The liver, spleen or lymph nodes are generally not enlarged. A complete blood count with differential, bone marrow aspiration and biopsy with measurement of red cell membrane or neutrophil CD59 by flow cytometry, and cytogenetics are indicated.<sup>24</sup> Diagnosis of AA is established by demonstration of pancytopenia and hypocellular bone marrow.<sup>25</sup> An important differential diagnosis is of hypoplastic myelodysplastic syndrome (MDS), which should be kept in mind due to significant difference in management and prognosis (Table 2) (Figure 3).

## Classification

Aplastic anemia is classified as moderate, severe (SAA) or very severe aplastic anemia (vSAA) as shown in Table 1.<sup>26</sup>

## Management

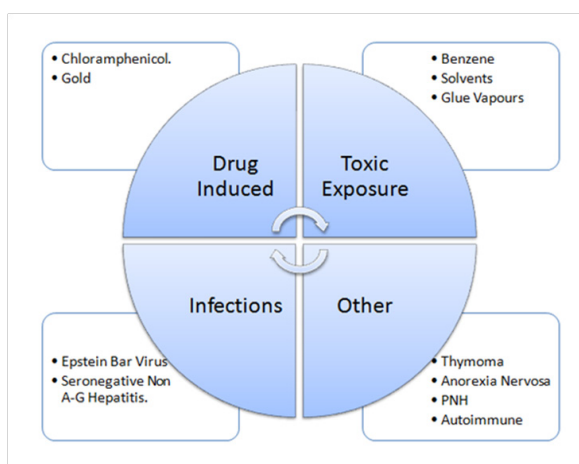
Patients with moderate AA are managed with individualized approach considering the symptoms, disease severity, and changes in the degree of cytopenia over time. Close monitoring often is appropriate, especially when symptoms and transfusion requirements are minimal.<sup>27</sup> SAA or vSAA on the other hand are successfully treated, over 70 percent will die within one year.<sup>1</sup> Patients should not be subject to initial trials of G-CSF or erythropoietin.<sup>28</sup> There are various treatment options available however; Immunosuppressive Therapy (IST) remains the most commonly used first line of therapy. Prognosis depends on the severity of aplastic anemia and the age of the patient (Figure 4).

**Table 1** Classification of aplastic anemia by severity<sup>23</sup>

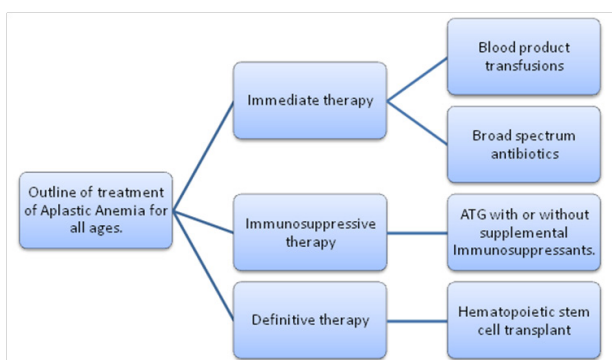
Moderate	Severe	Very severe
Decreased bone marrow cellularity	Bone Marrow Cellularity <30%	
Depression of at least two of the three hematopoietic lineages not fulfilling the severity criteria as specified in the right column.	Depression of at least two of the following three hematopoietic lineages.  Absolute neutrophil count <0.5 × 10 <sup>9</sup> /L. Transfusion dependence, with absolute reticulocyte count <60 × 10 <sup>9</sup> /L or platelet count <20 × 10 <sup>9</sup> /L.	Patients that fulfill criteria for severe aplastic anemia but with an absolute neutrophil count of <0.2 × 10 <sup>9</sup> /L.

**Table 2** Main diagnostic characteristics of aplastic anemia and hypoplastic myelodysplastic syndromes<sup>24</sup>

Criterion	Aplastic anemia	Hypoplastic MDS
Cytopenia	Present	Present
Bone Marrow Cellularity	Aplastic (<10% Cellularity)	Hypocellular
<b>Hematopoiesis</b>		
Erythropoiesis	Present in nests, or "Hot Spots"	Present
Myelopoiesis	Typically decreased	Present
Megakaryopoiesis	Decreased or absent	Present
<b>Dysplasia</b>		
Erythropoiesis	Possible	Possible
Myelopoiesis	Normal Morphology	Possible
Megakaryopoiesis	Normal Morphology	Possible
Blasts	Absent	Variable
CD34+ or CD117+	Nearly Absent	Normal or increased
Marrow Fibrosis	Absent	Possible
Karyotype	Clonal abnormality possible (about 12%)	-7 /del (7q) -5/del(5q)
PNH Clone	Frequent	Unusual
Splenomegaly at Diagnosis	Absent	Possible



**Figure 3** Depicting the various etiologies of the aplastic anemia.



**Figure 4** Figure depicting the Outline of treatment of Aplastic Anemia for all ages.

## Immediate measures

The immediate aim is to eliminate symptoms of anemia and thrombocytopenia.

- PRBC transfusion - no specific cutoff of hemoglobin and hematocrit is available. It is advised to transfuse only if patient is symptomatic from anemia, preferably use leucocyte reduced and irradiated blood. Overuse of blood products should be avoided.
- Platelet transfusion if the platelet count is less than 10,000/ $\mu$ L, or evidence of bleeding.
- Broad spectrum parenteral antibiotics should be instituted.

## Immunosuppressive therapy

Anti thymocyte globulin (ATG) - ImmunoglobulinG (IgG) against human antigen reactive T lymphocytes (equine-derived) causes either elimination of T lymphocytes in peripheral blood or alteration in T-lymphocyte function. In aplastic anemia these IgG may induce complete or partial hematologic response. It has half-Life of 1.5-12 days; it should only be prescribed by physicians experienced in immunosuppressive therapy and patients should only receive the drug in facilities equipped and staffed with adequate laboratory and supportive medical resources. It is required to be administered by a double lumen central line and platelet count should be  $\geq 20,000$ K/ $\mu$ L. Beta-blockers should be held before ATG administration to avoid suppressing physiologic responses to anaphylaxis. It is contraindicated in patients with a history of hypersensitivity to

antithymocyte globulin, and other equine gamma globulins. An ATG skin test should be performed for hypersensitivity to horse serum followed by desensitization if reacting to intradermal injection. The treatment should be discontinued if there is evidence of anaphylaxis, unremitting thrombocytopenia, or unremitting leukopenia. Aplastic anemia patients may need prophylactic platelet transfusions. Patients should be observed carefully for previously masked reactions when reducing dose of corticosteroids, and other immunosuppressants. A randomized trial by Scheinberg et al, concluded that rabbit ATG was inferior to horse ATG as the initial treatment of SAA as was reported by the hematological response and survival.<sup>29</sup>

## ATG with cyclosporin(CsA)

A more intensive regimen including ATG and cyclosporine appears to provide superior results compared with treatment with ATG alone in patients with SAA.<sup>30</sup> CsA administration is initiated on Day 1. Starting dose is 10 mg/kg per day (15 mg/kg/day in children). Target trough level is between 200 and 400 ng/mL. For high blood pressure, it is advised to start anti-hypertensives like amlodipine and start azithromycin for bothersome gingival hypertrophy. If renal functioning worsens or creatinine  $\geq 2$  mg/mL, temporary cessation of CsA therapy and later reintroduction at lower doses with further increases as tolerated is recommended. Antimicrobial prophylaxis for *Pneumocystis carinii* with monthly aerosolized pentamidine while patient is on therapeutic doses of CsA is recommended. Sulfa drugs are avoided, alternative regimen with Dapsone or Atovaquone are used when Pentamidine cannot be used or in very small children. Antibacterial, antiviral and antifungal prophylaxis is not routinely administered with standard horse ATG/CsA.<sup>31</sup>

## Agents added to ATG+CsA

Addition of agents like G-CSF, danazol, mycophenolate mofetil, sirolimus and erythropoietin have been studied in prospective randomized studies with no reported difference in response, relapse, clonal evolution or survival.<sup>32-36</sup>

## Other agents

High dose cyclophosphamide, modified high dose cyclophosphamide plus cyclosporine, anti-IL-2 receptor antibody, daclizumab IV every other week for a total of five doses, arsenic trioxide plus cyclosporine.<sup>37-40</sup> Simple definition of hematological response is no longer limited to meeting blood count criteria for SAA, which closely correlates with transfusion independence and long term survival. Majority (90%) of the hematological responses occurs within 3 months after ATG.<sup>41,42</sup>

Cyclosporine taper is a common practice but adequate prospective comparative studies of such strategy are lacking. Anecdotal and retrospective reports support taper to decrease the rate of relapse.<sup>4,43</sup>

## Hematopoietic stem cell transplantation (HSCT)

Allogeneic hematopoietic cell transplantation (HCT) is curative, but is limited by the availability of a HLA-matched sibling.<sup>44</sup> Bone Marrow is the preferred source of stem cells in AA, not peripheral blood, unlike hematological neoplasms.<sup>45,46</sup> Matched unrelated - donor transplantation should be reserved for patients for whom an initial course of IST has failed especially in children and young adults.<sup>47</sup>

In patients under the age of 20 with SAA or vSAA, with an HLA-matched sibling, treatment with allogeneic HCT over treatment with an immunosuppressive regimen is recommended [48]. In patients 20-50 years of age with SAA or vSAA in otherwise excellent health

with a fully HLA-matched sibling donor, it is recommended to treat with allogeneic HCT over treatment with an immunosuppressive regimen. For those individuals without a matched sibling donor, immunosuppressive therapy is recommended over the use of matched unrelated, mismatched related, or mismatched unrelated HCT [49]. In patients over 50 years with SAA or vSAA, the use of immunosuppressive therapy over HCT is suggested because of the very high risk of graft-versus-host disease in patients age  $\geq$  45 years.<sup>50,51</sup>

## Prognosis and survival

Without treatment patients with aplastic anemia have high mortality rate close to 70 percent within one year.<sup>52</sup> Usually clinical course is variable with complications due to pancytopenia (infections, bleeding), relapse and clonal evolution however with increasing availability of hematopoietic stem cell transplant and effective immunosuppressive therapy, survival rates have increased to as high as 80 percent.<sup>53</sup>

## Conclusion

The treatment of severe aplastic anemia, whether by allogeneic stem cell transplantation or immunosuppression, has improved dramatically over the years, and long-term survival of more than 75% of patients can be anticipated with either therapy.

In conclusion, a multidisciplinary approach is recommended to systematize relevant results and develop a treatment plan. Consideration should be given to seeking an expert advice on the diagnosis and management of patients where there is uncertainty, or when an inherited bone marrow failure syndrome is being considered and henceforth an enrollment in clinical trials should be encouraged.

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## Conflicts of interests

The authors declare that there is no conflict of interest.

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