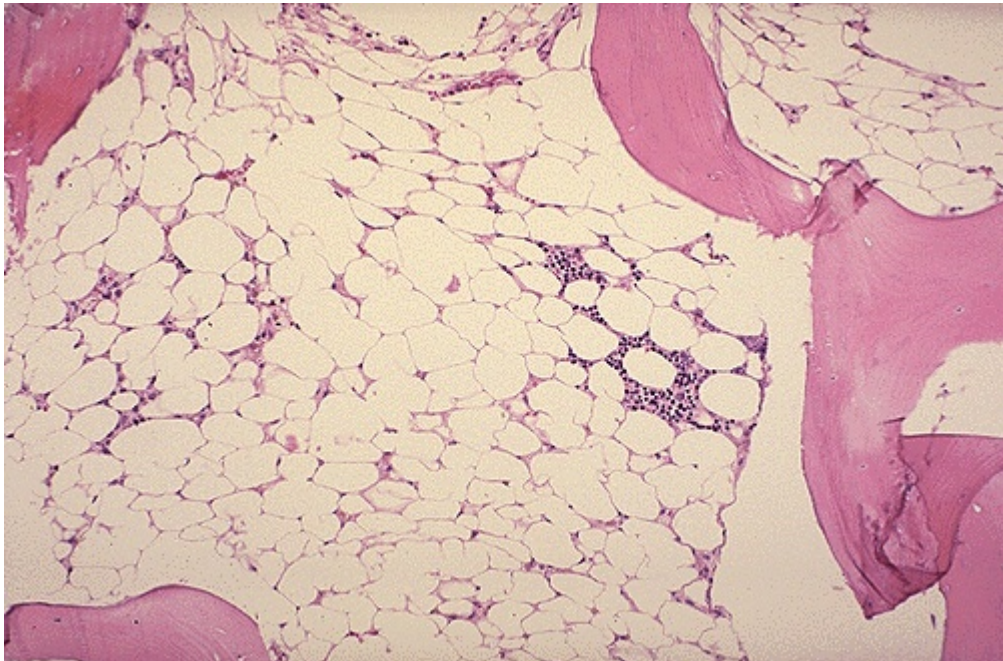


Aplastic Anemia in Children — Prognosis and Survival Rate

[See online here](#)

Aplastic anemia is a rare disease affecting 1–2 people per one million of the population. The hallmark of the disease is peripheral pancytopenia with hypocellular bone marrow in the absence of infiltrative disease to the bone marrow. It is classified into moderate, severe, and very severe aplastic anemia based on actual cell count. Major causes of morbidity and mortality are hemorrhage and infections. Supportive therapy focuses on the alleviation of suffering and improving the quality of life experienced by patients. Definitive treatment is mainly by stem cell transplantation.



Definition of Aplastic Anemia

The world health organization (WHO) defines anemia as **a blood hemoglobin level which is less than the reference lower limit for a specific age and sex**. Aplastic anemia is a disorder characterized by pancytopenia and hypocellular bone marrow in the absence of infiltrative disease to the bone marrow.

The disorder **should be distinguished from bone marrow failure** which is characterized by pancytopenia in the presence of fibrosis, disordered cell maturation, myelodysplasia, and hyperplasia of the bone marrow. Peripheral cell count defines the severity of aplastic anemia counts as postulated by the international aplastic anemia study group (IAASG):

Moderate aplastic anemia

This includes decreased bone marrow cellularity with peripheral pancytopenia that does not meet the criteria for severe aplastic anemia.

Severe aplastic anemia (SAA)

Important data:

Bone marrow cellularity < 25 %

Neutrophil count < $500 \times 10^6 /L$

Platelet count < $20,000 \times 10^6 /L$

Reticulocyte count³ < $60,000 \times 10^6 /L$

Very severe aplastic anemia (VSAA)

Neutrophil count is < $200 \times 10^6 /L$ in a patient fulfilling the criteria for severe aplastic anemia.

Epidemiology of Aplastic Anemia

Aplastic anemia is a rare disease **affecting 1 or 2 people per million each year in Europe.**

There are 300—600 new cases reported in the United States each year. The disease has no sexual predilection and research suggests that it is more common among **Asians** compared to Europeans and Americans. The risk is postulated to increase with exposure to the causative toxins such as pesticides containing benzene and arsenic, chemotherapy, radiotherapy, and medications such as chloramphenicol.

Etiology of Aplastic Anemia

Aplastic anemia **underlies a defect in bone marrow or stem cells leading to aplasia** of different cell lines including red blood cells. Although pediatric aplastic anemia is sometimes **idiopathic**, there is a number of etiological factors known that causes aplastic anemia. It may be congenital or acquired, but, **more than 80 % of the cases are of an acquired nature.**

Causes of congenital/inherited aplastic anemia in children

Congenital causes constitute up to 25 % of the cases of aplastic anemia in children:

- Fanconi anemia
- Dyskeratosis congenital
- Familial aplastic anemia (mutations in TERC and TERT genes)
- Cartilage-hair hypoplasia (mutation in RMRP gene)
- Pearson syndrome
- Shwachman-Diamond syndrome (mutation in SBDS gene)
- Dubowitz syndrome
- Diamond-Blackfan anemia

Causes of acquired aplastic anemia in children

Most cases of aplastic anemia (up to 80 %) in children are due to **acquired causes**:

- Infections ([hepatitis viruses](#), Epstein-Barr virus, and mycobacteria)
- Exposure to [ionizing radiation](#)
- Exposure to toxic chemicals (benzene or pesticides)
- Orthotopic liver transplantation for fulminant hepatitis
- [Anorexia](#)
- [Acute lymphoblastic leukemia](#) (ALL)
- Certain drugs, such as chloramphenicol and phenylbutazone

Classification of Aplastic Anemia

Congenital/inherited aplastic anemia

- Major causes of inherited aplastic anemia presented as syndromes with/without distinctive physical features
- Fanconi anemia
- Dyskeratosis congenital
- Shwachman-Diamond syndrome
- Amegakaryocytic thrombocytopenia

Acquired aplastic anemia

Main causes of acquired aplastic anemia include:

- Viral infections, such as Epstein Barr Virus, Parvovirus B19, [HIV](#) and Cytomegalovirus
- Toxins such as benzene and gold
- Drugs such as chloramphenicol
- Radiotherapy and chemotherapy use in the treatment of cancers

Pathophysiology of Aplastic Anemia

Several pathways have been put forward to explain the pathophysiology of aplastic anemia. However, studies suggest that **stem cell defect is the central mechanism of pathogenesis of the disease** and every pathway involves this process. The undifferentiated cells in the bone marrow are damaged until the balance between self-renewal and differentiation into mature cells is lost.

The damage is characterized by the sparing of the [bone marrow](#) stroma, [blood vessels](#) and the replacement of damaged cells with fat cells; therefore, [hematopoiesis](#) progresses normally after stem cell transplant since the supportive stroma is intact.

Idiopathic

The majority of acquired aplastic anemia in children are of unknown origin. The marrow is believed to be suppressed by **IFN- γ** whose gene is over-expressed in children with aplastic anemia. These patients respond to **immunosuppressive** therapy and stem cells transplantation.

Autoimmune

This pathophysiology is thought to be the causative pathology of the majority of the acquired cases. In this pathway, **suppression of hematopoiesis is thought to arise from an expansion of CD8 cytotoxic T lymphocytes** that secrete inhibitory cytokines such as **TNF- α** and **IFN- γ** which inhibit the cell cycle and promote apoptosis.

Moreover, they produce cytotoxic nitric oxide that causes direct damage to the stem cells. The theory is supported by the identification of an increased population of cytotoxic lymphocytes in patients with aplastic anemia and their response to immunosuppressive therapy.

Direct toxicity

The use of drugs such as **chloramphenicol** and toxins such as **benzene** and **gold** leads to toxic damage of the stem cells causing pancytopenia. This idiosyncratic reaction is thought to arise from the difference in metabolism among individuals. **The affected patients metabolize the precursors into more toxic products** that destroy the bone marrow stem cells.

Toxic viruses such as HIV are associated with T cell activation and increase in cytokines that inhibit progenitor cell growth. **Parvovirus B 19** is a common cause of aplastic anemia which selectively attacks proerythroblasts, resulting into red cell aplasia that worsens into pancytopenia, especially in immunocompromised patients.

Genetic mutations

Inherited aplastic anemia results from genetic mutations such as TERC and TERT in infantile aplastic anemia. Expression of these genes confers susceptibility to the damage of stem cells via immune mechanisms and thus leads to aplastic anemia. This type of disease commonly presents in association with other physical findings, such as **short stature, organ defects** involving the [liver](#), kidneys and the [heart](#) and poorly pigmented hair.

After stem cells are damaged and production is compromised, the deficiency spills over into peripheral circulation to cause depletion of all cell lines, i.e., pancytopenia ensues leading to the clinical manifestations of the disease.

Clinical Features of Aplastic Anemia

These children present with symptoms of **depressed cell lines**, such as **easy bruising** and **mucoctaneous bleeding** due to thrombocytopenia, fatigue, palpitations, tachycardia, and headache due to low levels of red blood cells and recurrent infections due to the depletion of white blood cells.

Symptoms

Symptoms might be clearly apparent in the advanced stages of aplastic anemia.

Common symptoms of aplastic anemia in children are:

- Fevers
- Headache
- Dizziness

- Shortness of breath
- Nosebleed
- Easy bruising
- Fatigue
- Chest pain
- A history of past hospitalization due to infections

Signs

General signs are pallor due to ineffective erythropoiesis, fever due to infections resulting from neutropenia and a mucosal ulceration.

Cardiovascular signs tachycardia:

1. [Tachycardia](#)
2. [Cardiomegaly](#)
3. [Arrhythmia](#)

Children with congenital syndromes present with physical stigmata such as:

- Short stature with short limbs
- Renal, cardiac, and gastrointestinal (GI) abnormalities
- Microcephaly
- Microphthalmia
- [Hypogonadism](#)
- Sparse and lightly pigmented hair
- Dysplastic nails
- [Oral leukoplakia](#)

Neutropenia presented clinically as:

Neutropenia could mainly be described as recurrent **bacterial infections that mostly affect the oral and pharyngeal mucosa** and the patients present with mucosal ulcerations, fevers, and a history of past hospitalization due to the infections.

Low levels of red blood cells and hemoglobin presented as a headache, dizziness, palpitations, and fatigue, dyspnea, and chest pain.

Thrombocytopenia is mostly presented by easy bruising, nosebleeds, mucosal bleeding, gingival bleeding, petechial rashes, and purpura ecchymosis.

Investigations of Aplastic Anemia

The workup of these patients focuses on the establishment of the diagnosis and grading of the severity of the disease. **Hemoglobin level estimation and a complete blood count are done to classify the severity** of the disease, while bone marrow aspirate and biopsy is done to establish the diagnosis.

The following investigations are significant in making a diagnosis:

Complete Blood Count (CBC)	<ul style="list-style-type: none"> • Low hemoglobin count for the patient's age and sex is the expected finding. • Pancytopenia with absolute reticulocytopenia is suggestive of aplastic anemia. • Further classification of the low hemoglobin into normocytic or macrocytic anemia is a common finding.
Peripheral Smear	<ul style="list-style-type: none"> • Lacks tear drop cells and leucoerythroblastic changes that are seen in myelodysplastic syndromes. • Normally shaped cells in the setting of a hypocellular marrow.

Bone Marrow Aspirate	<ul style="list-style-type: none"> This is the diagnostic test and expected findings include a hypocellular marrow with fat cells but normal stroma. <ul style="list-style-type: none"> The residual hematopoietic cells are normal in morphology. Malignancy and fibrosis are absent.
Bone Marrow Biopsy	<ul style="list-style-type: none"> This test is used to differentiate a hyperplastic bone marrow aspirate in aplastic anemia from a bone marrow aspirate seen in myelodysplastic syndromes.
MRI Scans	<ul style="list-style-type: none"> Bone marrow cellularity can be calculated from scans of the axial skeleton, especially if a hyperplastic site was selected during bone marrow aspirate.

Differential Diagnosis of Aplastic Anemia

Differential diagnosis of aplastic anemia in children is required to be made under the following conditions:

- Bone marrow failure
- Myelodysplastic syndromes
- Paroxysmal nocturnal hemoglobinuria
- Inherited syndromes associated with bone marrow failure can be distinguished from aplastic anemia due to the presence of associated physical stigmata in the former
- [Acute myeloid leukemia](#) and acute lymphoblastic leukemia are considered in patients who present with features such as hepatomegaly or splenomegaly
- [Non-Hodgkin's lymphoma](#) should be considered in patients with constitutional symptoms, hepatomegaly, and splenomegaly
- Multiple myelomas

Management of Aplastic Anemia

Medical Treatment

Supportive management

Note: Prophylactic blood transfusion for symptomatic relief is indicated in patients with a **platelet count of $< 10 \times 10^9 /l$** or all febrile patients with a count of $< 20 \times 10^9 /l$. This helps to replenish lost blood and alleviate the suffering of the patient. Blood from family members is avoided during transfusions to avoid sensitization of blood from a potential stem cell donor. Infections are a major cause of mortality in these patients and broad-spectrum antibiotic coverage is employed. With neutropenic counts, they are susceptible to bacterial and fungal infections; thus, an antibiotic and antifungal agent is indicated in patients with a count of $< 0.2 \times 10^9 /l$.

Definitive treatment

Immunosuppressive therapy (IST) is the most used therapy, especially in patients older than 40 years suffering from severe aplastic anemia (SAA), very severe aplastic anemia (VSAA) and non-severe aplastic anemia who are transfusion dependent.

The first line agents in use are **anti-thymocyte globulin (ATG)** at a dose of 40 mg/kg per day for four days and **cyclosporine** began on day five as divided doses amounting to 15 mg/kg/day until a response is achieved.

Hormonal/stimulant therapy has been tried and success reported in patients who are refractory to IST. Thrombopoietin receptor agonists such as eltrombopag, granulocyte stimulating factors such as filgrastim and granulocyte macrophage stimulating factors such as sargramostim, are administered to stimulate the stroma to encourage stem cell production and maturation.

Hematopoietic cell transplantation (HCT) is indicated in patients with less than 40 years of age and suffering from severe aplastic anemia (SAA) or very severe aplastic anemia (VSAA). The stem cells may be obtained from either A HLA matched and related donor or an HLA matched but unrelated donor. Another possibility would be cord blood in patients who lack an HLA match but have failed to respond to immunosuppressive therapy. It is the treatment of choice due to its high success rates.

Complications of Aplastic Anemia

If left untreated, the disease may progress into:

- Heart failure because of longstanding anemia
- Uncontrolled bleeding
- Severe infections
- Immunosuppressive therapy is associated with
- Relapse of the disease
- Induction of new cancers with prolonged use
- [Serum sickness](#)
- Avascular necrosis
- Opportunistic infections with suppression of the immune system
- Hematopoietic stem cell transplantation is associated with
- Graft Versus Host Disease (GVHD)
- Rejection of the graft

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