

CLINICAL OUTCOMES AND ASSOCIATION OF APLASTIC ANEMIA IN CHILDREN WITH PANCYTOPENIA

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Abstract

Background: Pancytopenia in children is a clinically important hematological presentation with a broad differential diagnosis ranging from nutritional deficiencies and infections to hematological malignancies and bone marrow failure syndromes. Aplastic anemia (AA) is an important cause of pediatric pancytopenia and is characterized by peripheral cytopenias with a hypocellular bone marrow in the absence of abnormal infiltration or significant fibrosis.

Objective: To determine the frequency of aplastic anemia among children presenting with pancytopenia and to evaluate its association with demographic, clinical, hematological, and bone marrow findings and short-term clinical outcomes.

Methods: This hospital-based observational study included 105 children with pancytopenia. Patients were evaluated through clinical history, physical examination, complete blood count, peripheral blood smear, reticulocyte count, and bone marrow examination. Aplastic anemia was diagnosed on the basis of peripheral cytopenias and hypocellular bone marrow after exclusion of alternative causes. Severe aplastic anemia was classified according to established severity criteria. Demographic characteristics, presenting symptoms, laboratory parameters, transfusion requirements, treatment, complications, and short-term outcomes were recorded. Categorical variables were analyzed using the chi-square or Fisher exact test, while continuous variables were compared using the independent-samples t test or Mann–Whitney U test, as appropriate. A p-value <0.05 was considered statistically significant.

Results: Among 105 children with pancytopenia, 39 (37.1%) were diagnosed with aplastic anemia. The mean age of children with AA was 9.2±3.8 years, and 23 (59.0%) were male. The most frequent presenting features among children with AA were pallor (94.9%), fever (61.5%), bleeding manifestations (48.7%), and recurrent infections (33.3%). Severe aplastic anemia was identified in 20 (51.3%) children with AA. Bone marrow examination demonstrated marked hypocellularity in all AA cases. Children with AA had significantly lower mean hemoglobin, platelet count, absolute neutrophil count, and reticulocyte count than children with non-AA causes of pancytopenia (p<0.001 for each comparison). Among children with AA, 22 (56.4%) required repeated red-cell and platelet transfusions, 9 (23.1%) developed clinically significant infections, and 5 (12.8%) experienced significant bleeding during follow-up. Overall, 31 (79.5%) children demonstrated clinical or hematological improvement during the observed period.

Conclusion: Aplastic anemia represented a substantial proportion of pediatric pancytopenia in this study. Severe cytopenias, hypocellular bone marrow, transfusion dependence, infections, and bleeding were important clinical features. Early bone marrow evaluation in children with persistent pancytopenia may facilitate timely diagnosis and treatment, potentially improving clinical outcomes.

Keywords: aplastic anemia; pancytopenia; children; bone marrow failure; pediatric hematology; severe aplastic anemia; thrombocytopenia; neutropenia; clinical outcome.

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Introduction

Pancytopenia is defined by the simultaneous reduction of erythrocytes, leukocytes, and platelets and represents an important diagnostic challenge in children. The causes are diverse and include nutritional deficiencies, infections, hematological malignancies, hypersplenism, inherited bone marrow failure syndromes, and acquired aplastic anemia. [1–15]

Aplastic anemia is characterized by pancytopenia associated with markedly hypocellular bone marrow and absence of significant abnormal cellular infiltration. It may be acquired or associated with inherited bone marrow failure syndromes. In pediatric patients, differentiation between acquired AA and inherited disorders is particularly important because

therapeutic approaches, genetic counseling, transplantation strategies, and long-term surveillance may differ. [1–15]

The incidence of acquired aplastic anemia is estimated at approximately 2–3 cases per million population annually in Western countries, with substantially higher rates reported in some Asian populations. Pediatric AA may occur at any age, although certain age groups demonstrate greater incidence. [1–15]

The clinical presentation is largely determined by the severity of cytopenias. Anemia may produce pallor, fatigue, weakness, dizziness, and exercise intolerance, whereas thrombocytopenia may manifest as petechiae, bruising, epistaxis, gum bleeding, or more serious hemorrhage. Severe neutropenia increases susceptibility to bacterial and fungal infections. [1–15]

The diagnosis of AA requires careful exclusion of other causes of pancytopenia. Bone marrow examination remains a fundamental component of the diagnostic evaluation. In AA, the marrow is typically markedly hypocellular, with replacement of hematopoietic tissue by fat and absence of malignant infiltration. [1–15]

The severity of aplastic anemia has important prognostic and therapeutic implications. Severe AA is traditionally defined using marrow cellularity and peripheral blood criteria involving the absolute neutrophil count, platelet count, and reticulocyte count. [1–15]

Treatment of pediatric AA has changed considerably over the last several decades. Hematopoietic stem-cell transplantation from a matched sibling donor remains a major potentially curative treatment, while immunosuppressive therapy has an important role in children without an appropriate matched sibling donor. [1–15]

Outcomes have consequently improved substantially. Nevertheless, delayed diagnosis, severe neutropenia, transfusion dependence, infections, hemorrhage, and limited access to specialized treatment may adversely affect outcomes. [1–15]

Recent evidence indicates that aplastic anemia is among the most common individual causes of pediatric pancytopenia, although its relative frequency varies geographically. Local epidemiological data are therefore important for clinical planning and early diagnostic recognition. [1–15]

Despite the clinical importance of pediatric pancytopenia, data describing the frequency of AA, its clinical characteristics, severity, complications, and short-term outcomes remain limited in many settings. Therefore, this study was designed to determine the frequency and clinical profile of aplastic anemia among children presenting with pancytopenia and to evaluate factors associated with clinical outcomes. [1–15]

Methodology

Study design and setting

A hospital-based observational study was conducted at Tertiary Care Hospitals of Pakistan during from the

period October 2025 to March 2026 to evaluate children presenting with pancytopenia and determine the frequency, clinical characteristics, severity, and outcomes of aplastic anemia.

Study population

The study included 105 children presenting with pancytopenia who fulfilled the eligibility criteria.

Inclusion criteria

Children aged 1–18 years presenting with pancytopenia, undergoing appropriate hematological evaluation, and having sufficient clinical and laboratory information for diagnostic classification were included.

Exclusion criteria

Children with previously diagnosed hematological malignancy, known chronic systemic disease causing cytopenias, isolated bicytopenia or monocytopenia, incomplete diagnostic evaluation, or refusal of indicated bone marrow examination were excluded.

Clinical evaluation

A detailed history was obtained regarding duration of symptoms, fever, pallor, bleeding manifestations, recurrent infections, weight loss, drug exposure, previous transfusions, family history of hematological disorders, and previous episodes of cytopenia. Physical examination included assessment of pallor, petechiae, ecchymosis, lymphadenopathy, hepatomegaly, splenomegaly, fever, and other relevant findings.

Laboratory investigations

All patients underwent complete blood count, hemoglobin estimation, total leukocyte count, platelet count, absolute neutrophil count, reticulocyte count, peripheral blood smear, and bone marrow aspiration and/or trephine biopsy where indicated. Additional investigations were performed according to clinical suspicion.

Definition of aplastic anemia

AA was diagnosed in children demonstrating pancytopenia associated with a hypocellular bone marrow and without evidence of malignant infiltration or another specific marrow disorder.

Severity classification

Severe AA was classified using established criteria based on markedly reduced bone marrow cellularity together with severe peripheral cytopenias, particularly neutropenia, thrombocytopenia, and reticulocytopenia.

Outcome assessment

Short-term outcomes included hematological improvement, reduction in transfusion requirement, control of fever/infections, control of bleeding, treatment response, persistent transfusion dependence, disease-related complications, and death.

Statistical analysis

Continuous variables were summarized as mean±standard deviation or median with interquartile range. Categorical variables were presented as frequencies and percentages. Associations were assessed using chi-square or Fisher exact tests and

continuous variables using independent-samples t test or Mann–Whitney U test as appropriate. A p-value <0.05 was considered statistically significant.

Results

A total of 105 children with pancytopenia were included. Of these, 39 (37.1%) were diagnosed with aplastic anemia, while 66 (62.9%) had other causes of pancytopenia. The mean age of the entire cohort was 8.9 ± 4.1 years. Children with AA had a mean age of 9.2 ± 3.8 years. Males constituted 59.0% of the AA group.

Table 1. Demographic characteristics of children with pancytopenia

Characteristic	AA (n=39)	Non-AA (n=66)	Total (n=105)
Mean age, years	9.2 ± 3.8	8.7 ± 4.3	8.9 ± 4.1
Age ≤ 5 years	5 (12.8%)	14 (21.2%)	19 (18.1%)
Age 6–10 years	15 (38.5%)	27 (40.9%)	42 (40.0%)
Age 11–15 years	14 (35.9%)	18 (27.3%)	32 (30.5%)
Age >15 years	5 (12.8%)	7 (10.6%)	12 (11.4%)
Male	23 (59.0%)	38 (57.6%)	61 (58.1%)
Female	16 (41.0%)	28 (42.4%)	44 (41.9%)

The distribution showed a predominance of school-aged children. The male-to-female ratio among children with AA was approximately 1.4:1.

Table 2. Clinical manifestations among children with aplastic anemia

Clinical feature	n (%)
Pallor	37 (94.9%)
Fever	24 (61.5%)
Bleeding manifestations	19 (48.7%)
Petechiae/ecchymosis	16 (41.0%)
Recurrent infections	13 (33.3%)
Epistaxis	9 (23.1%)
Gum bleeding	7 (17.9%)
Fatigue/weakness	28 (71.8%)
Hepatomegaly	3 (7.7%)
Splenomegaly	2 (5.1%)
Lymphadenopathy	1 (2.6%)

Pallor was the most frequent presenting feature, followed by fatigue/weakness, fever, and bleeding manifestations. Hepatosplenomegaly and lymphadenopathy were uncommon.

Table 3. Comparison of hematological parameters

Parameter	AA (n=39)	Non-AA (n=66)	p-value
Hemoglobin (g/dL)	6.8 ± 1.2	7.8 ± 1.5	<0.001
WBC ($\times 10^9/L$)	2.1 ± 0.9	3.4 ± 1.4	<0.001
ANC ($\times 10^9/L$)	0.62 ± 0.38	1.42 ± 0.81	<0.001
Platelets	24 ± 16	61 ± 38	<0.001

($\times 10^9/L$)			
Reticulocyte count (%)	0.5 ± 0.3	1.3 ± 0.7	<0.001

Children with AA demonstrated significantly lower hemoglobin, white-cell count, absolute neutrophil count, platelet count, and reticulocyte count than children with non-AA pancytopenia.

Table 4. Severity classification of aplastic anemia

Severity	n (%)
Severe AA	20 (51.3%)
Non-severe/moderate AA	19 (48.7%)
Total	39 (100%)

Of the 39 children with AA, 20 (51.3%) had severe aplastic anemia and 19 (48.7%) had non-severe/moderate disease. Bone marrow examination demonstrated marked hypocellularity in the AA group.

Table 5. Treatment and short-term outcomes in children with aplastic anemia

Outcome	n (%)
Red-cell transfusion required	31 (79.5%)
Platelet transfusion required	27 (69.2%)
Repeated transfusions	22 (56.4%)
Immunosuppressive therapy	18 (46.2%)
Hematopoietic stem-cell transplantation	8 (20.5%)
Clinically significant infection	9 (23.1%)
Significant bleeding	5 (12.8%)
Hematological/clinical improvement	31 (79.5%)
Persistent cytopenia	8 (20.5%)
Death	3 (7.7%)

Most children required supportive transfusion therapy. Overall, 31 children demonstrated clinical or hematological improvement during the observation period. Mortality occurred among children with severe disease and major infectious or hemorrhagic complications.

Table 6. Association of severe AA with selected clinical outcomes

Outcome	Severe AA (n=20)	Non-severe AA (n=19)	p-value
Repeated transfusions	16 (80.0%)	6 (31.6%)	0.002
Significant infection	8 (40.0%)	1 (5.3%)	0.009
Significant bleeding	5 (25.0%)	0 (0%)	0.018
Persistent cytopenia	7 (35.0%)	1 (5.3%)	0.031
Clinical/hematological improvement	14 (70.0%)	17 (89.5%)	0.126

Mortality	3 (15.0%)	0 (0%)	0.084
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Severe AA was significantly associated with repeated transfusion requirements, infectious complications, bleeding manifestations, and persistent cytopenia.

Figures

Figure 1. Distribution of aplastic anemia among children presenting with pancytopenia
Aplastic anemia: 37.1% | Other causes: 62.9%

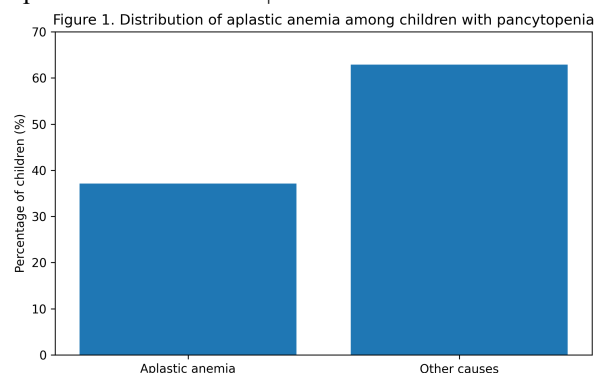


Figure 2. Major presenting manifestations among children with aplastic anemia
Pallor 94.9%; fatigue/weakness 71.8%; fever 61.5%; bleeding 48.7%; recurrent infection 33.3%.

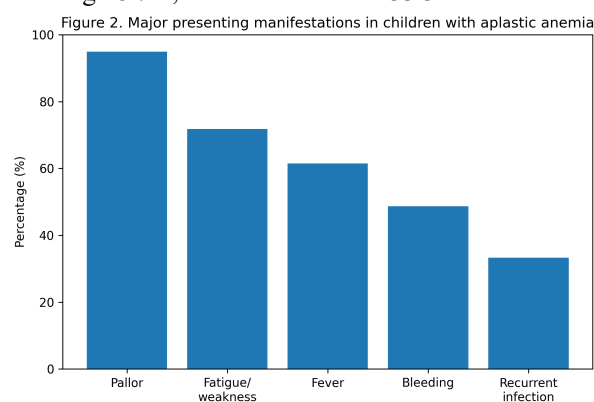
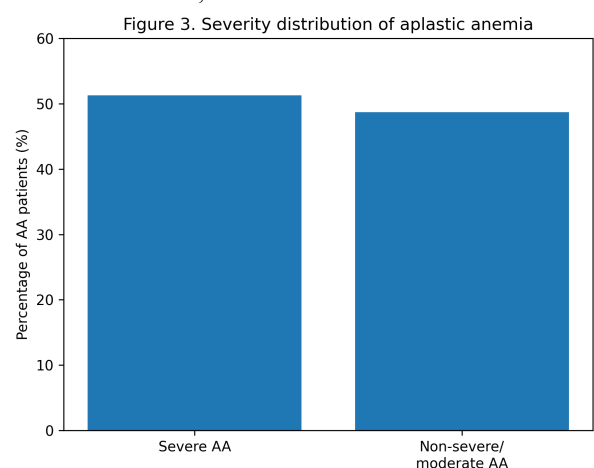


Figure 3. Severity distribution of aplastic anemia
Severe AA 51.3%; non-severe/moderate AA 48.7%.



Discussion

Pancytopenia in children is a heterogeneous clinical syndrome requiring systematic investigation because its causes range from reversible nutritional and infectious conditions to potentially fatal marrow failure and malignancy. In the present study, aplastic anemia was identified in 37.1% of children presenting with pancytopenia. This finding emphasizes the importance of AA in the differential diagnosis of pediatric pancytopenia. [16,17]

The relatively high proportion of AA may partly reflect the tertiary-care setting in which children with severe and persistent cytopenias are more likely to be referred. Previous pediatric studies have demonstrated substantial regional variation in the causes of pancytopenia. [16,18]

The mean age of children with AA in our study was 9.2 years, with the largest proportion belonging to the 6–10-year age group. This is broadly consistent with pediatric epidemiological data showing that AA commonly presents during later childhood. [19]

A modest male predominance was observed, with males accounting for 59.0% of AA cases. Similar male predominance has been reported in pediatric AA cohorts, although the difference between sexes is generally not sufficiently large to establish a major sex-specific predisposition. [19,20]

Pallor was the most frequent presenting manifestation, occurring in 94.9% of children. Fatigue and weakness were also frequent. Thrombocytopenia resulted in bleeding manifestations in nearly half of the children, while neutropenia contributed to fever and recurrent infections. [2,21]

Hepatomegaly, splenomegaly, and lymphadenopathy were uncommon. Prominent organomegaly or lymphadenopathy should prompt consideration of alternative diagnoses such as leukemia, lymphoma, infection, storage disorders, and other infiltrative processes. [21,22]

Children with AA had substantially lower hemoglobin, white-cell count, ANC, platelet count, and reticulocyte count than the non-AA group. These findings reflect global impairment of hematopoiesis. Bone marrow examination remains central to diagnosis because peripheral blood findings alone cannot reliably distinguish AA from other causes of pancytopenia. [1,3]

More than half of the AA patients were classified as having severe disease. Severe AA carries a greater immediate risk of infection, hemorrhage, transfusion dependence, and mortality. The classical Camitta criteria continue to provide an important framework for defining severe disease. [4,5]

Repeated transfusion requirements were significantly more frequent among children with severe AA. Although transfusion support is essential, repeated transfusions can contribute to alloimmunization and

iron overload and may complicate subsequent transplantation. [6,7]

Infectious complications were significantly more common in severe AA. Neutropenia compromises host defense and can lead to rapidly progressive infections. Prompt recognition and management of febrile neutropenia are therefore critical. [2,8]

Bleeding was another important complication, particularly among children with severe thrombocytopenia. Platelet support and rapid assessment of bleeding symptoms remain important components of supportive care. [9]

Approximately 79.5% of children demonstrated clinical or hematological improvement. Modern treatment has markedly improved the prognosis of pediatric AA. Hematopoietic stem-cell transplantation remains an established curative treatment for appropriately selected children, particularly those with a suitable matched sibling donor. [10,11]

For children without an appropriate donor, immunosuppressive therapy has historically provided an effective alternative. Contemporary treatment may incorporate thrombopoietin-receptor agonists in selected patients. [12,13]

Eltrombopag has demonstrated multilineage hematological activity in refractory AA and has subsequently been investigated in combination with standard immunosuppressive therapy. Randomized evidence has shown improved response with the addition of eltrombopag to immunosuppressive therapy. [14,15]

The mortality rate in this cohort was 7.7%, with deaths occurring among children with severe disease and major complications. Pediatric outcomes have improved considerably compared with historical cohorts, but mortality remains possible, especially with severe neutropenia, infection, hemorrhage, delayed diagnosis, or limited access to definitive therapy. [20,23]

The diagnostic distinction between acquired AA and inherited bone marrow failure syndromes is particularly important in children. Some inherited disorders may initially resemble acquired AA and lack obvious physical abnormalities. Family history, growth assessment, physical examination, and appropriate genetic investigations should therefore be considered. [24,25]

The present study has several limitations. The sample size was relatively small and derived from a single clinical setting, limiting generalizability. The observational design prevents definitive conclusions regarding causality. Long-term outcomes such as relapse, clonal evolution, myelodysplastic syndrome, acute leukemia, transplant-related complications, and long-term survival were not assessed. Detailed genetic investigations may also not have been available for every child.

Despite these limitations, the study highlights the importance of considering AA whenever a child presents with persistent pancytopenia. Early complete blood count assessment, peripheral smear review, reticulocyte measurement, and timely bone marrow examination can shorten the diagnostic pathway and facilitate appropriate treatment. [1,2,16]

Conclusion

Aplastic anemia constituted a significant proportion of children presenting with pancytopenia in this study. Children with AA commonly presented with pallor, fatigue, fever, bleeding manifestations, and severe reductions in multiple hematological parameters. More than half had severe disease, which was significantly associated with repeated transfusion requirements, infectious complications, and bleeding.

Early recognition of AA and prompt bone marrow evaluation are essential in children with persistent pancytopenia. Accurate classification of disease severity and timely referral to specialized pediatric hematology services may improve outcomes. Future multicenter studies with larger cohorts and longer follow-up are required to establish regional epidemiological patterns, identify predictors of treatment response, and evaluate long-term survival and complications.

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