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ORIGINAL ARTICLE

Clinical spectrum, laboratory profile and outcome of aplastic anemia in children presenting at tertiary care hospital.

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ABSTRACT… Objective: To evaluate the clinical presentation, laboratory profile, etiological factors, and short-term outcomes of children with aplastic anemia presenting to a tertiary care pediatric hospital in Karachi, Pakistan. **Study Design:** Analytical, Cross-sectional study. **Setting:** Department of Pediatrics, National Institute of Child Health (NICH), Karachi, Pakistan. **Period:** November 2024 to April 2025. **Methods: A total of 114 c**hildren aged 6 months to 15 years with clinical features of bone marrow failure and confirmed aplastic anemia based on peripheral cytopenias and hypocellular marrow biopsy were included. Classification into non-severe, severe, and very severe aplastic anemia was done using modified Camitta criteria. Chi-square/ Fisher's exact, and Mann-Whitney U tests were used, with $p<0.005$ considered significant. **Results:** Out of 114 children enrolled, 70 (61.4%) were male. The median age was 8.00 years (Interquartile range: 5.00-10.00 years). Fever (86.0%), fatigue (68.4%), and bleeding (64.0%) were the most common presenting features. Antibiotic exposure (25.4%) and hepatitis C infection (5.3%) were notable etiological associations. Eight children left against medical advice, and were excluded from the final analysis. Among 106 children, mortality was reported in 34 (32.1%) and was significantly associated with fatigue ($p<0.001$), bleeding ($p=0.001$), pallor ($p<0.001$), severe cytopenias ($p<0.001$), and very severe aplastic anemia ($p<0.001$). Bone marrow severity correlated strongly with outcome ($p<0.001$). **Conclusion:** Aplastic anemia in children carries high short-term mortality, particularly in those with very severe disease, severe hypocellularity, and drug-related etiologies. Early identification and access to definitive therapy are crucial.

Key words: Aplastic Anemia, Bone Marrow, Child, Fatigue, Mortality.

INTRODUCTION

Aplastic anemia is an acquired hematological disorder characterized by pancytopenia and hypocellular bone marrow, resulting from immune-mediated destruction or suppression of hematopoietic progenitor cells.[1] It represents a serious and potentially life-threatening condition that, if left untreated, can lead to a mortality rate exceeding 70% within the first year of diagnosis.[2] Globally, the incidence of aplastic anemia is estimated to be 2–3 cases per million population.[3-5]

The etiology of acquired aplastic anemia is multifactorial and includes direct marrow toxicity from drugs, chemicals, and radiation, as well as indirect immune-mediated suppression following viral infections, autoimmune diseases, or pregnancy.[6-8] Evolving molecular insights have shown that a subset of patients initially diagnosed with aplastic anemia may subsequently manifest clonal hematopoiesis, developing into myelodysplastic syndrome or acute myeloid leukemia.[6] Diagnostic confirmation necessitates a thorough clinical assessment, complete blood count with differential, peripheral smear analysis, reticulocyte count, and flow cytometry, followed by bone marrow aspiration and trephine biopsy for morphological and cytogenetic evaluation.[9] In pediatric cases, it is imperative to rule out inherited bone marrow failure syndromes such as Fanconi anemia using chromosomal breakage studies.[9,10]

Prompt diagnosis and management are essential to improving outcomes. While earlier treatment modalities included corticosteroids

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and androgens with limited long-term success, the current mainstay for curative treatment is allogeneic hematopoietic stem cell transplantation (HSCT), particularly for patients with a matched sibling donor.[11,12] For those without a suitable donor, immunosuppressive therapy comprising anti-thymocyte globulin (ATG) and cyclosporine remains the standard, albeit with risks of relapse upon cessation. The introduction of thrombopoietin receptor agonists such as eltrombopag has further broadened first-line options, with promising efficacy and tolerability profiles.[13]

Despite growing literature on aplastic anemia, there remains a paucity of data on its clinical characteristics and outcomes specifically in the pediatric population of low-resource countries. Understanding the disease spectrum, laboratory parameters, and response to therapy in these settings is crucial for timely diagnosis, targeted management, and mortality reduction. This study was conducted to evaluate the clinical presentation, laboratory profile, and short-term outcomes of children with aplastic anemia presenting to a tertiary care pediatric hospital in Karachi, Pakistan. This study may help to bridge existing knowledge gaps and inform local treatment practices.

METHODS

This analytical, cross-sectional study was conducted at the department of pediatrics of National Institute of Child Health, Karachi, Pakistan following approval from the Institutional Ethical Review Board (IERB-15/2024, dated: 26th October 2024) during November 2024 to April 2025. Inclusion criteria were children aged 6 months to 15 years who presented with clinical features of bone marrow failure and met the diagnostic criteria for aplastic anemia. Diagnosis was confirmed through peripheral blood counts as hemoglobin <10 g/dL, platelet count <50,000/μL, absolute neutrophil count <1500/μL and hypocellular marrow findings on biopsy. Further classification into severe, very severe, and non-severe aplastic anemia was done based on modified Camitta criteria.[6] Children with known inherited bone marrow failure syndromes, leukemia, myelodysplastic syndrome, myelofibrosis, or neoplastic marrow infiltration were excluded. Using OpenEpi online software, a sample size of 114 was calculated based on proportion of infection as underlying etiology 12.1%[14], with 95% confidence level and 6% margin of error. Patients were recruited via non-probability consecutive sampling. After obtaining informed written consent from parents or guardians, data were collected using a structured proforma.

Among children fulfilling the eligibility criteria, demographic, clinical and laboratory parameters were documented. Bone marrow aspirates and trephine biopsies were reviewed to document cellularity, morphology, and overall architecture. Management was conducted in accordance with institutional protocols, including supportive transfusions and initiation of immunosuppressive therapy or referral for transplant evaluation when appropriate. Statistical analysis was carried out using IBM-SPSS Statistics, version 26.0. Continuous variables such as age, hemoglobin levels, absolute neutrophil count, and platelet count were reported as median and interquartile range (IQR) as data as non-normally distributed (as per Shapiro-Wilk test). Categorical variables, including presenting symptoms and disease severity classifications, were expressed as frequencies and percentages. Association of final outcome was determined applying chi-square or fisher's exact test between categrical variables. Mann-Whiteny U test was applied to compare the association of quantitative variables and final outcome. $P<0.005$ was considered significant.

RESULTS

In a total of 114 children, 70 (61.4%) were male, and 44 (38.6%) females. The median age, and weight were 8.00 years (IQR: 5.00-10.00 years), and 20.00 kg (IQR: 14.75-25.00 kg), respectively. Fever was the most common presenting complaint, noted in 98 (86.0%) children, while fatigue or lethargy was documented in 78 (68.4%) children. On clinical examination, pallor was observed in 92 (80.7%) cases, bruises or petechiae in 73 (64.0%), and shortness of breath in 49 (43.0%) children. Most common etiological factors identified were recent

use of antibiotics, hepatitis C virus infection and antimalarial drugs, seen in 29 (25.4%), 6 (5.3%), and 5 (4.4%) children, respectively. Table-1 is showing details of demographical, clinical, and etiological features in children with aplastic anemia.

In a total of 114 children, 8 (7.0%) left against medical advice so were excluded from the final analysis. In the remaining 106 children, 72 (67.9%) were discharged successfully, whereas, mortality was reported in 34 (32.1%) cases. Fatigue or lethargy (88.2% vs. 52.8%, p<0.001), bleeding manifestations (88.2% vs. 55.6%, p=0.001), and infections (38.2% vs. 15.3%, p=0.008) were significantly more common in children who died. Clinical signs of pallor (100% vs. 69.4%, p<0.001), bruises or petechiae (79.4% vs. 54.2%, p=0.012), and shortness of breath (14.7% vs. 77.8%, p<0.001) were significantly associated with mortality. Among etiological factors, antibiotic use was significantly associated with mortality (47.1% vs. 13.9%, p<0.001). HIV infection (11.8%, p=0.003), Hakeem medications (11.8%, p=0.003), and idiosyncratic drugs (5.9%, p=0.038) were reported only in children who died and were found to have significant association with mortality. There were no deaths among children with hepatitis C virus or hepatitis B virus infections (Table-II).

The median hemoglobin level was significantly lower among children who died (p<0.001). The absolute neutrophil count was markedly lower among children who died (p<0.001). Platelets count was significantly lower in children who died (p<0.001). The median reticulocyte percentage was significantly lower among children who had mortality (p<0.001). Table-3 is showing comparison of laboratory parameters with final outcome.

Regarding disease severity, all children with very severe aplastic anemia (n=24, 70.6%) died, demonstrating a strong association between very severe disease and poor outcome (p<0.001). Bone marrow biopsy findings revealed that severely hypocellular marrow was seen in 32 (94.1%) non-survivors compared to only 17 (23.6%) survivors (p<0.001), while moderately hypocellular marrow was observed in 40 (55.6%) of discharged children versus only 2 (5.9%) of those who died. Mild hypocellularity was observed exclusively among survivors (n=15, 20.8%). Table-4 is showing details about the association of final outcome with disease severity and bone marrow status.

Characteristics		Frequency (%)
Gender	Male	70 (61.4)
	Female	44 (38.6)
Age groups	6 months to 5 years	32 (28.1)
	Above 5 to 12 years	77 (67.5)
	Above 12 up to 15 years	5 (4.4)
Presenting features	Fever	98 (86.0)
	Fatigue/lethargy	78 (68.4)
	Bleeding	73 (64.0)
	Infection	25 (21.9)
Clinical examination	Pallor	92 (80.7)
	Bruises/petechia	73 (64.0)
	Shortness of breath	49 (43.0)
Etiological factors	Antibiotics	29 (25.4)
	Hepatitis C virus infection	6 (5.3)
	Antimalarials	5 (4.4)
	Human immunodeficiency virus infection	4 (3.5)
	Hakeem medications	4 (3.5)
	Hepatitis B virus infection	2 (1.8)
	Idiosyncratic drugs	2 (1.8)

Table-I. Demographic, clinical, and etiological features of children with aplastic anemia (n=114)

DISCUSSION

The male predominance observed in this study (61.4% males vs. 38.6% females) aligns with the gender distribution reported by Tan-Lim and Melendres in the Philippines[15], where 25 of 39 pediatric patients with aplastic anemia were male (64%). Ramzan et al.[16], in their 7-year retrospective review in Karachi, reported a male-to-female ratio of approximately 1.5:1, further reinforcing a possible gender predisposition, though the pathophysiological basis of this remains unclear.

Characteristics		Discharged (n=72)	Death (n=34)	P-Value
Gender	Male	40 (55.6%)	22 (64.7%)	0.372
	Female	32 (44.4%)	12 (35.3%)	
Age groups (years)	6 months to 5 years	24 (33.3%)	8 (23.5%)	0.129
	Above 5 to 12 years	43 (59.7%)	26 (76.5%)	
	Above 12 up to 15 years	5 (6.9%)	-	
Presenting features	Fever	60 (83.3%)	32 (94.1%)	0.126
	Fatigue/lethargy	38 (52.8%)	30 (88.2%)	<0.001
	Bleeding	40 (55.6%)	30 (88.2%)	0.001
	Infection	11 (15.3%)	13 (38.2%)	0.008
Clinical examination	Pallor	50 (69.4%)	34 (100%)	<0.001
	Bruises/petechia	39 (54.2%)	27 (79.4%)	0.012
	Shortness of breath	56 (77.8%)	5 (14.7%)	<0.001
Etiological factors	Antibiotics	10 (13.9%)	16 (47.1%)	<0.001
	Hepatitis C virus infection	4 (5.6%)	-	0.161
	Antimalarials	2 (2.8%)	1 (2.9%)	0.962
	Human immunodeficiency virus infection	-	4 (11.8%)	0.003
	Hakeem medications	-	4 (11.8%)	0.003
	Hepatitis B virus infection	2 (2.8%)	-	0.327
	Idiosyncratic drugs	-	2 (5.9%)	0.038

Table-II. Association of final outcome with demographic, clinical, and etiological features in children with aplastic anemia (n=106)

Parameters	Discharged (n=72)	Death (n=34)	P-value
Hemoglobin (g/dl)	6.80 (5.50-8.20)	4.50 (3.05-6.13)	<0.001
Absolute Neutrophil Count	483.50 (350.00-817.50)	112.50 (70.00-156.25)	<0.001
Platelets (/ul)	20000.00 (15000.00-31500.00)	10000 (4750.00-16000.00)	<0.001
Reticulocytes (%)	0.40 (0.30-0.60)	0.20 (0.10-0.30)	<0.001

Table-III. Association of final outcome with laboratory parameters (n=106)

Variables		Discharged (n=72)	Death (n=34)	P-Value
Severity of aplastic anemia	Not severe	32 (44.4%)	-	<0.001
	Severe	40 (55.6%)	10 (29.4%)	
	Very severe	-	24 (70.6%)	
Bone marrorw findings	Mildly hypocellular marrow	15 (20.8%)	-	<0.001
	Moderately hypocellular marrow	40 (55.6%)	2 (5.9%)	
	Severely hypocellular marrow	17 (23.6%)	32 (94.1%)	

Table-IV. Association of final outcome with disease severity and bone marrow status

In contrast, Panda et al.[17], reported a female predominance in pancytopenic children, with a female-to-male ratio of 1.4:1, although their study encompassed a broader spectrum of hematological disorders rather than focusing solely on aplastic anemia.

The age distribution in the present cohort, with the majority (67.5%) falling between 5 to 12 years of age, is consistent with findings from Zubair et al.[18], where the mean age of children with pancytopenia was approximately 5.8 years. Tan-Lim and Melendres[15], also noted that most

patients with aplastic anemia were in their early teenage years, with a median age of 13 years. A slightly younger trend in this study may reflect earlier exposure to potential triggers or earlier access to tertiary care services in urban settings like Karachi, Pakistan.

Fever (86.0%), fatigue or lethargy (68.4%), and bleeding manifestations (64.0%) were the predominant presenting complaints in this study. Zubair et al.[18], documented fever in 71.87% of pancytopenic patients and pallor in 85%. Memon et al.[19], found pallor and petechial hemorrhages to be the most common presenting signs in children with pancytopenia. The prevalence of bleeding and pallor in this study mirrors findings from Ramzan et al.[16], where severe anemia and bleeding tendencies were hallmark symptoms, particularly in patients with very severe aplastic anemia.

This study found a significant burden of infectious etiologies and drug exposures among children with aplastic anemia. Antibiotic use was reported in 25.4% of cases, and this factor was strongly associated with mortality (47.1% vs. 13.9%, $p<0.001$). This observation aligns with Ashraf et al.[14], who identified drugs as the causative factor in 9.8% of their patients. In the current study, the mortality association with antibiotic exposure may reflect either inappropriate use of marrow-suppressive antibiotics or more severe illness necessitating antibiotic use. The inclusion of Hakeem medications as a significant factor associated with death (11.8%, $p=0.003$) is particularly relevant in the Pakistani context, where traditional medicines are often used without regulation.[20] This trend was similarly noted in Ashraf et al.[14], where 14.3% of cases were attributed to Hakeem medication exposure.

Among viral etiologies, hepatitis C virus was identified in 5.3% of children, though no associated deaths were reported in these cases. This is consistent with Memon et al.[19], who also reported hepatitis-related bone marrow failure in a subset of patients. The current study found a significant association between HIV infection and mortality (11.8%, $p=0.003$), though the sample size was small. The mortality associated with HIV may reflect underlying immune suppression or delay in diagnosis and treatment initiation.[21]

This study found that children who died had significantly lower median hemoglobin (4.50 g/dL vs. 6.80 g/dL, $p<0.001$), absolute neutrophil count (112.50/μL vs. 483.50/μL, $p<0.001$), platelet count (10,000/μL vs. 20,000/μL, $p<0.001$), and reticulocyte percentage (0.20% vs. 0.40%, $p<0.001$) compared to those discharged. Hama et al.[22], observed that children with aplastic anemia had significantly lower neutrophil, platelet, and reticulocyte counts compared to children with refractory cytopenia of childhood and refractory cytopenia with multilineage dysplasia. These findings not only reinforce the marrow failure phenotype in aplastic anemia but also suggest that severe cytopenias may serve as predictors of adverse outcome.[23,24]

Severity of disease showed a strong correlation with outcomes. All 24 children with very severe aplastic anemia died (70.6% of total deaths), while none in the non-severe category died ($p<0.001$). Ramzan et al.[16], found that children with severe aplastic anemia had significantly poorer outcomes unless treated adequately with suitable approach. Some researchers have suggested that marrow architecture is a strong prognostic factor.[16,22]

The overall mortality rate in this study was 32.1%, which is comparable to that reported by Samanta et al., who found a 42% mortality rate among febrile neutropenic episodes in children with severe aplastic anemia. Ashraf et al.[14], noted that untreated severe cases had a high mortality rate, underscoring the critical need for early identification and management. In contrast, Ramzan et al.[16], reported improved overall survival of 74.4% at four years in children treated with immunosuppressive therapy, and 100% survival for those who received a bone marrow transplant. The lower survival rate in the present study may reflect limited access to curative therapy such as matched donor transplantation and financial barriers to prolonged immunosuppressive therapy.

The clinical implications of these findings are considerable. The identification of fatigue, bleeding, pallor, and infections as strong predictors of mortality can inform early risk stratification. Recognizing the contribution of drug-related marrow suppression, particularly from unregulated traditional medications, highlights the need for public education and pharmacovigilance. The high mortality observed among patients with very severe aplastic anemia and severe hypocellularity suggests that these parameters should be integrated into treatment triage protocols, potentially prioritizing these patients for urgent transplant evaluation or enrollment in immunosuppressive therapy programs.

Several limitations must be acknowledged. The study was conducted at a single tertiary care center and may not reflect community-level incidence or presentation patterns. The observational design precludes inference of causality, particularly regarding etiological factors such as antibiotics or traditional medications. The exclusion of patients who left against medical advice might have introduced some bias in outcome estimates. Long-term follow-up data, including response to immunosuppressive therapy or transplantation, were not captured, limiting the ability to evaluate sustained outcomes beyond hospital discharge.

CONCLUSION

Aplastic anemia in Pakistani children presents most commonly during middle childhood with fever, fatigue, pallor, and bleeding tendencies. Antibiotic exposure, HIV infection, and traditional medication use were notable etiological associations with mortality. Clinical signs such as pallor, bruising, shortness of breath, and severe laboratory derangements including low hemoglobin, neutrophils, platelets, and reticulocytes were predictive of poor outcomes. Children with very severe aplastic anemia and severely hypocellular marrow were at highest risk of death. These findings underscore the importance of early diagnosis, risk stratification, public awareness about potentially myelotoxic medications, and expansion of access to curative therapies such as bone marrow transplantation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Nimra Fatima:** Data collection, drafting, data integrity, approval for publication.
2	**Muhammad Ashfaq:** Study concept, critical revisions.
3	**Wajid Hussain:** Proof reading, design, study concept.
4	**Mariam Raza:** Critical revisions, approval for publication.
5	**Atiya Anwar:** Literature review, Analysis, critical revisions.