



## **Clinico Haematological Profile in Paediatric Patients with Bicytopenia and Pancytopenia in a Tertiary Care Referral Centre of North India**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

**Background:** Bicytopenia and Pancytopenia are relatively common presentations in adults as compared to paediatric patients. Clinical features present in different manifestations in children with Pancytopenia/Bicytopenia, which can range from bone marrow suppression temporarily to marrow infiltration by life-threatening malignancies.

**Aim:** To study the clinical and haematological profile in the paediatric age group with Cytopenias. The study aims to analyze the severity of hematological findings as per causative factors in patients with Pancytopenia and Bicytopenia.

**Methods:** Prospective Observational Study conducted in the Department of Paediatrics in Dr.RPGMC Tanda Himachal Pradesh (INDIA). The study included all patients except those falling in the exclusion criteria. It was performed after oral and written informed consent. A total of 50 children admitted with bicytopenia and pancytopenia were enrolled from March 2013 to March 2014.

**Results:** Infection was the commonest etiology observed in 22(44%) patients with bicytopenia and

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pancytopenia. Bicytopenia was seen in 14 (20%) and pancytopenia in 8 (16%) cases with infection. Scrub typhus was the commonest Infection seen in 18(32%).Leukaemia was noted in 11(22%) cases.

**Conclusions:** The commonest age group affected was 11-15 years with female domination with a Male: Female ratio of 0.78:1. The commonest symptom was fever 37(74%) then generalized weakness in 29 (58%) cases.Pallor was the most common sign in 43(86%) followed by Hepatomegaly 32(64%), Lymphadenopathy 30(60%), and Splenomeagly in 29 (58%) patients. Infection was the commonest etiology followed by leukemia and megaloblastic anaemia. Scrub typhus was the commonest infection encountered in the present study.

*Keywords: Paediatric; bicytopenia; pancytopenia; megaloblastic anaemia; scrub typhus.*

## 1. INTRODUCTION

There is a wide spectrum of causes which can range from congenital to acquired diseases of Pancytopenia and Bicytopenia. Nutritional causes of pancytopenia are relatively more common in developing countries when compared to western countries. The most common causes reported in children are aplastic anemia, Megaloblastic anaemia, infections like malaria, enteric fever, leishmaniasis, Fanconi anaemia, malignancies like acute leukemia, and myelodysplasia [1]. Pancytopenia presents due to bone marrow replacement or failure but can occur due to splenic pooling or peripheral destruction of mature cells. In patients, pancytopenia is mostly due to cytotoxic immunosuppressant drugs [2]. Pancytopenia is a presenting feature in many severe diseases. Clinical presentation of bicytopenia and pancytopenia vary from fever, mild pallor to severe anemia, bleeding tendencies including petechial, bruises, and bleeding in the vital organs leading to life-threatening emergencies [3]. The bone marrow findings may vary depending on the causative factors, from normocellular with non-specific changes to hypercellular being overshadowed by malignant cells. Decrease in production of haemopoietic cells can occur as a result of infections, drugs, toxins, or malignant cells infiltration leading to hypocellular bone marrow whereas normocellular or hypercellular marrow can be found in conditions of ineffective hematopoiesis, maturation arrest of lines, and peripheral sequestration of blood cells including megaloblastic anemia and hypersplenism [4].

## 2. MATERIAL AND METHODS

A detailed history and physical examination were carried out as per the performa/case form. Complete blood count, peripheral smear, and

reticulocyte count were performed in all cases, whereas bone marrow biopsy/aspiration, blood culture, FNAC, IgM Elisa, and Weil Felix for scrub typhus, Dengue IgM, HBsAg, and Anti HCV Antibody was done whenever required. Bone marrow aspiration was carried out under strict aseptic precautions after informed oral and written consent from the patient or their guardian. After getting written consent from the patient, bone marrow aspiration and trephine biopsy wherever possible were done by using Salah's needle and Jamshidi needle respectively at the posterior superior iliac spine. Bone marrow aspiration smears were prepared by either of the two techniques: (1) smears of aspirated marrow are made directly from the fluid marrow in a method like blood smears, (2) particles of marrow are isolated, placed on slides or coverslips, and gently squashed with a second slide or coverslip to prepare particle smears. Imprint smears were made from biopsy and the biopsy specimen were put in buffered formalin and taken for routine processing. The paraffin-embedded sections were made on a rotary microtome. In all the cases Haematoxylin and Eosin stain was done. Special stains such as Perl's stain, PAS stain, Reticulin stain, etc. were done wherever necessary.

### 2.1 Inclusion Criteria

1. Hospitalized children aged between 1 to 18 years.
2. Showing all or any two of the following: and measured by automatic cell counter and reconfirmed by blood culture, which is defined as
  - a. Haemoglobin < 10gm/dl.
  - b. White Blood Cell count <  $4 \times 10^9 / L$
  - c. Platelet count <  $1500 \times 10^9 / L$
  - d. Consent given by guardian or the patient.

## 2.2 Exclusion Criteria

1. Age > 18 yrs.
2. Chemotherapy and radiation-induced bicytopenia and pancytopenia cases.
3. Recent history of blood transfusion.
4. Patients not willing to study.

## 2.3 STATISTICAL ANALYSIS

Chi-square was used for statistical analysis. A p-value of <.01 was taken as statistically significant.

## 3. RESULTS

A total of 50 children admitted with bicytopenia and pancytopenia were enrolled from March 2013 to March 2014 (A one-year prospective study). The following results were recorded and analyzed: Distribution of Bicytopenia and Pancytopenia in Different Age Groups Age range in the study group was 1-18 years with a mean of  $11.77 \pm 4.67$  years. The commonest age group affected was 11-15 years 21 (42%) and the least age group affected was 1-5 years (14%).

### 3.1 Haemoglobin

All 50 children had anaemia. Haemoglobin varied from 1.7 –9.9 gm/dl With a mean of  $6.634 \pm 2.5208$  gm /dl. Hemoglobin of 19 (38%) Children ranged between 8.1- 9. 9gm/dl. Fourteen (28%) had severe anaemia with hemoglobin less than 5 gm/dl. The least count of 1.7gm/dl was recorded in a case of leukaemia which had 80% blasts on peripheral smear. Haemoglobin (gm/dl) ranges are shown in table.

### 3.2 Total Leukocyte Count

Total leukocyte count ranged from 1100-55800 cells/mm<sup>3</sup> with a mean of  $9056.00 \pm 9019.484$  cells/mm<sup>3</sup>. Leucopenia was seen in 19 (38%)

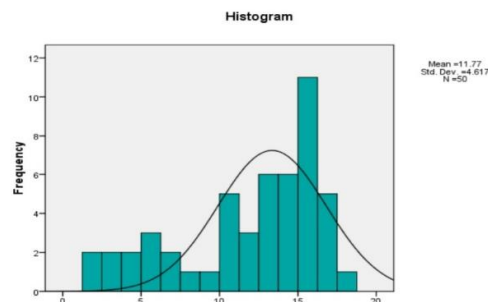
and Leukocytosis was seen in 16(32%) children. The highest count of 55800 Cells / mm<sup>3</sup> was seen in a 12-year male child who had 5% blasts on peripheral smear, on bone marrow aspiration had hypercellular bone marrow with lymphoblastic cells. Lowest count of 1100 cells/mm<sup>3</sup>Total leukocyte count ranged from 1100-55800 cells/mm<sup>3</sup> with a mean of  $9056.00 \pm 9019.484$  cells/mm<sup>3</sup>. Leucopenia was seen in 19 (38%) and Leukocytosis was seen in 16(32%) children. The highest count of 55800 Cells / mm<sup>3</sup> was seen in a 12-year male child who had 5% blasts on peripheral smear, on bone marrow aspiration had hypercellular bone marrow with lymphoblastic cells. Lowest count of 1100 cells/mm<sup>3</sup>.

### 3.3 Platelet Counts

Mean platelet count was  $49226.00 \pm 49193.44$  cells/mm<sup>3</sup>. Ten (20%) Children had a platelet count of fewer than 10000 cells/ mm<sup>3</sup>. The least count of 2000 cells/ mm<sup>3</sup> was observed in a 15-year male adolescent who had Hypoplastic bone marrow aspiration. Twenty (40%) patients ranged between 50001-100000 cell/ mm<sup>3</sup>. The range of platelet count is shown in table.

### 3.4 Peripheral Smear

Peripheral smear revealed anisocytosis in most cases of bicytopenia and pancytopenia. Hypersegmented polymorphs were observed exclusively in patients having megaloblastic anaemia. Circulating blasts were observed in 11(22%) cases of bicytopenia and pancytopenia. Leukocyte count decreased in 19 (38%) and increased in 16(32%) children on the peripheral smear. Platelet count was decreased in almost all children. In this study, dimorphic anaemia was observed in 21 (42%) cases, 7(14%) of cases showed microcytic hypochromic anaemia.



**Fig. 1. Distribution of Bicytopenia and Pancytopenia in Different Age Groups Distribution in Different Sex Groups There were 22 boys and 28 girls with a Male: Female ratio of 0.78:1**

**Table 1. Distribution in Different Sex Groups**

SEX	TOTAL%
Male 22 (44)	22 (44)
Female	28 (56)

**Table 2. Type of Bicytopenia Anaemia and thrombocytopenia were seen in 31 (96.9%), anaemia with leukopenia in 1(3.1%), and none had leukopenia with thrombocytopenia**

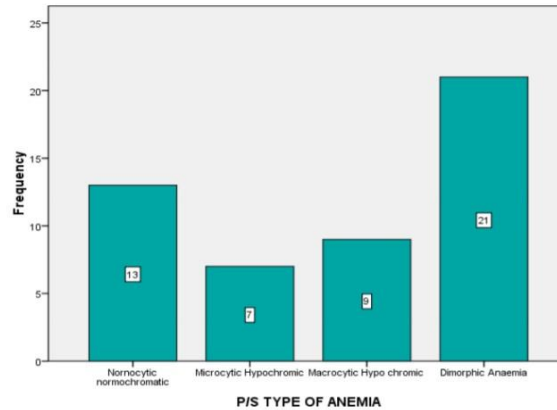
S.NO	CYTOPENIA	NUMBER (%)
1.	BICYTOPENIA	32 (64)
2.	PANCYTOPENIA	18 (36)
	TOTAL	50 (100)

**Table 3. SYMPTOMS The commonest symptom was fever 37(74%) followed by generalized weakness in 29 (58%) cases. Bone pain, joint pain, and Oedema were rare symptoms. The major clinical symptoms are shown in figure**

S.NO	SYMPTOMS	Number (%)
1.	Fever	37(74)
2.	Generalised Weakness	29(58)
3.	Headache	15(30)
4.	Paleness	15(30)
5.	Weight loss	14(28)
6.	Bleeding Manifestations	9(18)
7.	Bone pain and joint pain	4(8)
8.	Oedema	3(6)

**Table 4. Signs of Haemoglobin Ranges**

S.NO	SIGNS	Number (%)
1.	Pallor	43(86)
2.	Hepatomegaly	32(64)
3.	Lymphadenopathy	30(60)
4.	Splenomeagly	29(58)
5.	Bleeding manifestations	12(24)
6.	Jaundice	9(18)
7.	Knuckle hyper pigmentation	6(12)
8.	Bone tenderness	6(12)



**Fig. 2. Rate of Anemia respect to ages**

### 3.5 Bone Marrow Diagnosis

Malignant infiltration was observed in seven patients, out of the six had acute lymphoblastic leukaemia and one had acute myeloid leukaemia. Two cases had aplastic anaemia and two had megaloblastic Anaemia. One patient showed a megakaryocytic picture consistent with Idiopathic thrombocytopenic purpura. One case with aspiration showed iron-deficient anaemia.

### 3.6 Other Investigations

For diagnosis of scrub typhus Weil Felix titer of more than 1:80 was considered positive. The diagnosis was confirmed by an Enzyme-linked immune assay Ig M antibody in a positive Weil Felix test. In 18(36%) patient's both Weil Felix and Enzyme-linked immune assay Ig M antibody were positive. Blood cultures were done in cases with suspected sepsis. In 8 cases vitamin B12 level was done which presented with symptoms and signs of megaloblastic anaemia. All cases had a low level of Vitamin B12.

### 3.7 Diagnosis

Infection was the commonest etiology noted in 22 (44%) patients with bicytopenia and pancytopenia. Bicytopenia was seen in 14 (20%) and pancytopenia in 8 (16%) cases with Infection. Scrub typhus was the commonest Infection seen in 18 (32%). The other four cases had Symptoms and signs of infection but blood cultures were sterile in all. All four cases had anaemia and thrombocytopenia along with leukocytosis. Leukaemia was seen in 11 (22%) cases. All had blasts on peripheral smear. Bone marrow aspirations were done in 7 children and others were referred to higher institutes at

parent's request. Seven cases had pancytopenia and four had bicytopenia with leukaemia. Megaloblastic anaemia was seen in 9(18%) cases. Hypersegmented neutrophils were observed in most of the cases. Vitamin B12 levels were done in eight cases. Bone marrow aspiration was done in two cases. Bicytopenia was seen in seven cases and pancytopenia in only 2 cases. The other four cases had idiopathic thrombocytopenia, two had aplastic anaemia, one had iron deficiency anaemia and one had extrahepatic portal hypertension.

## 4. DISCUSSION

Bicytopenia and pancytopenia are frequently encountered hematological disorders in adults as compared to paediatric patients. In the present study, a total of 50 children admitted with bicytopenia and pancytopenia were enrolled during one year (2013-2014) were evaluated. The age range in the study group was 1-18 years with a mean  $\pm$ S.D age of  $11.8 \pm 4.62$  years. The most common age group affected in the present study was in the range 11-15 years with 42% of the cases being reported from this age group and the least affected age group with 14% cases was 1-5 years. As far as the distribution of these two hematological disorders in different sex groups was concerned, the number was greater in females (28%) than in males (22%) with a male to female ratio of 0.78:1. Our present study observed the incidence of bicytopenia (64%) was significantly higher than that of pancytopenia having only 36% cases reported in a sample of 50 children admitted with these hematological deficiencies. These findings are similar to Naseem et al 2 but contrary to Chhabra et al [5]. Anaemia and thrombocytopenia was the

commonest type of bicytopenia with 31 of the 32 patients reported to possess anemia and thrombocytopenia accounting for 96.9% of the total bicytopenia children. Only 1 child was reported to possess anaemia and leukopenia and none of the bicytopenic children possessed leukopenia and thrombocytopenia. The most common type of symptoms observed in the patients during the present study was fever (74%) followed by generalized weakness (58%). Headache, paleness, and weight loss were observed in 14-15% of the cases whereas bone pain, joint pain, and oedema were the rare symptoms observed in these children. However recent studies by Gayathri and Rao [6] (2011) and Khan et al [7] generalized weakness was the commonest symptom in 100% and 75% cases respectively. The present study revealed pallor as the most frequently encountered sign (86%) followed by hepatomegaly (64%), lymphadenopathy (60%), and splenomegaly (58%). Pallor was also reported as the commonest sign by Khan et al [7] in 95%, and Santra and Das in 84.68% of cases. Similarly, hepatomegaly was a major sign observed by Santra and Das [8] (2010) and Hirachand et al. [9] However, lymphadenopathy was reported by Khan et al [3] in 4.4%, Kumar et al [10] in 6.25%, and Sharif et al [11] in 5.7% cases as a rare symptom. These were however dependent on the primary cause. Splenomegaly was also a prominent sign observed by Kumar et al [9] in 33.33% and Santra and Das [8] in 44.41% cases. All of the 50 children evaluated during the present study had anaemia. Haemoglobin varied from 1.7–9.9 gm/dl with a mean of  $6.634 \pm 2.5208$  gm /dl. Nineteen (38%) patients had hemoglobin ranging between 8.1 and 9.9 gm/dl whereas 14 (28%) had severe anaemia with hemoglobin less than 5 gm/dl. where they found 25.7% of patients having severe anemia (Haemoglobin < 5gm %). [11] Sweta et al, [12] Santra and Dass [8] studied severe anemia in 52% and 57.66% cases respectively. During the present study, the total leukocyte count ranged from 1100-55800 cells/mm<sup>3</sup> with a mean of  $9056.00 \pm 9019.484$  cells/mm<sup>3</sup>. Leucopenia was observed in 38% of the cases while leukocytosis was seen in 32% of the children. The highest count of 55800 cells/mm<sup>3</sup> was seen in a 12-year male child who had 5% blasts on peripheral smear, whereas on the bone marrow aspiration, hypercellular bone marrow and lymphoblastic cells were observed. The lowest count of 1100 cells/mm<sup>3</sup> was observed in the 15-year male adolescent who had hypoplastic bone marrow aspiration. The mean platelet

count in our study was observed to be  $49226.00 \pm 49193.44$  cells/mm<sup>3</sup>. Ten (20%) patients however exhibited a platelet count of fewer than 10000 cells/ mm<sup>3</sup> whereas the lowest count of 2000 cells/ mm<sup>3</sup> was found in the 15-year male adolescent who had hypoplastic bone marrow aspiration. Forty percent of the patient's platelet count was found to range between 50001 and 100000 cell/ mm<sup>3</sup>. About 60.36% of the patients had a mild degree of thrombocytopenia, 25.23% had moderate and 14.41% had severe thrombocytopenia. In the present study, dimorphic anaemia was seen in 42% of cases, 14% of children showed microcytic hypochromic anaemia. Peripheral smear showed anisocytosis in almost all cases of bicytopenia and pancytopenia. Hypersegmented polymorphs were seen exclusively in patients with megaloblastic anaemia. Circulating blasts were seen in 22% of cases of bicytopenia and pancytopenia. On peripheral smear, leukocyte count was decreased by 38% and increased in 32% of children. Platelet count was found to be decreased in almost all children. Pancytopenia and bicytopenia have several causes. In the present study, many disease entities emerged as recognizable causes of the varying degrees of bicytopenia and pancytopenia in children. The infection however proved to be the commonest etiology and was observed in 44% of the patients admitted with bicytopenia and pancytopenia. Scrub typhus was the commonest type of infection and was observed in 32% of the patients and the reports on scrub typhus as the most common cause of such bicytopenia and pancytopenia is probably a new addition to the treasure of knowledge. Leukemia was observed in 22% of the cases and was 2<sup>nd</sup> the commonest aetiology in the present study. Tareen et al [13] reported leukemia as the second common cause of pancytopenia and was observed in 17.22% of the cases. Megaloblastic anaemia was seen in 9 (18%) cases. Hypersegmented neutrophils were seen in the majority of these cases.

## 5. CONCLUSION

Bicytopenia and Pancytopenia is a common hematological problem encountered in clinical practice and should be suspected on clinical grounds when a patient presents with unexplained anemia, prolonged fever, and tendency to bleed. This study analyzed the clinical hematological profile of bicytopenia and pancytopenia in children. 1. Fifty children admitted with bicytopenia and pancytopenia were

included in the study. 2. The commonest age group affected was 11-15 years with female preponderance with a Male: Female ratio of 0.78:1. 3. The commonest symptom was fever 37(74%) followed by generalized weakness in 29 (58%) cases. 4. Pallor was the commonest sign in 43(86%) followed by Hepatomegaly 32(64%), Lymphadenopathy 30(60%), and Splenomegaly in 29 (58%) patients. 5. Infection was the commonest aetiology followed by leukemia and megaloblastic anaemia. 6. Of the infectious causes scrub typhus was the commonest infection encountered in the present study. 7. In malignant conditions, bicytopenia was seen in 8% and pancytopenia in 14% cases.

## 6. RECOMMENDATION

Although cytopenia is reported to be commonly associated with the malignant condition but in our study infection illness emerged as the major cause for cytopenia. Scrub typhus was a common infection associated with cytopenia in our study. It is therefore recommended that in all geographical areas where scrub typhus is endemic, an appropriate investigation for this treatable infection must be performed.

## CONSENT

A written informed consent both in English and Hindi was taken from the guardian or the patient.

## ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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