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Study Of Clinico-Etiological Profile And Outcomes Of Children Having Bicytopenia And Pancytopenia

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Abstract :
Objectives:
The aim of this study was to find out various etiologies, clinical profile and outcomes of children admitted with pancytopenia and bicytopenia in Department of Paediatrics, Maharaja Yeshwantrao Hospital, Indore over the study period.
Methods:
150 patients from 1 month–14 years age presenting with new onset pancytopenia or bicytopenia were included. Detailed history and physical examination findings were noted and all relevant investigation reports were recorded and tabulated.
Results:
In bicytopenia group, fever was the most common symptom(99%). In pancytopenia group, fever was observed in all patients, lethargy-91.7% and abdominal pain-64.6%. In bicytopenia group, most common sign was pallor-58.8%. In pancytopenia group, pallor was seen in 93.8% and hepatomegaly in 52.1%. Most common causes for bicytopenia were due to infectious etiology. Most common cause of pancytopenia was non-infectious etiology (Megaloblastic anemia). All causes of pancytopenia showed significant difference in their ARC.
Conclusion:
The most common cause of bicytopenia was infectious etiologies; most common cause of pancytopenia was non-infectious non-malignant diseases. Clinical features and specific investigations can help target early diagnosis and can minimise unnecessary invasive procedures.
Keywords: *Anemia, Leukocytopenia, Thrombocytopenia, Aplastic Anemia, Megaloblastic Anemia, Dengue Fever*

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I. INTRODUCTION

Peripheral cytopenia is defined as reduction in either of the cellular elements of blood, i.e.red cells, white cells or platelets.(1)

There is considerable overlap between the causes and diagnostic approach of bicytopenia and pancytopenia. Bicytopenia is reduction in any of the twoss cell lines and pancytopenia is reduction in all the three. The etiology of bicytopenia and pancytopenia varies widely in children and it can range from transient marrow viral suppression to marrow infiltration by life-threatening malignancy. The bone marrow picture varies depending on the etiology, from normocellular with non-specific changes to hypercellular being replaced completely by malignant cells. **Patients can present with manifestations of any of the decreased cell lines.** (2) This study is done to evaluate clinical symptoms, signs and blood investigations which can help in early diagnosis and in differentiating transient illness from life threatening ones and categorise need for invasive procedures.

II. METHODS:

This was a hospital based prospective observational study, conducted over a period of 1 year from June 2020 to May 2021 after approval from Institutional ethics committee.

150 cases presenting with new onset pancytopenia and bicytopenia were included in the study. Detailed history was taken and through physical examination was done on admission. Complete hemogram, peripheral smear findings, Reticulocyte count and Absolute Reticulocyte Count (ARC) was done. Other investigations like Erythrocyte sedimentation rate (ESR), Vitamin B12 levels, C-reactive protein , Culture reports, viral tests (IgM Elisa for Dengue, HbsAg, Anti HCV), Liver function tests, bone marrow aspiration/biopsy results and other

relevant investigations were done on a case-to-case basis. Above details were recorded in the prestructured proforma.

Cytopenia was defined as Hemoglobin <10gm%, Total leukocyte count <4000/mm3, Platelet count <1lac/mm3. **Severe pancytopenia was defined** if patient presented with **Hb <7 gm%, ANC <0.5 x 10^9/L**, and **platelet count <20 x 10^9/L**

Bicytopenia is defined as reduction in any of the two above parameters. Pancytopenia is defined as reduction in all three parameters.

Bone marrow aspiration and biopsy was done as per the clinical indication on a case-to-case basis. It was also done in children who had atypical cells or blast cells in peripheral smear report. The diagnosis was established by morphological examination of bone marrow smears or biopsy and wherever required immunohistochemistry and cytogenetic analysis were done.

We also assessed the short-term outcome of bicytopenia and pancytopenia i.e., recovered or relapsed or treatment failure/death.

Inclusion Criteria

All children in age group of 1 month to 14 years with new onset pancytopenia or bicytopenia admitted in the Department of Pediatrics during the study period.

Exclusion criteria

Patients with prediagnosed haematological disorder and those on myelotoxic therapy and those not giving consent were excluded from the study.

III. STATISTICAL ANALYSIS :

The collected data was processed through spreadsheet using epi info statistical software and tabulated in the form of tables and graphs.

Pearson chi square test and One-Way ANOVA test was used to test relationship between variables. A probability value (P value) of less than 0.05 was considered statistically significant.

IV. RESULTS:

Of the 150 children 102 (68%) had bicytopenia and 48(32%) had pancytopenia.

TABLE 1 - FREQUENCY OF SYMPTOMS AND SIGNS IN BICYTOPENIA AND PANCYTOPENIA.

PRESENTING SYMPTOMS AND SIGNS				
Symptom/Sign	**Bicytopenia (n=102)**		**Pancytopenia (n=48)**	
	No.	**%**	**No.**	**%**
Fever	101	99.0	48	100.0
Lethargy	75	73.5	44	91.7
Abdominal pain	64	62.7	31	64.6
Vomiting	50	49.0	28	58.3
Limb pain	28	27.5	15	31.3
Bleeding manifestations	9	8.8	11	22.9
* Malena	2		0	0
Loss of appetite	74	72.5	40	83.3
Loss of weight	5	4.9	12	25.0
Abdominal distension	3	2.9	1	2.1
Jaundice	0	0.0	0	0.0
Pallor	60	58.8	45	93.8
Hepatomegaly	27	26.5	25	52.1
Lymphadenopathy	13	12.7	12	25.0
Splenomegaly	11	10.8	8	16.7
Petechie / purpura	4	3.9	9	18.8

TABLE 2 - ETIOLOGICAL PROFILE OF BICYTOPENIA AND PANCYTOPENIA

	Bicytopenia (n=102)		**Pancytopenia (n=48)**	
	No.	**%**	**No.**	**%**
MALIGNANT	**16**	**15.7**	**14**	**29.2**
• B cell ALL	12	11.8	7	14.6
• T cell ALL	4	3.9	2	4.2
• AML	0	0	5	10.4
INFECTIOUS	**58**	**56.9**	**3**	**6.25**
• Dengue fever	50	49	2	4.2
• Enteric fever	8	7.8	1	2.1

• Tuberculosis	0	0	0	0
• Malaria	0	0	0	0
NON INFECTIOUS	**28**	**27.4**	**31**	**64.6**
• Megaloblastic anemia	28	27.4	22	45.8
• Aplastic anemia	0	0	7	14.6
• SLE with MAS with lupus	0	0	1	2
• Evans syndrome	0	0	1	2
Total	**102**	**100.0**	**48**	**100.0**

Pearson chi-square test applied.Chi-square value = 43.760, df=9, P value = 0.001, Significant

TABLE 3 - HEMATOLOGICAL PROFILE IN BICYTOPENIA

S.No	Peripheral findings in bicytopenia cases	Etiology	No: of cases
1	Anemia with thrombocytopenia [n=51 (50%)]	Megaloblastic anemia	27
		Malignancy – ALL	16
		Dengue fever	8
2	Leucopenia with thrombocytopenia [n= 42 (41.2%)]	Dengue fever	41
		Enteric fever	1
		Megaloblastic anemia	0
		Malignancy	0
3	Anemia with leucopenia [n= 9 (8.8%)]	Enteric fever	7
		Dengue fever	1
		Megaloblastic anemia	1

Severe pancytopenia was noted in 31 out of 48 children with pancytopenia.

Table 4 - ETIOLOGIES OF SEVERE PANCYTOPENIA

S.No	Diagnosis	No: of cases
1	Malignancy	12 (38.7%)
2	Megaloblastic anemia	10 (32.2%)
3	Aplastic anemia	7 (22.6%)
4	Evans syndrome	1 (3.2%)
5	HLH	1 (3.2%)
TOTAL		31

The comparison of mean absolute retic count in relation to final diagnosis was found to be statistically significant (P=0.001), showing a varying absolute retic count in relation to final diagnosis. The mean absolute retic count was highest in infectious etiology and lowest in aplastic anemia. Absolute reticulocyte count was significant in study. All causes of pancytopenia showed significant difference in their absolute reticulocyte count with ARC Aplastic anemia ($<25x10^9$/L) , megaloblastic anemia ($50–75x10^9$ /L) ,leukemia ($76–100\ x10^9$ /L) and in infections ($101–125x10^9$ /L)**.**

TABLE 5 - COMPARISON OF MEAN ABSOLUTE RETIC COUNT IN RELATION TO FINAL DIAGNOSIS

Final Diagnosis	Pancytopenia	
	No. of cases	ARC (Mean ± SD)
Aplastic anemia	7	18.90 ± 0.00
Infection	3	104.98 ± 2.86
Leukemia	14	68.17 ± 28.06
Megaloblastic anemia	25	56.82 ± 5.52
Others	2	62.25 ± 23.19

One-way ANOVA test applied. P value = 0.001, Significant

Out of 48 children with pancytopenia, bone marrow examination could be done in 33 patients and in 15 patients, it was not done as in some cases diagnosis was established clinically or by other non-invasive investigations and in some cases death occurred before diagnosis could be made. Out of these 33 cases, 21 cases were found to have hypocellular marrow and 12 were found to have cellular/hypercellular marrow. All cases who had hypocellular marrow (n=21) were found to have reduced ARC in peripheral blood. All cases with cellular/ hypercellular marrow(n=12) were found to have normal or increased ARC**.**

TABLE 6 - BONE MARROW CELLULARITY AND ABSOLUTE RETIC COUNT IN PANCYTOPENIC CHILDREN.

Bone Marrow Cellularity	Etiology	ARC		
		Increased	Normal	Reduced
Hypocellular (n=21)	Malignant(n=6)	0	0	6
	Megaloblastic Anemia(n=6)	0	0	6
	Aplastic Anemia (n=7)	0	0	7
	HLH (n=1)	0	0	1
	Evan's syndrome (n=1)	0	0	1
Cellular / Hypercellular (n=12)	Malignant (n=8)	6	2	0
	Megaloblastic Anemia (n=4)	2	2	0
	Aplastic Anemia (n=0)	0	0	0
	HLH (n=0)	0	0	0
	Evan's syndrome (n=0)	0	0	0

In bicytopenia group, 82 (80.4%) patients were successfully treated and discharged, 12(11.8%) are on treatment/follow up and 8 (7.8%) were certified. In pancytopenia group, 30 (62.5%) patients were successfully treated and discharged, 12 (25%) on treatment/ follow up and there were 6 (12.5%) deaths**.**

V. DISCUSSION:

Among children with bicytopenia, most common presenting symptom was fever, seen in 99% cases, followed by lethargy in 73.5% cases, abdominal pain and vomiting, seen in 62.7% and 49% cases respectively. Similar findings were reported in study done by **Neelima Bahal et al** and **Yalaki et al** with fever being the most common symptom, followed by lethargy.(3) (4)

Among children with **pancytopenia** also, **fever** was the most common presenting symptom, **which was seen in 100% of cases**, followed by lethargy in 91.7% cases, loss of appetite in 83.3% cases, abdominal pain and vomiting in 64.6% cases and 58.3% cases respectively. Similar finding were reported in study done by **Rawat et al** and **Chaure Varsha P et al** that fever was the most common symptom in patients of pancytopenia followed by lethargy, abdominal pain and vomiting.(5)(6)

In our study, among bicytopenic children, pallor was found to be the most common sign, which was present in 58.8% cases, followed by hepatomegaly, seen in 26.5%, lymphadenopathy in 12.7%, splenomegaly in 10.8% and petechiea/purpura seen in 3.9% cases. These results differed from study done by **Naseem et al**, where they found that hepatomegaly was the most common sign (69.2%), followed by splenomegaly (60.5%), lymphadenopathy (41.8%), pallor (40.9%) and bleeding manifestations(12.2%).(7)

In our study, among **pancytopenia** cases, **pallor** was found to be the **most common sign (93.8%)**, followed by hepatomegaly in 52.1%, lymphadenopathy in 25%, bleeding manifestations in 18.8% and splenomegaly in 16.7% cases. Results of study done by **Alim et al** demonstrated pallor as most common sign of presentation (70%) and 49 % cases had episodes of bleeding.(8) The variation in signs and symptoms of Pancytopenia and Bicytopenia in our region could be owed to the difference in the etiologies of the same in our region.

The **most common etiology of bicytopenia** in our study was **infectious diseases (56.9%),** followed by non-infectious diseases (27.4%) and malignant causes (15.7%). The most common infectious conditions causing bicytopenia were dengue fever 50 (49%), followed by enteric fever 8 (7.8%). Most common non-infectious etiology causing bicytopenia was megaloblastic anemia 28 (27.4%).

Most common malignant etiology causing bicytopenia in the present study was B cell ALL 12(11.8%) followed by T cell ALL 4 (3.9%).

In the study by **Naseem et al** done in children in 2011, the most common cause of bicytopenia was malignant conditions, with acute leukemia in 66.9% cases. The most common non-malignant conditions causing bicytopenia were megaloblastic anemia (5.2%), followed by idiopathic thrombocytopenic purpura (ITP), marrow hypocellularity and visceral leishmaniasis(7). In the above study, malignant conditions were found to be the most common cause of bicytopenia but in our region, we found that the most common etiology of bicytopenia is infectious diseases and dengue fever being the most common cause.

In the present study, the most common **etiology causing pancytopenia** was found to be **non-infectious conditions (64.6%),** followed by malignant conditions (29.2%) and infectious diseases (6.25%). Most common non-infectious condition causing pancytopenia was megaloblastic anemia 22(45.8%), followed by aplastic anemia 7(14.6%), SLE 1(2%) and Evans syndrome 1 (2%). In our study we found that **megaloblastic anemia is the commonest cause for pancytopenia**. This could be due to high vegetarian population in our region. Most

common malignant etiology was observed to be B cell ALL 7(14.6%), followed by AML 5(10.4%) and T cell ALL 2 (4.2%). Infectious etiology was the least common condition causing pancytopenia with Dengue fever 2(4.2%), followed by Enteric fever 1(2.1%).

The study done by **Naseem et al** in children in 2011 also reported non-malignant condition (56.1%) as the most common etiology for pancytopenia (n=175). But in their study, aplastic anemia (33.8%) was the commonest etiology, followed by megaloblastic anemia (13.7%). Malignancy leading to pancytopenia was acute leukemia (26.6%) in all the cases in their study.(7)

Bhatnagar et al studied the etiological profile of pancytopenia in children and reported that megaloblastic anemia 28.4% was the single most common cause of pancytopenia, followed by aplastic anemia (20%) and acute leukemia (21%). Infections such as enteric fever, malaria, kala-azar and bacterial septicemia caused pancytopenia in 21% of patients.(9)

The most common hematological profile of children with bicytopenia in our study was observed to be anemia with thrombocytopenia seen in 50% cases, followed by leucopenia with thrombocytopenia in 41.2% and anemia with leucopenia in 8.8% cases.

The most common cause of **leucopenia with thrombocytopenia** was found to be dengue fever seen in 97.6% of patients, followed by enteric fever seen in 2.4% cases. So if the child had leucopenia with thrombocytopenia on admission, infectious etiology should be considered first.

Among children who presented with **anemia with thrombocytopenia** (n=51), Megaloblastic anemia was seen in 52.9% cases, followed by acute leukemia in 31.4% cases and dengue fever in 15.7% cases. So, if a child presents with anemia and thrombocytopenia, Megaloblastic anemia and malignancy should be considered first.

In our study **anemia and leucopenia** were caused by enteric fever, dengue fever and megaloblastic anemia.

Naseem et al reported similar findings that thrombocytopenia and anemia was the most common form of bicytopenia, followed by anemia and leukopenia and thrombocytopenia and leukopenia.(7)

Absolute reticulocyte count represents the **bone marrow cellularity** to a great extent; hence, it is a very important investigation in the diagnosis of etiologies of pancytopenia.

ARC was done in all cases of pancytopenia. Absolute reticulocyte count was found to be significant in our study. All etiologies of pancytopenia showed significant differences in their absolute reticulocyte counts – all cases of Aplastic anemia had low ARC values $<25x10^9$/L, all cases of megaloblastic anemia had ARC in range of $50–75x10^9$ /L, all leukemia cases showed ARC within 76–100 $x10^9$ /L and all cases of infection had ARC values in range of $101–125x10^9$ /L.

In our study, every independent etiology of pancytopenia showed differences in absolute reticulocyte count; thus ARC plays an important role in the initial workup of pancytopenia before going for more invasive procedures such as bone marrow biopsy or aspiration. Absolute reticulocyte count is the marker of production of red blood cells. It is a non-invasive investigation and can give an idea about the cellularity of the bone marrow.Out of 48 children with pancytopenia, bone marrow examination could be done 33 patients.

The study performed by **Priya et al** in 2014 in adult patients showed low absolute reticulocyte count $<25x10^9$/L in Aplastic anemia , $25–50x10^9$ /L for nutritional anemias and $>100x10^9$ /L in bone marrow infiltration and sepsis.(10) We could not find any literature on the Absolute Reticulocyte Counts in pancytopenia in pediatric age group and we might be the first to study ARC in pediatric age group.

All cases who had hypocellular marrow(n=21) were found to have reduced ARC in peripheral blood. All cases with cellular/ hypercellular marrow (n=12) were found to have normal or increased ARC thus showing that ARC can be used as a non-invasive preliminary investigation in reaching the diagnosis of pancytopenic cases.

In bicytopenia group, 80.4% patients were discharged and death occurred in 7.8% cases; and the remaining 11.8% are on regular treatment and follow up.

In pancytopenia group, 62.5% patients were discharged and 12.5% patients certified and the remaining 25% are on regular treatment and follow up.

Death rate was higher in children with pancytopenia than among those with bicytopenia.

Recovery rate in children with bicytopenia was higher because most cases were due to infections.

Most common cause of death among children with pancytopenia and bicytopenia was due to shock (DSS), septicemia and bleeding including intracranial bleed. Many patients presented in critical condition because of delay in reaching hospital due to lockdown.

A wide range of etiologies can be detected ranging from transient suppression to malignancies, nutritional deficiencies to inflammatory diseases.

We concluded from our study that bicytopenia is more common than pancytopenia in our region. Fever was the most common presentation. Infections were the most common etiology in children admitted with bicytopenia and non-infectious causes predominated in cases of pancytopenia. Commonest cause of bicytopenia in our study was dengue fever. It is due to increased incidence and outbreaks of dengue fever in our region. If a

febrile child presents with leucopenia and thrombocytopenia, we should consider infectious etiology. Megaloblastic anemia should be considered first in the etiology of pancytopenia and bicytopenia in developing countries.

Present study highlighted that systematic approach in cases of pancytopenia is essential to avoid unnecessary invasive procedures such as bone marrow aspiration. ARC could be incorporated routinely in the investigation protocol of all pancytopenic patients. Every independent cause of pancytopenia showed difference in absolute reticulocyte count, so it might help in diagnosis of pancytopenia.

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