## **Original Research Article**

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# Pancytopenia: the perspective from Western Gujarat, India

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## **ABSTRACT**

**Background:** Pancytopenia is one of the common laboratory findings in patients presenting to us with varied clinical presentations. Risks of untreated Pancytopenia are high causing anxiety to treating doctors and patients alike. It also involves long list of investigations including a very painful marrow biopsy, life-threatening complications and treatment involves multiple blood component therapy. A total of 101 cases of pancytopenia over a period of 1 year were analysed retrospectively to find i) commonest presenting symptoms ii) commonest cause of pancytopenia, response to treatment iii) Depending on the cause, to consider if any measures can be taken for prevention

**Methods:** Cross sectional study of 101 admitted patients of Pancytopenia on the basis of information extracted from the case sheets. The data was analyzed and presented as frequencies and Percentages.

**Results:** Out of 101 cases analysed, 53 (52.47%) were females 48 (47.52%) patients males. Fatigue 74 patients (73.2%) was the commonest presenting symptom followed by fever 33 (32.6%), breathlessness 13 (12.87%) and bleeding 4(3.8%). Vitamin B12 deficiency 58 (57.6%) patients showed and was the commonest cause of pancytopenia. Infections in 24 (23.7%) like malaria16 (15.6%), dengue 5 (4.96%), PLHA 1(0.96%) and hepatitis B 2 (1.96%) was the second common cause in present study. Recovery of pancytopenia was prompt in Malaria Dengue. HIV, Hepatitis B viral infection showed persistent pancytopenia with hypoplastic marrow. Chronic liver disease portal hypertension splenomegaly accounted for 9 (8.9%) patients. Drug induced marrow suppression due to ongoing treatment for underling disease resulted in pancytopenia in 4 (3.96%) patients. Aplastic anaemia in3 (2.9%), myelodysplastic syndrome 2 (1.9%) and acute leukaemia 1 (0.96%) were the less common causes.

Conclusions: Commonest symptom on presentation were related more to anaemia than to neutropenia and thrombocytopenia. megaloblastic anaemia due to Vitamin B12 deficiency was the leading reversible cause of pancytopenia in present study followed by infections like Malaria Dengue. Gujarat, India being predominantly vegetarian state, local dietary habits are thought to be responsible for inadequate B12 daily consumption, hence we suggest fortifying the daily diet with B12 supplementation at a larger scale just like iodisation of salt to counter iodine deficiency.

Keywords: Bone marrow studies, B12 deficiency, Megaloblastic anaemia, Pancytopenia

## INTRODUCTION

Pancytopenia is a common hematological condition seen in patients presenting with varied symptoms at our medical centre in Western Gujarat, India. Pancytopenia refers to a condition when all cell lines red blood cells, white blood cells and platelets are suppressed.<sup>1</sup> It is usually to disruption of the bone marrow's ability to produce new cells. Reasons could be destruction of marrow cells by cancerous cells, failure of stem cells to mature into new blood cells, fibrosis or scarring of marrow cells or immune system destroying healthy marrow cells etc.<sup>2,3</sup> The conditions which cause

pancytopenia are varied like: aplastic autoimmune conditions, leukemia, fanconi's anemia, infections, medications affecting marrow cells, deficiency of vitamin B12 or folate for marrow cell maturation etc. It is evident that first few conditions stated above are very difficult to treat while last few are easily reversible. in the. Presentation could be varied ranging from fatigue fever or bleeding tendencies depending on the predominantly affected cell line. Hypersplenism has different mechanism where marrow function is maintained. The etiology of pancytopenia varies in different populations depending on nutritional status, cultural background, climate, season and prevalence of infections in the society. This is evident from etiological spectrum seen in different studies varying from malignancy seen in Imbert et al, Megaloblastic anemia in Tilak V et al, and other studies, Infections as seen in Agarwal R et al, Hypersplenism in study by Jain A et al, and Aplastic anemia described in various studies. 4-18 Aim of this study was to identify the clinical profile, etiological spectrum and to identify the treatable, reversible causes identified in our patients.

#### **METHODS**

This cross-sectional study was conducted at our institute, GMERS Medical college Gotri Vadodara western Gujarat, India over period of 1 year from January to December 2017. 101 patients of both genders presenting to inpatients department of Medicine with hemogram suggestive of pancytopenia were included in the study. Pancytopenia was defined as hemoglobin of<9gm/dl, WBC<4,000/mm, and platelets<100,000/mm.

The study population was recruited as:

#### Inclusion criteria

- Adults patients >18 years,
- CBC on admission fulfilling criteria of pancytopenia as mentioned above.

### Exclusion criteria

- Patients with recent history of blood transfusion,
- Patients>80years.

Once selected, patients detailed history taken and meticulous physical examination conducted. Investigations as per guidelines for pancytopenia 2 for all patients included CBC with peripheral smear, ferritin levels S.B12 levels, LDH, RFT, LFT, TSH, RA factor, ANA, Dengue serology, HIV, HbsAg, HCV USG abdomen. Upper GI scopy, Bone marrow aspiration and trephine biopsy done wherever indicated and feasible only after patient consent. Last two tests were not done in all patients as i) History and laboratory investigations were conclusive ii) patients refused. All this information was extracted from the case sheets of the admitted patients which was then entered in Microsoft excel worksheet. Data was analyzed in excel and presented as frequencies and percentages.

#### **RESULTS**

Table 1 shows age and sex wise distribution of the 101 patients analyzed, 48 (47.52%) were males and 53 (52.47%) were females showing slight preponderance of females in the study. Mean age of the patients was 48.5 years with SD of 15.05 years. Younger population in the productive age group from 18 years to 50 years. was observed to be the most 74 (73.26%) involved.

Table 1: Age and gender wise distribution of pancytopenia patients (N=101).

Age group	Male	Female	Total
18-28 years	13	18	31
29-38 years	13	7	20
39-48 years	10	13	23
49-58 years	5	10	15
59-68 years	5	4	9
68-80 years	2	1	3

Analysis of the clinical manifestations as seen in (Table 2), showed fatigue in 74 (73.2%) of patients as the commonest symptom, followed by fever in 33 (32.6%) and breathlessness in 13 (12.87%) patients.

Table 2: Presenting complaints and physical findings in pancytopenia patients (N=101).

Presenting complaint and physical findings	No. of cases	Percentage
Fatigue	74	73.2
Fever	33	32.6
Breathlessness	13	12.87
Bleeding	4	3.8
Pallor	79	78.7
Oedema	9	8.7
Hepatomegaly	19	18.8
Splenomegaly	31	30.69
Lymphadenopathy	4	3.8

Bleeding as presenting symptom was seen in relatively few patients 4 (3.84%). Analysis of the signs was found to be in tandem with the presenting complaints. Pallor was seen in 79 (78.7%) of patients, edema in 9 (8.7%). Splenomegaly is relatively common 31 (30.69%) than hepatomegaly 19 (18.8%) patients. Palpable lymph nodes detected in only 4 (3.8%) patients. As seen from (Table 3), complete hemogram with indices showed that 45(44.6%) patients had severe anemia (Hb <5gram%). This explains fatigue as the commonest symptom in present study. 37 (36.8%) patients had moderate anemia (Hb5-7gm%) while 19 (18.7%) patients had Hb7-9gm%. RBC indices and peripheral smear showed rbc's with high MCV in only 25 (24.7%) patients while MCV was <80 in 55 (54.9%) patients.

Table 3: Hematological parameters in pan-cytopenic patients (N=101).

Hematological parameters	Number	Percentage
Haemoglobin (gm%)		
<5 gm%	45	44.6
5-7 gm%	37	36.8
7-9 gm%	19	18.7
MCV levels (femtolit)		
<80	55	54.9
80-96	21	20.5
>96	25	24.7
Vit. B12 levels (picogm/r	nl)	
<100	28	27.6
101-160	18	17.8
161-200	12	11.88
201-500	33	32.67
501-1000	4	3.96
>1001	1	0.96
LDH levels (U/L)		
100-200	12	11.88
201-500	23	22.7
501-1000	18	17.6
1001-2000	16	15.8
2001-10000	17	16.8
>10000	13	12.9

Serum Vit B12 levels was low (<200 picogm /ml) in 58 (57.6%) patients. In 28 pts (27.6%) severe deficiency with levels <100pico gm/ml was seen while 38 (37.7%) patients had S. Vit B12 levels >200. S.LDH levels done, showed 64(63.36%) patients had LDH more than 500. LDH values between 200-500 were seen in 23 (22.7%) patients, normal LDH values (100-190) seen in12 (11.8%) patients. S.LDH values are suggestive of B12 deficiency as also for hemolytic anemia. Liver function and Renal function tests were done in all patients, however not tabulated here as no specific correlation was seen. To rule out different causes of pancytopenia, patients underwent further laboratory investigations as per guidelines like S.TSH, ANA screening etc. None of the patients was positive for ANA screening test hence further profile was not done. S.TSH was in normal range in all patients. 2 patients were positive for RA factor on treatment of Rheumatoid arthritis and 1 patient for scleroderma, all 3patients were on oral Azoran therapy. Both these patients showed hypoplastic marrow picture and pancytopenia in these cases was attributed to drug. Drug free interval improved their cell counts and patients showed recovery from pancytopenia.16 (15.7%) patients were positive for malarial parasite with 8 patients each having P. Falciparum and P. Vivax. They also showed recovery from pancytopenia after treatment of malaria. dengue IgM was positive in 5 patients and they also recovered from pancytopenia on treatment of dengue. Hepatitis B antigen positive in 2 patients, with high HBVDNA copies, pancytopenia was attributed to viral infection.1 patient was PLHA on ART.

All patients were subjected to ultrasonography of abdomen, 62 (61.38%) showed no abnormality on the scan. 10(9.8%) patients showed cirrhosis of liver while 1 patient had fatty liver. Splenomegaly seen in 26 (25.74%) patients with hepatosplenomegaly in 7 (6.9%) as seen in (Table 4).

Table 4: USG and endoscopy findings of pancytopenia patients (N=101).

USG findings	No. of cases	Percentage
Normal	62	61.38
Cirrhosis	10	9.8
Hepatomegaly	4	3.96
Splenomegaly	26	25.74
Hepatosplenomegaly	7	6.9
Fatty liver	1	0.96
<b>Endoscopy findings</b>		
Scopy not done	69	68.2
Normal	19	18.8
Portal HT (varices)	9	8.9
Gastritis	4	3.96

Upper GI scopy was done in 32 (31.7%) patients who had history/lab findings suggestive of chronic liver disease to rule out varices which can be an evidence of portal hypertension. 9 patients had varices and 4 patients had findings of gastritis.

Bone marrow aspiration and trephine biopsy was conducted in 56 patients while 45 patients did not undergo the procedure. Marrow findings suggestive of Megaloblastic changes were seen in 35 patients (63%). Normal marrow picture seen in 8 (14%) patients and1 (2%) patient was diagnosed to have acute leukemia on marrow aspiration. Aplastic anemia marrow picture seen in 3 patients (5%),2 (4%) patients were diagnosed to have myelodysplastic syndrome.

Table 5: Distribution of various causes of pancytopenia on the basis of bone marrow findings (N-56).

Bone marrow findings	No. of cases	Percentage
Megaloblastic	35	63
Normal	8	14
Hypocellular	7	13
Aplastic	3	5
MDS	2	4
Leukemia	1	2

7 patients (13%) showed hypocellular marrow, of which 2 patients were positive for hepatitis B with high DNA copies, 4 patients were drug induced marrow suppression (2 patients of rheumatoid arthritis on azoran,1 patient of

scleroderma on immunosuppressant, 1 patient of CML on imatinib) and 1 patient of hypocellular marrow was PLHA positive. Distribution is tabulated in (Table 5).

45 patients did not undergo the bone marrow aspiration and biopsy. In some cases, patient consent could not be obtained and in remaining underlying illness were thought to be contributing to pancytopenia.

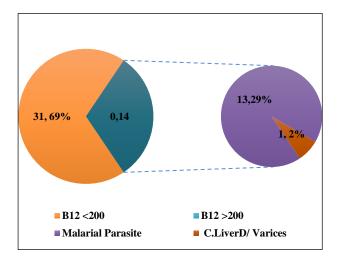


Figure 1: Breakup of causes in patients not undergoing bone marrow examination (N=45).

In Figure 1, can see the analysis of underlying etiology/reasons of pancytopenia. Out of them 31 patients (68%) had S B12 levels below 200p/ml.

Hence pancytopenia was attributed to same. The 14 patients whose B12 levels were more than 200p/ml marrow was not done as 13 of them were positive for malarial parasite and 1 patient was diagnosed to have chronic liver disease as shown in the following figure 1.

Table 6: Etiological breakup of pancytopenia patients (N=101).

Etiological cause	No. of cases	Percentage	
Vit. B12 deficiency	58	57.42	
Malaria	16	15.8	
Dengue	5	4.8	
Hepatitis B	2	1.98	
HIV	1	0.96	
CLD with portal HTN	9	8.9	
Drug induced	4	3.96	
Aplastic anemia	3	2.9	
MDS	2	1.8	
Acute leukemia	1	0.96	

Analyzing the various investigation results in (Tables 3 to 5), (Table 6) shows the common etiology seen in descending order. Vit B12 deficiency was found to be the commonest cause for Pancytopenia in present study. Out of 101 patients 58 (57.42%) patients showed B12 levels

on lower side (details as per Table 2). Total 24 (23.6%) patients had pancytopenia due to infections like malaria 16(15.8%) dengue 5 (4.8%) hepatitis B2 (1.98%) HIV 1(0.96%) and was the second common cause. Chronic liver disease (cirrhosis)with portal hypertension splenomegaly attributed to pancytopenia in 9 (8.9%) patients. Drug induced marrow suppression was seen in 4 (3.96%) while aplastic anemia, myelodysplastic syndrome, acute leukemia resulted in pancytopenia in 3 (2.9%), 2 (1.8%) and 1(0.96%) patient respectively.

Present study had B12 deficiency related megaloblastic anemia as commonest cause which was easily reversible.

## **DISCUSSION**

Pancytopenia is a common hematological condition often encountered in day to day clinical practice. It is characterized by decrease in all the three cell lines of blood viz., red blood cells, leucocytes, and platelets. Pancytopenia is defined as hemoglobin of <9 gm/dl, WBC <4,000/mm, and platelets <100,000/mm.<sup>1</sup> Severe pancytopenia is defined as absolute neutrophil count<500/cmm, platelet count<20,000/mm, corrected reticulocyte count <1%.¹ Clinical presentations related to pancytopenia can be attributed to anemia, leucopoenia, and/or thrombocytopenia. Anemia presents with fatigue, breathlessness, and cardiac symptoms. In present study 45% of patients had severe anemia <5 gm% hence the commonest presenting symptoms in present study was fatigue 74% and breathlessness seen in 13% of patients. Also, pallor was the commonest (79%) physical finding. Neutropenia presents with febrile illness due to increased susceptibility to infections. In present study 33% **Patients** had fever on presentation. Thrombocytopenia may present with mucocutaneous bleed or bruising however bleeding tendency is seen when platelets are <10,000. Authors had only 4% patients having bleeding as one of the presenting symptoms. The severity of pancytopenia and underlying etiology determine the management and prognosis. Pancytopenia patients can be relatively stable on presentation, however, can develop overwhelming sepsis without any focal sign of infection, with malaise and fever being the only clinical features. Hence it is imperative to find the cause and treat accordingly. The underlying mechanisms are decrease in hematopoietic cell production, marrow replacement by abnormal cells, suppression of marrow growth and differentiation, ineffective hematopoiesis with cell death, peripheral destruction of cells, antibody mediated sequestration or destruction of cells and trapping of cells in a hypertrophied and over active reticuloendothelial system. 23 Various lab tests including bone marrow biopsy are involved in the diagnostic workup. In present study 56 (55.44%) patients underwent marrow biopsy. On basis of history and various laboratory investigations mentioned earlier, in 45 (44.55%) patients cause could be ascertained without marrow biopsy. Treatment was initiated on basis of the investigation reports and quick recovery was seen in

terms of cytopenia. As seen in figure 1, Serum B12 levels were significantly low in 31 patients who did not undergo marrow biopsy. Treatment with B12 supplements led to reversal of pancytopenia thus averting need for further evaluation. Remaining 14 patient were positive for Malaria and showed recovery on treatment. If patient does not show any recovery with close hematological follow-up within appropriate timeframe then, can be subjected to biopsy to find associated cause. The commonest cause in the present study was megaloblastic anaemia 58 (57.7%) patients. Bone marrow was hyper cellular in majority of cases with megaloblastic erythropoiesis. Megaloblastic anemia due to vitamin B12 or folic acid deficiency is a well-recognized and established cause of cytopenia. It can either present as bicytopenia or pancytopenia or rarely thrombocytopenia only. The approximately comparable series of pancytopenia is from Iqbal W et al, Aziz T et al, Qazi RA et al. 7-9 In all these studies, megaloblastic anemia was found to be the major cause of pancytopenia. 10 In these studies, the cause of B12 deficiency was said to be mostly due to poverty, malnutrition. Our Centre in western Gujarat, India is in an agriculturally rich area with decent standard of livings. The local population is predominantly vegetarian. Vit B12 is not available in plant-based foods and only dairy based foods are source of Vit B12 in this population. In dairy foods only milk and milk-based foods are commonly consumed locally. Authors feel that this is the main reason for megaloblastic anemia as the leading cause of pancytopenia in our patients. It is easily reversible condition and if identified earlier, will help avoid other expensive tests and painful bone marrow biopsy. It will also ensure early recovery from pancytopenia.

Infection induced pancytopenia was the next common cause of pancytopenia in present study.16 patients were positive for malarial parasite, both falciparum and vivax. positive for dengue 5patients were serology, thrombocytopenia was more predominant in them. Pancytopenia may occur in the acute phase of dengue viral infection. Leukopenia (in range of 2000/cu mm) is seen in 'classical' dengue fever. 11 Thrombocytopenia is universally seen in dengue hemorrhagic fever. Also, in DHF during clinical shock, a rise in hematocrit (20% or more than baseline) is seen. 11 Secondary hemophagocytic syndrome is also mentioned as rare cause of pancytopenia, cytopenia in malaria also follow similar mechanism however all our patients of vector borne infections recovered from cytopenia within short period as soon as infection was under control.<sup>12</sup> Bone marrow aspiration was not done in these patients as pancytopenia due to vector borne disease is known and it did recover as patients recovered from malaria and dengue. 2 patients were positive for hepatitis B and 1 was PLHA. Agarwal R et al, has described malaria as the commonest cause of pancytopenia in their center. Infection induced bone marrow suppression; immune destruction of the cells are the mechanisms of pancytopenia described.<sup>13</sup> Various drugs are known to cause pancytopenia like chloramphenicol, antiepileptics, chemo drugs, azathioprine, NSAIDS etc. to name a few. In present study we had 2 patients of Rheumatoid arthritis 1 of were on immunosuppressant, scleroderma who Azathioprine presenting with pancytopenia.1pt of chronic myeloid leukemia on Imatinib, he recovered after withdrawal of drug and referred to haemato-oncologist for further management.

Table 7: Commonest cause cited in different studies.

Authors	Year	No. of cases	Commonest cause
Imbert et al <sup>4</sup>	1989 France	213	Malignant myeloid and lymphoid disorders
Varma et al <sup>15</sup>	1992 India	203	Aplastic anemia
Tilak et al <sup>5</sup>	1999 India	77	Megaloblastic anemia
Kumar et al <sup>16</sup>	2001 India	166	Aplastic anemia
Khunger et al <sup>6</sup>	2002 India	200	Megaloblastic anemia
Memon et al <sup>17</sup>	2008 Pakistan	230	Aplastic anemia
Jha et al <sup>19</sup>	2008 Nepal	148	Hypoplastic marrow
Santra G et al, Das Bk et al <sup>18</sup>	2010 Calcutta, India	111	Aplastic anemia
Jain Naniwadekar <sup>14</sup>	2013 India	250	Hypersplenism
Ridhi Agarwal et al <sup>13</sup>	2015Meerut, India	70	Malaria
Iqbal W et al <sup>7</sup>	2001 Pakistan	208	Megaloblastic anemia
Monika et al <sup>10</sup>	2016 India	169	Megaloblastic anemia
Ghartimagar et al <sup>20</sup>	2017 Nepal	138	Hypoplasia of marrow

All these patients 7 (13%) underwent marrow analysis and were found to have hypocellular marrow as shown in (Table 5). Bone marrow biopsy analysis also helped to

diagnose Aplastic anemia 3 (5%), Myelodysplastic syndrome 2 (4%), Acute Leukemia 1 (2%) patients in present study. 9 patients (9%) who had clear evidence of

cirrhosis of liver portal hypertension splenomegaly did not undergo marrow analysis. Here hypersplenism, liver cell failure (decreased thrombopoietin), ongoing variceal bleed, B12 deficiency were the multifactorial causes for pancytopenia in this group. In a similar study in India, JainA et al, Naniwadekar M et al. Hypersplenism was the commonest cause of pancytopenia, while in present study it was seen only in 9% patients. Other similar studies conducted at different places and times show different predominant cause for a commonly seen condition of pancytopenia. As seen in (Table 7).

Few studies from India and Indian subcontinent reported Aplastic anemia as the leading cause of pancytopenia in their study. <sup>15-18</sup> Jha A et al, Ghartimagar D et al, reported Hypoplasia of marrow as the leading cause while in present study 13% patient had hypocellular marrow. <sup>19,20</sup> This variation could be due to local food preferences, poverty, prevalence of infections, geographical location, climate season. Various causes cited in different studies is presented below in a tabulated form. <sup>14</sup>

#### **CONCLUSION**

Pancytopenia is a common entity with varied causes ranging from easily reversible like Vit B12 deficiency to difficult to treat conditions like Malignancies, Aplastic anemia. If not addressed promptly it can lead to life threatening complications, investigations involve long list of tests along with painful marrow biopsy. Megaloblastic anemia was the commonest cause of pancytopenia in the present study as well as other studies in Indian subcontinent. There is early reversibility with Vit B12 folic acid supplementation.

In significant number of patients 45 (44.55%) etiological causes could be diagnosed without bone marrow biopsy. In our center rather than only poverty we feel that vegetarian diet preferences of the local population lead to megaloblastic anemia related pancytopenia. Being an easily remedial problem, we suggest that since local food habits can't be changed, it should be fortified with Vit B12 on daily basis just like iodised salt which has helped combating issue of iodine deficiency. This will definitely have an impact on decreasing the loss of productive days of the younger population in which it was predominantly seen.

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