

# Clinical and etiological profile of acute febrile illness with thrombocytopenia

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## Abstract

**Background:** Acute febrile illness (AFI) in tropical country like India is usually have an infectious etiology. They pose a therapeutic and diagnostic challenge as they lack organ specific signs and symptoms. When AFI associated with thrombocytopenia they narrows down differential diagnosis and help to reach at specific diagnosis. **Methods:** We enrolled 113 patients of AFI with thrombocytopenia. All the patients >14 year of age and having febrile illness of <2-week duration along with thrombocytopenia were included in the study. Detailed history, examination, various biochemical and hematological examinations were done for the organ dysfunction and diagnosis of the patient. **Results:** Out of 113 patients studied 67(59.27%) were male and 46 (40.70%) female. Malaria 52(46%) is most common cause of AFI with thrombocytopenia. other etiologies identified are dengue fever 31(27.43%), Viral fever 17(15.04%), septicemia 7(6.19%), Leptospirosis 4(5.34%), Enteric fever 2 (1.76%). Very severe thrombocytopenia (Platelet count < 25,000/ $\mu$ l) observed in 8(7.07%) cases. 35 cases shows complications related to thrombocytopenia, petechiae in 15(42.85%) cases is most common. Mortality seen in 11(9.73%) cases. Malaria with 5(45.45%) is leading cause. **Conclusion:** Malaria is commonest cause of AFI with thrombocytopenia. Asymptomatic thrombocytopenia is present in maximum number of cases. Chances of bleeding manifestation increases with severity of thrombocytopenia.

**Key words:** AFI

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## INTRODUCTION

Acute febrile illness is common cause of people seeking health care in India. various tropical and subtropical infection present as acute febrile illness (AFI). They pose major diagnostic and therapeutic challenge to health care workers, particularly those working in limited resource setting. Fever is the most ancient hallmark of disease.

Fever is known as pyrexia from Greek “pyretus” meaning fire; Febrile is from the Latin word Febris, meaning fever. Unlike the fever of unknown origin which enjoys the standard definition, acute febrile illness (AFI) or ‘acute undifferentiated febrile illness’(AUFI), ‘short febrile illness’ lacks international consensus definition. Since FUO require duration of fever greater than three weeks, some authors define AFI as fever that resolves within three weeks<sup>1</sup>. More traditionally however AFI has been defined as fever of two weeks or shorter in durations and that lacks localized or organ specific clinical findings<sup>2</sup>.

Fever by definition is an elevation of body temperature above the normal circadian range as a result of change in thermoregulatory centre located in the anterior hypothalamus. An AM temperature of >37.2°C (98.9°F) or a P.M. temperature of >37.7°C (99.9°F) would define fever.<sup>3</sup> Normal blood platelet count is 150,000-450,000/ $\mu$ l. Thrombocytopenia is subnormal platelet count, usually less than 150,000/ $\mu$ l. This is due to decreased production,

increased destruction (immunogenic and non-immunogenic), and increased sequestration in spleen. Infections being the commonest cause of thrombocytopenia.<sup>4</sup> Commonly dengue, malaria, scrub typhus and other rickettsial infections, meningococci, leptospira and certain viral infections present as fever with thrombocytopenia<sup>5</sup>. Occasionally these patients can go on to develop a stormy course with multiorgan dysfunction requiring intensive care unit admission associated with high morbidity and mortality<sup>6,7</sup>. Thrombocytopenia in bacterial infections can occur as a part of sepsis with disseminated intravascular coagulation. Patients with sepsis may also develop hemophagocytic histiocytosis with phagocytosis of platelets and leucocytes in the bone marrow histiocytes. Both Gram-positive and Gram-negative bacterial infections can lead to sepsis. Viruses produce thrombocytopenia by various mechanisms like impaired platelet production as a result of direct viral invasion, toxic effect of viral proteins on thrombopoiesis, virus-induced hemophagocytosis and increased platelet destruction caused by binding of virus-induced autoantibodies or viral antigen antibody complexes.<sup>5</sup> Thrombocytopenia in malarial infection may appear even before fever, anemia and splenomegaly become manifest.<sup>8</sup> immune mediated lysis, sequestration in the spleen and a dyspoietic process in marrow with diminished platelet production have all been postulated. During early stages of malaria, platelet agglutination as a result of endothelial cell activation and release of activated von Willebrand factor occurs which may cause thrombocytopenia<sup>9</sup>. Occasionally platelets can be invaded by malarial parasite. when AFI is associated with thrombocytopenia narrows down the differential diagnosis and help to reach at definite diagnosis. Patients of AFI with thrombocytopenia many times do not have bleeding manifestations. Hence study of correlation between platelet counts and hemorrhagic manifestations will help us to know the correct time for infusion of platelets, thus avoiding unnecessary platelet transfusion.

## MATERIAL AND METHODS

**Study design and patients :** This prospective non-centric study was undertaken at department of general medicine, VIMSAR, Burla in Sambalpur district of state of odisha, from October 2013 to October 2015.

### Inclusion criteria:

1. The patient of both sexes aged >14 years
2. Patient admitted with fever of  $\leq 2$  week duration and found to have thrombocytopenia are included in study. (Fever defined as oral A.M. temperature of  $>37.2^{\circ}\text{C}$  ( $>98.9^{\circ}\text{F}$ ) or a P.M. temperature  $>37.7^{\circ}\text{C}$  ( $>99.9^{\circ}\text{F}$ ))

### Exclusion criteria:

1. Patients presenting with thrombocytopenia without fever
2. Diagnosed cases of Thrombocytopenic purpura on treatment
3. Patients with thrombocytopenia already diagnosed to have hematological disorder/malignancy, on treatment with chemotherapy and other immunosuppressant's
4. Patients on treatment with antiplatelet drugs and other drugs causing thrombocytopenia
5. Patients having other causes of thrombocytopenia like patients With cardiac prosthetic valves, diagnosed cases of cirrhosis of liver, portal hypertension, connective tissue disorders like SLE.

Once the case admitted with acute febrile illness (AFI) and thrombocytopenia, a careful history was recorded, general physical examination and Detailed examination of various systems was done.

### Laboratory investigation:

This was followed by routine investigations which included complete blood count, total leucocyte count. renal function test, liver function test, PT and INR, urine routine, ECG, USG, X-ray chest were done where ever indicated. The platelet counting was done by 2 methods. Crude method: A film was made from EDTA blood and stained with romansky stain. The count was considered adequate if there was 1 platelet found per 10-30 red cells. At 1000X magnification 7-20 platelet/oil immersion field. 3 part cell counter is an automated cell counter with features of counting RBC's, WBC's, platelets, blood indices and Hb concentration all together. Repeat platelet count was done on day 0, 3, 5 and then on discharge in patients with platelet count between 50000/ $\mu\text{l}$  – 150000/ $\mu\text{l}$ . In patients with platelet count less than 50000/ $\mu\text{l}$  – or having bleeding manifestation platelet count was repeated daily for at least 3 days or till rising trend of platelet is seen. Special investigations were done in order to achieve the diagnosis. Once the specific diagnosis was reached the patients were treated for it specifically and symptomatically. Platelet transfusion were considered in patients with platelet count of 10000/ $\mu\text{l}$  as absolute indication. Bleeding manifestation with any platelet count was another absolute indication for platelet transfusion.

## RESULTS

The study of 113 patients of AFI with Thrombocytopenia, of which 67(59.27%) male, and 46(40.70%) were female. There was 15(13.27%), 31(27.43%), 17 (15.04%), 26(23%),13(11.50%), 6(5.30%), 5(4.425) patients within the age group of 14-19, 20-29, 30-39, 40-49, 50-59, 60-69, >70 years respectively. Majority 31(27.43%) cases were between 20-29 years of age. The mean age (in years) for male (37.11 +14.49) and for females (36.67+15.62).

Etiology is confirmed in 96(84.95%) cases out of 113, undiagnosed cases 17(15.04%) were referred as viral fever. Malaria is most common cause with 52(46%) cases, of which PF comprise 35 cases, PV 11 cases, mixed infection (PF+PV) comprise 6 cases. Second common cause is dengue fever 31(27.43%) cases, followed by viral fever 17(15.04%), septicemia 7(6.19%), leptospirosis 4(5.35%), enteric fever least common cause with 2(1.76%) cases.

**Table 1:** Etiology of AFI with thrombocytopenia

Diagnosis	No of cases	Percentage
Malaria	52	46%
PF	35	
PV	11	
PF+PV	6	
Dengue fever	31	27.43%
Viral fever	17	15.04%
Septicemia	7	6.19%
Leptospirosis	4	5.35%
Enteric fever	2	1.76%
<b>Grand Total</b>	<b>113</b>	<b>100%</b>

### Thrombocytopenia and bleeding manifestations

There is increased trend of bleeding manifestations as the platelet count decreased. In the study 17 (15.04%) cases have count between 100,000-150,000/ $\mu$ l, 57(50.44%) cases between 50,000-100,000 / $\mu$ l, 31(27.43%) cases between 25,000-50,000/ $\mu$ l, and 8(7.07%) cases below 25,000/ $\mu$ l platelet count.

**Table 2:** Severity of thrombocytopenia

Platelet count	No of patients	Percentage
<25,000/ $\mu$ l	8	7.07%
25000-50000/ $\mu$ l	31	27.43%
50000-100000/ $\mu$ l	57	50.44%
10000-150000/ $\mu$ l	17	15.04%
<b>Total</b>	<b>113</b>	<b>100%</b>

Bleeding manifestations are seen in total 35 cases, of which petechiae in 15(42.85%) cases were most common, ecchymosis in 7(20%) cases, subconjunctival bleeding 4(11.42%), bleeding gums 3(8.57%) cases, malena in 6(17.14%) cases.

**Table 3:** Bleeding manifestations

Bleeding manifestations	Total no of patients	Mean platelet count ( $\mu$ l)
Petechiae	15	29733
Ecchymosis	7	38280
Subconjunctival bleeding	4	31000
Bleeding gums	3	28000
Malena	6	19000
<b>Total</b>	<b>35</b>	

### Outcome of the patients

Of the total 113 cases studied, mortality seen in 11 (9.73%) cases . maximum mortality is seen in malaria with 5 cases followed by 3 cases of septicemia , 2 cases of leptospira , and 1 case of dengue fever. Death were due to multiorgan failure in all the cases.

**Table 4:** Outcome of patients

Diagnosis	Good outcome	Mortality	Total
Malaria	47	5	52
Dengue fever	30	1	31
Viral fever	17	0	17
Septicemia	4	3	7
Leptospirosis	2	2	4
Enteric fever	2	0	2

## DISCUSSION

In our study the etiology of AFI with thrombocytopenia is malaria (52), dengue fever (31), viral fever (17), septicemia (7), leptospirosis (4), enteric fever (2) cases. Comparing these results with other studies conducted by prithviraj patil *et al.*<sup>10</sup>., srinivas *et al.*<sup>11</sup> in which malaria is most common cause of febrile thrombocytopenia, while in Nair *et al.*<sup>12</sup> study septicemia is most common cause.

**Table 5:** Etiology of AFI with thrombocytopenia

Diagnosis	Prithwiraj <i>et al.</i>	Srinivas <i>et al.</i>	Nair <i>et al.</i>	Present study
Malaria	54	41	9	52
Dengue fever	15	14	14	31
Septicemia	4	19	26	7
Enteric fever	6	24	15	2
Other	21	2	18	21

### Comparing the bleeding manifestations

In our study bleeding manifestations are seen in 35(30.97%) cases, as compared to 23% case in prithwiraj<sup>10</sup> study and 22.22% in Nair *et al.*<sup>12</sup> study. Purpura (15 cases) is most common form of bleeding manifestation in our study. Similar results were observed in prithwiraj<sup>10</sup> study, in which 17(17%) cases developed petechiae as a most common form of bleeding manifestation. In our study ecchymosis observed in (7) cases, gum bleeding (3) cases, subconjunctival bleed (4) and malena (6) cases. Prithwiraj *et al.*<sup>10</sup> observed epistaxis in (1) cases, Hematuria (3) cases and PR bleed in (2) cases.

### Comparing outcome of cases

In our study out of 113 cases studied, mortality observed in 11(9.37%). Good outcome seen in 90.63% cases. Malaria is most common cause of mortality with 5(45.45%) of total deaths. Followed by septicemia 3(27.27%), leptospirosis 2(18.18%), dengue fever 1(9.09%) cases. In prithwiraj *et al.*<sup>10</sup> study septicemia is most common cause of mortality, contributing 60% of total deaths. In Srinivas *et al.*<sup>11</sup> study septicemia account for 78% and dengue fever in 22% of mortality cases.

**Table 6: outcome of patients**

Disease	Prithwiraj <i>et al.</i> %	Sriniwas <i>et al.</i> %	Present study %
Malaria	20	-	45.45
Septicemia	60	78	27.27
Dengue fever	--	22	9.09
Other	20	-	18.18

## CONCLUSION

Malaria is commonest cause of AFI with thrombocytopenia. Asymptomatic thrombocytopenia is present in maximum number of cases. Chances of bleeding manifestation increases with severity of thrombocytopenia. Petechiae are the most common form of bleeding manifestation observed, apart from gum bleeding, ecchymosis, malena and subconjunctival hemorrhage.

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