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# Clinical and laboratory predictors of enteric fever in children with special reference to eosinopenia

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***ABSTRACT:***

- ***Objective:*** Enteric fever remains a leading cause of febrile illness, especially in developing countries. Due to limited resources, all investigations are not available in every health facility, but simpler investigations and clinical examinations may help in the early diagnosis of the disease. In this study, we evaluated the usefulness of eosinopenia and clinical features in predicting enteric fever in children.
- ***Patients and Methods:*** A cross-sectional study was conducted from March 2018 to March 2019. A total of 100 children with a fever of a minimum of 5 days duration and without any focus of infection were included in the study. Investigations such as hemogram with absolute eosinophil count, liver function test, Widal test, and blood culture were performed. Absolute eosinopenia was defined as the eosinophilic count of 0 µg/dl. Sensitivity, specificity, PPV, and NPV of absolute eosinopenia and other clinical indicators were calculated.
- ***Results:*** We analyzed data from 100 children, including 75 cases in the enteric fever group (culture/Widal positive) and 25 cases in the suspected enteric fever group. The presence of eosinopenia was statistically significant in the enteric group (*p*-value = 0.02). Absolute eosinopenia was seen in 52% of confirmed enteric cases, compared to 4% of the suspected enteric group (*p*-value = 0.001). The positive predictive values for relative bradycardia and coated tongue were 84.3% and 91.4%, respectively. Absolute eosinopenia had a specificity of 96% and PPV of 97.5%. Relative bradycardia, eosinopenia, and absolute eosinopenia were significantly more present in the culture-positive group (*p*-value = 0.02, 0.04, 0.02, respectively).
- ***Conclusions:*** Absolute eosinopenia can be used as a strong predictor of the disease and can help in the early institution of appropriate therapy, especially in a resource-limited setting. Relative bradycardia, coated tongue, along with low TLC, thrombocytopenia, and eosinopenia can be used as other predictors.

- ***Keywords:*** *Enteric fever, Eosinopenia, Absolute eosinopenia.*

## INTRODUCTION

Enteric fever is a significant health problem in the global community, causing an estimated 12-27 million cases and 129,000-223,000 deaths each year[1]. In India alone, there are an estimated 6,345,776 cases found every year, including absolute cases and drug-resistants[2]. Enteric fever has varied clinical presentations, which include mild illness with low-grade fever, dry cough, and malaise to a severe form presenting with altered senses, abdominal discomfort, and complications like intestinal hemorrhage or peritonitis secondary to intestinal perforation. Although the clinical presentation of enteric fever is similar in both children and adults, there may be slight differenc-



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es in symptom severity and frequency. In children, the symptoms may be milder and may include non-specific symptoms such as lethargy, poor appetite, and irritability. However, recent studies[3,4] suggest that children are more susceptible to complications such as meningitis or sepsis compared to adults, where GIT complications like perforation are more commonly seen. It has been noted[5,6] that *Salmonella typhi* is more commonly isolated in children <5 years of age, whereas the incidence of *Salmonella paratyphi* isolation increases with age.

The presence of variable and overlapping clinical features with other infectious diseases and lack of precise clinical investigations have made the diagnosis often difficult, especially in resource-limited settings. Various predictors in the form of clinical features like fever, headache, abdominal pain, relative bradycardia, hepatosplenomegaly, rose spots, and laboratory findings like leucopenia, eosinopenia, thrombocytopenia, and elevated AST levels have been studied[7] and found to be useful as predictors to diagnose enteric fever. Eosinopenia, as a response seen in acute infection, is well defined and has been well characterized[8]. There are recent studies[8] suggesting that absolute eosinopenia can be seen in up to 73% of the confirmed enteric fever cases.

While previous studies[8-10] have investigated diagnostic predictors of enteric fever in adults globally, few studies exist[11,12] on the same topic in Indian children. Therefore, this study aimed to identify clinical and laboratory predictors, particularly eosinopenia, in children with enteric fever to enable early appropriate therapy.

## PATIENTS AND METHODS

This was a cross-sectional study performed in the Department of Pediatrics of a tertiary hospital located in New Delhi, India, between March 2018 and April 2019, after obtaining institutional ethical clearance. We enrolled all previously healthy children under the age of 12 who had a fever of 38°C or higher that persisted for more than five days and did not exhibit any focus of infection, after obtaining informed consent/assent. Children who received any antibiotic before presentation, with known atopic dermatitis and drug allergy, hematological malignancies, and bronchial asthma, were excluded from the study. The cases of fever were further categorized as confirmed enteric (culture positive), probable enteric (Widal positive), and suspected enteric cases that did not show either of these tests positive but clinical symptoms and signs suggestive of enteric illness. Children with confirmed enteric fever and probable enteric fever were classified as enteric fever and were compared with the suspected enteric cases. This classification was done based on 2011 WHO guidelines[13] for the management of enteric fever. Confirmed cases and probable cases were analyzed together with the suspected as the probability of getting culture-positive cases only at low resource settings is very low.

Detailed history and clinical examination were carried out. Routine investigations like hemogram with absolute eosinophil count, liver function tests, kidney function tests, and prothrombin time/INR were performed. The absolute eosinophil count was done by eosinophil counting fluid (Dunger's fluid) in a Neubauer's chamber. Eosinopenia is defined when the eosinophilic count is lower than 1% of the white cell count, whereas Absolute Eosinopenia is labeled when the count is 0/microliters. In children, a Widal test using the tube method was performed, and a cutoff value of 1 in 160 dilutions was used to determine the presence of antibodies against both Salmonella typhi H and O antigens. Blood culture and drug sensitivity were done for all. To rule out the possibility of other infections that can mimic enteric fever in probable cases, we conducted serological tests for dengue, malaria, leptospirosis, and other suspected infections.

### Statistical Analysis

Data entry was done using Microsoft Excel and statistically analyzed using SPSS software version 24 for Windows (IBM Corp., Armonk, NY, USA). Mean and standard deviation were calculated for baseline characteristics like age and anthropometric parameters. Appropriate tests with a 90% confidence interval and to check the significant *p*-value of 0.05 were applied. To examine the relationships between qualitative variables, we used Chi-square or Fisher exact tests, while for quantitative variables, we employed student *t*-tests or Mann-Whitney U tests as appropriate. Results were reported in various formats, including mean ± standard deviation, standard deviation scores, frequency, and percentages, depending on the nature of the data. Additionally, we calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of absolute eosinopenia and other clinical indicators.

### Results

A total of 100 children below 12 years of age were included, 94% of cases were more than 3 years of age. Male preponderance was observed with 57% males and 43% females. The majority (87%) of fever cases were residents of Delhi. The majority of children (78%) had weight and height measurements within the normal range, indicating they were previously healthy.

Out of 100 cases of fever, 65% were "Probable", 10% were "Confirmed Enteric" cases, and 25% were "Suspected Enteric". The mean age of enteric fever cases was 7.03 ± 3 years (median 8 years). The mean age of suspected enteric fever cases was 7.12 ± 2.6 years (median 7 years). Presenting complaints of 100 fever cases were recorded based on a thorough history review. In addition to fever, the commonest presenting complaint was mild abdominal pain (69%). Also, diarrhea was seen in 51% of children, and frontal headache in 33% of cases. Frontal headache was seen in 24 out of 75 cases (32%) of enteric fever (confirmed and probable), while 9 out of 25

**Table 1.** Presenting complaints of enteric and suspected enteric cases.

| Parameters | Enteric fever (75) n (%) | Suspected enteric fever (25) n (%) | *p*-value |
|---|---|---|---|
| Gender (M/F) | 40/35 | 17/8 | 0.20 |
| Headache | 24 (32) | 9 (36) | 0.26 |
| Diarrhoea | 39 (52) | 12 (48) | 0.7 |
| Constipation | 8 (10.7) | 0 | 0.08 |
| Relative bradycardia | 43 (57.3) | 8 (32) | 0.02 |
| Pallor | 29 (38.7) | 4 (16) | 0.03 |
| Coated tongue | 32 (42.7) | 3 (12) | 0.05 |
| Rose spot | 1 (1.3) | 0 | 0.43 |
| Hepatomegaly | 32 (42.7) | 16 (64) | 0.06 |
| Hepatosplenomegaly | 20 (26.7) | 2 (8) | 0.05 |

suspected enteric cases also had a headache (36%), but the comparison was not significant statistically (*p*-value = 0.26). Malaise was seen in 49.3% of enteric cases as opposed to 20% in suspected enteric cases. Amongst clinical signs, relative bradycardia was seen in 51% of cases, and 48% had isolated hepatomegaly at presentation. Rose spot was seen in only one case. The coated tongue was seen in 32 out of 75 enteric fever cases (42.7%) and was of intermittent significance (*p*-value = 0.05). Relative bradycardia was seen in 57.3% of enteric cases *vs.* 32% in the suspected group (*p*-value = 0.02). Isolated hepatomegaly was seen in 32 out of 75 enteric fever cases (42.7%) (Table 1).

Baseline investigations in the form of hemograms and LFTs were done for all 100 fever cases. A hemogram with a peripheral smear and absolute eosinophil count by eosinophil diluting fluid on a Neubauer chamber was performed for all enrolled cases. In these 100 children, the mean total leucocyte count was 6,681 cells/$mm^{3,}$ and the mean platelet count was 2.09 cells/$mm^3$. Eosinopenia was seen in 67 % of children, with absolute eosinopenia in 40% of cases. The mean eosinophil count was 74.6. Eosinopenia was seen in 55 out of 75 (73.3%) cases of enteric fever cases (confirmed and probable), while 12 out of 25 cases of suspected enteric fever had eosinopenia (48%), and it was statistically significant (*p*-value = 0.02). Among the confirmed enteric fever cases, 70% (7 out of 10) showed absolute eosinopenia. For probable enteric fever cases, 49.2% (32 out of 65) exhibited this condition, whereas only 4% (1 out of 25) of non-enteric cases had absolute eosinopenia (Figure 1). Absolute eosinopenia was seen in 39 out of 75 (52%) cases of enteric fever as compared to 1 out of 25 suspected enteric cases, and this was highly significant statistically (*p*-value < 0.0001) (Table 2).

Relative bradycardia and coated tongue had positive predictive values of 84.3% and 91.4%, respectively. Absolute eosinopenia had 96% specificity and 97.5% positive predictive value for enteric fever (Table 3).

Finally, culture-positive cases were compared to culture-negative cases based on various clinical signs, symptoms, and hematological parameters. It was seen that children with culture-proven enteric were all more than 3 years of age. Frontal headache and eosinopenia were seen in 100 % of cases that were culture-positive (Table 3). The presence of relative bradycardia, eosinopenia, and absolute eosinopenia was significantly higher in the culture-positive group (*p*-values = 0.02, 0.04, 0.02, respectively).

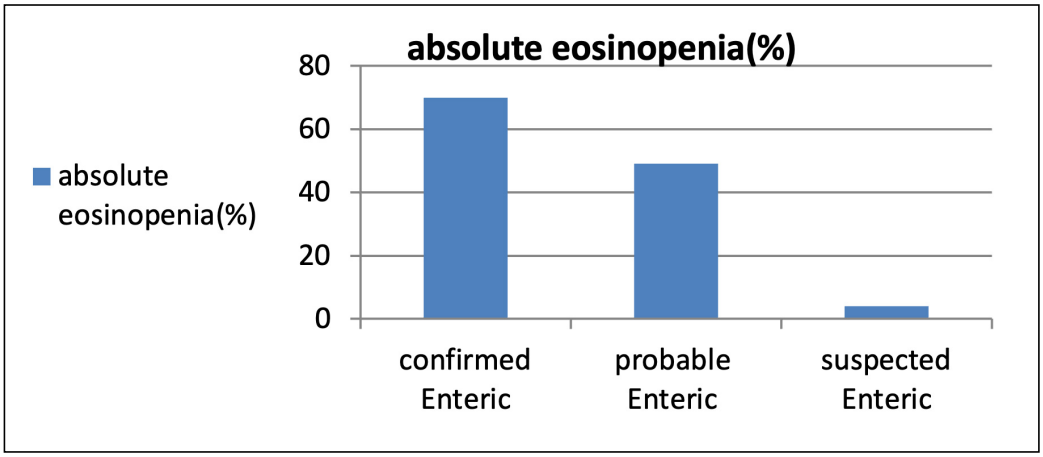


**Figure 1.** Absolute eosinopenia in three groups.

**Table 2.** Hematological parameters of enteric/suspected enteric fever cases.

| Parameters | Enteric (75) n (%) | Suspected enteric (25) n (%) | *p*-value |
|---|---|---|---|
| Anemia (<11 g/dl) | 46 (61.3) | 14 (56) | 0.41 |
| TLC (<4,000 cells/mm$^3$) | 17 (22.7) | 3 (12) | 0.24 |
| TLC (>11,000 cells/mm$^3$) | 4 (5.3) | 2 (8) | 0.62 |
| Platelet (<1.5 L/mm$^3$) | 36 (48) | 6 (24) | 0.03 |
| Platelet (>4 L/mm$^3$) | 7 (9.3) | 1 (4) | 0.39 |
| Eosinopenia | 55 (73.3) | 12 (48) | 0.02 |
| Absolute eosinopenia | 39 (52) | 1 (4) | <0.001 |

**Table 3.** Diagnostic predictive values of enteric fever.

| Characteristics | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| Absolute eosinopenia | 52 | 96 | 97.5 | 40 |
| Eosinopenia | 73.3 | 52 | 82 | 39.4 |
| Relative bradycardia | 57.3 | 68 | 84.3 | 34.7 |
| Headache | 32 | 64 | 72.7 | 23.8 |

## DISCUSSION

Enteric fever is a prominent cause of febrile illness in children, particularly in developing nations such as India. While diagnosis typically involves more complex testing methods like the Widal test or blood culture, these may not be accessible in all healthcare settings. In contrast, hemogram tests are more widely available. Recent research[9,10] has shown that absolute eosinopenia is frequently observed in cases of enteric fever. However, there is limited information on the use of eosinopenia and other clinical features to identify enteric fever in Indian children with febrile illness. This study has assessed the diagnostic potential of eosinopenia and other clinical indicators in predicting enteric fever in children.

It was seen in this study that 94% of children were older than 3 years of age. The mean age of children was 7.03 ± 3 years. This was in accordance with a previous study by Walia et al[11] from India, conducted retrospectively at Safdarjung Hospital between January 1999 and December 2003, which revealed the maximum occurrence of the disease in children aged 5-12 years. A systematic review and meta-analysis of all the studies from India published between 1950 and 2015, reporting the incidence or prevalence of typhoid/paratyphoid fever, also found the highest incidence to be in the age group 2-4 years[12]. Male preponderance, as in this study, has been reported in other studies[13-16] published both in India and other parts of the world.

It was seen that the majority of children had their weight and height normal for their age and sex, indicating that these children were previously healthy, apparently free from any chronic illness, and had presented with an acute febrile illness. The occurrence of enteric fever in these cases could be explained by ingestion of contaminated food and water. According to a background document[17] published by WHO on the management of typhoid fever, the highest incidence of the disease occurs where large populations are being served with feces-contaminated water for household use, and the same was also reflected by a study by Prasad et al[18] on the epidemiology of typhoid fever in Fiji.

In addition to fever, the commonest presenting complaints were mild abdominal pain, seen in 69% of cases. Also, diarrhea was seen in 51% of children, and frontal headache in 33% of cases. Other associated complaints included malaise (42%), and myalgia in 23% of children. The common occurrence of abdominal pain and diarrhea in enteric fever has been highlighted in other studies, such as Gosai et al[19], where abdominal pain was reported in 80.6% of cases. However, unlike our study where diarrhea was a major symptom, this study reported vomiting (86%) as a predominant feature. Another study from West Bengal, India, by Ghosh et al[20] showed comparable results, with abdominal pain, headache, and myalgia accounting for 68%, 55%, and 58% of cases, respectively. Diarrhea was reported in 30.4% of cases in a study from Turkey by Hosoglu et al[21]. Constipation as a salient feature, as shown in some of the studies like Ghosh et al[20] (50%) and Vollaard et al[22] (34%), was infrequent in our study and seen in only 8% of cases.

Clinical examination revealed relative bradycardia in 51% of cases. The association of relative bradycardia with enteric fever has been reported in other publications from all over the world. In a study by Kuvandik et al[7] from Turkey, relative bradycardia was seen in 76.7% of cases and was found to be one of the predictors of enteric fever (OR: 17.26; 95% CI: 3.20-25.59). Similarly, Matono et al[9], in their study from Japan, demonstrated relative bradycardia in 88% of the subjects, and sensitivity was found to be 87.5%, which

was higher compared to our study (57.3%). However, the positive predictive value of relative bradycardia in our study was 84.3%, which was higher than the study mentioned above. Relative bradycardia has been infrequently reported in previous Indian studies[14,23,24]. Another common physical finding was hepatomegaly, seen in 70% of children. Hepatomegaly, as in our study, has been seen as an important clinical finding in previous Indian studies by Walia et al[11], Jog et al[14], Ghosh et al[20], and Dheer et al[23].

In the 100 children included in our study, the mean total leucocyte count was 6,681 cells/mm$^3$ and the mean platelet count was 2.09 cells/mm$^3$. The association of lower leucocyte count and platelet count with enteric fever has also been established in previous studies in literature. In a study by Ghosh et al[20] from India, on evolving clinical features and laboratory parameters in typhoid cases, leucopenia was observed in 28.2% of the enteric cases, which is comparable with our results (22.7%). Thrombocytopenia was seen in 20% of cases, which is lower than in our study (48%). Similar studies by Hosogluet al[21] and Abro et al[16] demonstrated thrombocytopenia in 48% and 40% of the subjects, respectively.

Eosinopenia was seen in 67 % of children, with absolute eosinopenia in 40% of the enrolled fever cases. The association of eosinopenia with gram-negative infections, particularly, sepsis and bacteremia, has been reported by multiple studies[25-27] in recent decades. The mechanism of decreased eosinophil count can be explained by rapid peripheral sequestration of circulating eosinophils as a result of the release of chemotactic substances like C5a and fibrin released as an early response to infection[28]. In fact, eosinopenia was found in 72-90% of cases of enteric fever in several studies[7,9,20,21,25].

Published literature in children highlighting the occurrence of eosinopenia in enteric fever in Indian children is few. In a study by Ghosh et al[20], absolute eosinopenia was seen in 61.7% of cases, which was slightly higher than our study. Jog et al[14] from Mumbai also demonstrated absolute eosinopenia of 76.7% in enteric cases. However, the mean age of this study was 21.7 years. Similar studies by Matono et al[9] and Lokhandwala et al[8] had demonstrated absolute eosinopenia in 63% and 73%, respectively. There are no large studies in culture-positive enteric cases from India highlighting the diagnostic value of absolute eosinopenia.

The 100 cases of fever were further categorized as confirmed enteric (culture positive), probable enteric (Widal positive), and suspected enteric cases that did not have either positive. Children with confirmed enteric fever and probable enteric fever were classified as enteric fever and were compared with the suspected enteric cases. This classification was done based on 2011 WHO guidelines[25] for the management of enteric fever.

Overall, 10% of the cases tested positive for *Salmonella typhi* in blood cultures, 65% showed positive results in the Widal test, and the remaining 25% were suspected enteric cases that did not test positive for either. In all, there were 75 children in the enteric fever group (blood culture positive or Widal positive or both) and 25 cases in the suspected enteric fever group (who did not test positive for either). The two groups (enteric *vs.* suspected enteric) were compared to see if any characteristic presenting complaint in the enteric group could be identified. The pattern and grade of fever in the two groups were not statistically significant. The two groups were comparable in terms of various presenting complaints like frontal headache ($p$-value = 0.26), cough ($p$-value = 0.46), diarrhea ($p$-value = 0.72), constipation ($p$-value = 0.08), mild abdominal pain ($p$-value = 0.26), vomiting ($p$-value = 0.5), myalgia ($p$-value = 0.33), arthralgia ($p$-value = 0.62). The incidence of malaise was higher in the enteric fever group ($p$-value = 0.03). Thus, it appears that accurately identifying cases of enteric fever based solely on patient symptoms is a challenging and less dependable approach. Among the clinical signs, it was seen that the presence of relative bradycardia, pallor, coated tongue, and hepatosplenomegaly was statistically more significant in the enteric fever group ($p$-value < 0.05). Thus, in children with fever, the presence of these physical signs can help identify children with enteric fever.

The hematological parameters in the two groups were compared. The presence of eosinopenia was statistically higher in the enteric group ($p$-value = 0.02) than in the other. Absolute eosinopenia was seen in 52% (39 out of 75 cases) of confirmed enteric cases compared to 4% (1 out of 25) in the suspected enteric group. This was highly significant.

The sensitivity, specificity, positive predictive value, and negative predictive value of various symptoms and signs were compared in the two groups. The frontal headache had a positive predictive value of 72.7% in identifying enteric fever. Mild abdominal pain had a sensitivity of 72% and a positive predictive value of 78.2% for identifying enteric fever. Diarrhea had a sensitivity of 52% in enteric fever and a 76.4% positive predictive value. The highest positive predictive values were seen for relative bradycardia (84.3%) and coated tongue (91.4%). Thus, these clinical signs are useful in identifying enteric fever among children presenting with unidentified prolonged fevers in hospitals, especially in resource-limited settings.

Among the laboratory findings, low TLC, thrombocytopenia, eosinopenia, and had positive predictive values of 85%, 85.7%, and 82%, respectively. Thus, in combination with clinical signs, these laboratory findings are useful in identifying cases of enteric fever pending Widal and blood culture reports. Also, in this study, absolute eosinopenia had a sensitivity of 52%, a specificity of 96%, a positive predictive value of 97.5%, and a negative predictive value of 40%. Thus, absolute eosinopenia is very useful for identifying enteric fever.

Finally, culture-positive enteric fever cases were compared with those with culture-negative (Widal-positive cases). Frontal headache was seen in 100% of cases that were culture-positive. The presence of relative bradycardia, eosinopenia, and absolute eosinopenia was significantly higher in the culture-positive group ($p$-values = 0.02, 0.04, 0.02, respectively). There was no mortality in this study.

## Limitations

The small sample size of the study was a limiting factor. The inclusion of a large number of febrile children would have yielded many more culture-positive enteric fever cases. This would have enabled us to compare a large number of culture-positive cases *vs.* culture-negative cases. The limited study period was the main limiting factor.

## CONCLUSIONS

Clinical signs like relative bradycardia and coated tongue, in combination with low TLC, thrombocytopenia, and eosinopenia, can be used as predictors of the disease. The presence of absolute eosinopenia can give a strong clue to the diagnosis of enteric fever. It can be used as a strong predictor of the disease so that early institutions of appropriate therapy can be done, especially in a resource-limited setting where blood culture facilities are not easily available.

**Authors' Contributions:**
AK: Developed the detailed outline of the manuscript, prepared the initial draft of the manuscript, and revised and constructed the final manuscript.
KR: Conceived the idea, helped in manuscript preparation, and provided critical inputs in preparation and finalizing the manuscript.
DK: Provided critical inputs in preparing and finalizing the manuscript.

**Informed Consent:**
The authors certify that they have obtained all appropriate patient consent forms.

**Conflict of Interest:**
None.

**Ethics Approval:**
Institutional ethical clearance was obtained from Maulana Azad Medical College, New Delhi, India (Ethics approval number- File No. 17/IEC/MAMC/2017/Paeds/12).

**Availability of Data and Materials:**
Data can be provided upon request.

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