Original Research Article

Utility of Clinical and Laboratory Markers in Diagnosis of Culture Positive Enteric Fever in Children

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Abstract

Introduction: Enteric fever, an infectious disease affects children mostly those who are deprived of basic sanitation and potable water. This increases the burden on the healthcare system. Moreover children are more prone to complications if treatment is not initiated early. **Aim:** To study the utilities of clinical (hepatomegaly, splenomegaly, coated tongue and abdominal tenderness) and laboratory markers (CRP, eosinopenia, Typhidot and Widal) in diagnosis of culture positive enteric fever in children. **Methods**: This prospective, observational study was done on 201 children over a period of one year in a tertiary care hospital. **Result:** Blood culture positive fever had a statistically significant correlation with abdominal pain (p- 0.001), vomiting (p-0.004) and loose stools (p-0.002). Blood culture positive enteric fever was significantly associated with coated tongue (p-0.007), hepatomegaly (p-<0.001), splenomegaly (p-<0.001) and abdomen tenderness (p-<0.001). 70(61.9%) of culture positive patients had positive widal. Typhi dot was positive among 70(61.9%) of blood culture positive Enteric fever. Eosinopenia has a high sensitivity (92.9%) but low specificity (25%) in diagnosis of Enteric fever.CRP has a high sensitivity (93.8%) but low specificity (17%) in diagnosis of Enteric fever. Best AUC was observed for Widal test 0.719 (95% CI 0.647-0.790). **Conclusion:** Clinical and laboratory findings can help the clinician to diagnose enteric fever in the absence of microbiological confirmation and initiation of antimicrobial therapy at an early stage preventing complications.

Keywords: Enteric fever, Widal test, Typhidot, eosinopenia, blood culture.

Introduction

Enteric fever is a major public health problem in India, caused by *Salmonella enterica* serotype *Typhi*. The disease has social circumstances which favors its transmission into various social strata. The disease is acquired through consumption of water or food contaminated by feces of an acutely infected or convalescent person or a chronic, asymptomatic carrier. Humans are the only source of these bacteria; no animal or environmental reservoirs have been identified.

Enteric fever is the common name given for typhoid and paratyphoid diseases [1]. It still remains as an important infectious cause of morbidity and mortality in many developing countries [2, 3].

In 2018, WHO estimated the global typhoid fever disease burden at 11-20 million cases annually, resulting in about 128000–161000 deaths per year[4]. India, South and Central America and Africa are the regions where the disease is seen endemically due to the rapid population increase, increasing urbanization, restricted water resources and insufficient infrastructure and health services [2, 5]. Serious complications are encountered in the enteric diseases that are untreated. These are intestinal bleeding, intestinal perforation, and rarely splenic abscess [1].

Clinical sign of enteric fever are diverse that can be observed with other infectious diseases. This leads to unnecessary use of antibiotics in some other diseases which cause fever. The definitive diagnosis of enteric fever is possible with the isolation of the causative agent.

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However, the availability of microbiological culturing facilities is often limited in regions in which enteric fever is endemic. In addition cultures can be negative when patients used antibiotic therapy prior to diagnosis [6, 7].

Aim of study

To study the utilities of clinical (hepatomegaly, splenomegaly, coated tongue and abdominal tenderness) and laboratory markers (CRP, eosinopenia, Typhidot and Widal) in diagnosis of culture positive enteric fever in children.

Objectives

Primary objective

To determine the predictive value of clinical features and laboratory markers (CRP, eosinopenia, Typhidot, Widal) in diagnosing culture positive enteric fever in children presenting with suspected enteric fever with duration ≥5 days.

Secondary objective

To start treatment of enteric fever on the basis of clinical features (hepatosplenomegaly, coated tongue and abdominal tenderness) and laboratory markers (CRP, Eosinopenia, Typhidot and Widal)

Material and method

Study area

Holy Family Hospital, New Delhi

Study Population

Children between 1- 12 years with suspected Enteric fever having at least 5days of fever with no localization.

Study Design
Prospective, Observational Study

Sample Size
Previously researches (Kuvandik C et al[8], Choo KE ET al[16], Lalremruata R et al[9], Islam K et al[10]) have performed studies on Utility of clinical and laboratory markers (CRP, eosinopenia, Typhidot, and Widal) in diagnosis of culture positive enteric fever in children. The sensitivity found in articles ranges 60% to 90%. Therefore, assuming (p)=85% as the sensitivity of laboratory markers with 5% margin of error, the minimum required sample size at 5% level of significance is 196 patients.

Formula used

$$n = \frac{Z^2_{\alpha/2} pq}{d^2}$$

where, p is the observed sensitivity of laboratory markers
$q = 1 - p$
d is the margin of error
$Z_{\alpha/2}$ is the ordinate of standard normal distribution at α% level of significance

Duration of study
One year (June 2016 to May 2017)

Inclusion Criteria
1. Age – children with age 1 to 12years
2. Fever >5 days without localization

Exclusion Criteria
Clinical features suggestive of any other diagnosis.

Methodology
After approval of Institutional Ethical Committee children of age 1 year to 12 years with fever of more than 5 days with no localization were included in the study. After taking informed written consent from the parents, children fulfilling inclusion criteria were enrolled. All enrolled children were examined clinically and findings such as hepatomegaly, splenomegaly, coated tongue and skin rash, abdominal tenderness were evaluated. Blood investigations [CBC, CRP, LFT, SE, Blood urea, serum creatinine, Typhi-dot, WIDAL, Blood culture (BACTEC)] were done in all enrolled patients. Laboratory parameters were entered in a predesigned proforma. Blood culture results were compared to the Laboratory parameters.

Data Analysis
Statistical analysis was performed by the SPSS program for Windows, version 17.0 (SPSS, Chicago, Illinois). Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analysed using either the Chi square test or Fisher's exact test. A receiver operating characteristics (ROC) analysis was calculated-the area under the curve with 95% CI to analyze the diagnostic accuracy of various parameters.

Observation & Results
Out of 201 patients studied, 113 were blood culture positive and 88 were negative for blood cultures.

Table1: Distribution of study population

Fever	Frequency (%)	Age (in years)
Blood culture positive	113 (56%)	5.92 ± 3.21
Blood culture negative	88 (44%)	7.45 ± 3.22
Total	201	

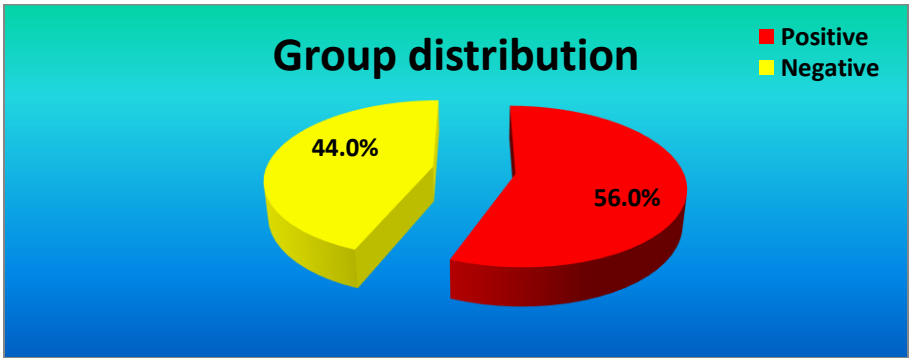

Fig 1: Group distribution

Clinical parameters
Patients presented with clinical complaints of fever, cough, abdominal pain, Vomiting, loose stool and constipation.
Blood culture positive fever had a statistically significant correlation with abdominal pain (p- 0.001), vomiting (p-0.004) and loose stools (p-0.002).Presence of cough was against the diagnosis of culture positive enteric fever (p-value - <0 .001)

Table 2: Correlation of clinical symptoms with diagnosis of enteric fever

Clinical Complaints		BLOOD CULTURE				P Value
		Positive (n=113)		Negative (n=88)		
Duration of Fever	n, %	113	100.0%	88	100.0%	–
	Mean ± SD, Median (IQR)	6.81 ± 1.72	6.00 (6.00 - 8.00)	6.60 ± 2.12	6.00 (5.00 - 7.00)	0.067
Cough	n, %	14	12.4%	33	37.5%	<0.001
	Mean ± SD, Median (IQR)	4.64 ± 2.13	4.50 (3.00 - 5.25)	5.53 ± 2.45	5.00 (5.00 - 6.00)	0.056
Abdominal Pain	n, %	71	62.8%	34	38.6%	0.001
	Mean ± SD, Median (IQR)	3.04 ± 1.75	3.00 (2.00 - 3.00)	3.06 ± 1.63	3.00 (2.00 - 3.00)	0.804
Vomiting	n, %	52	46.0%	23	26.1%	0.004
	Mean ± SD, Median (IQR)	2.50 ± 1.09	2.00 (2.00 - 3.00)	2.91 ± 1.97	2.00 (2.00 - 3.00)	0.878

Loose Stool	n, %	47	41.6%	17	19.3%	0.002
	Mean ± SD, Median (IQR)	2.62 ± 0.92	2.00 (2.00 - 3.00)	2.94 ± 1.75	2.00 (2.00 - 3.00)	0.927
Constipation	n, %	23	20.4%	11	12.5%	0.219
	Mean ± SD, Median (IQR)	4.68 ± 1.00	5.00 (4.00 - 5.00)	4.56 ± 1.24	5.00 (4.00 - 5.00)	0.924
Skin Rash	n, %	1	0.9%	1	1.1%	1.000
	Mean ± SD, Median (IQR)	2.00 ± 0.00	2.00 (2.00 - 2.00)	2.00 ± 0.00	2.00 (2.00 - 2.00)	1.000

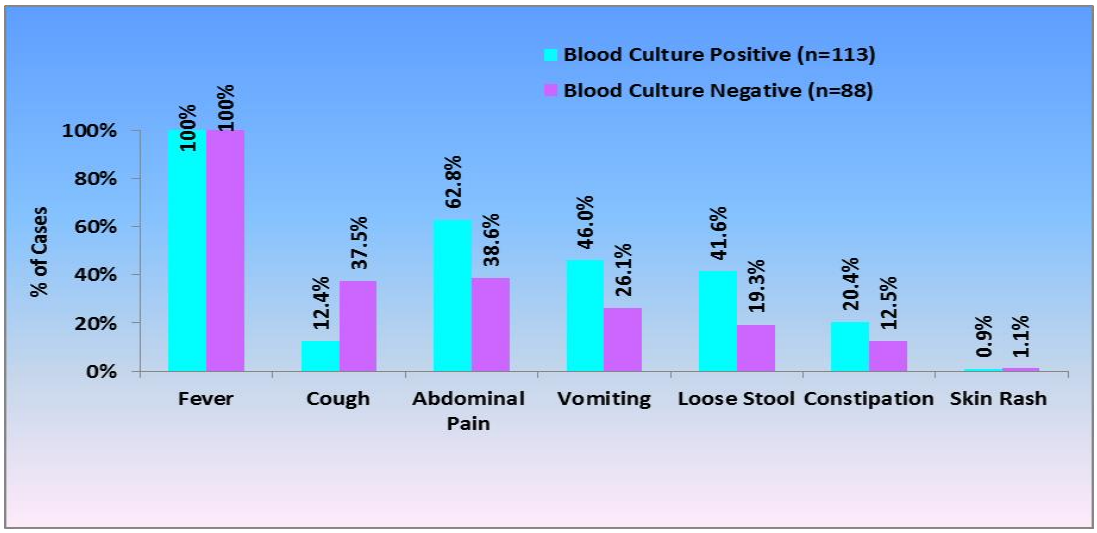

Fig 2: Correlation of clinical symptoms with diagnosis of enteric fever

The mean temperature was 38.32 ± 0.53 and 38.13± 0.52 respectively in patients with blood culture positive enteric fever and culture negative fever, and was statistically significant (p-0.015).

Table 3: Correlation of vitals in diagnosis of culture positive enteric fever

	BLOOD CULTURE		P Value
	POSITIVE	NEGATIVE	
	Mean ± SD	Mean ± SD	
HR	88.27 ± 10.68	89.07 ± 11.27	0.610
RR	24.26 ± 3.25	24.51 ± 2.82	0.560
TEMP	38.32 ± 0.53	38.13 ± 0.52	0.015
SBP	102.37 ± 5.17	101.77 ± 4.05	0.372
DBP	63.20 ± 4.36	64.05 ± 4.03	0.162

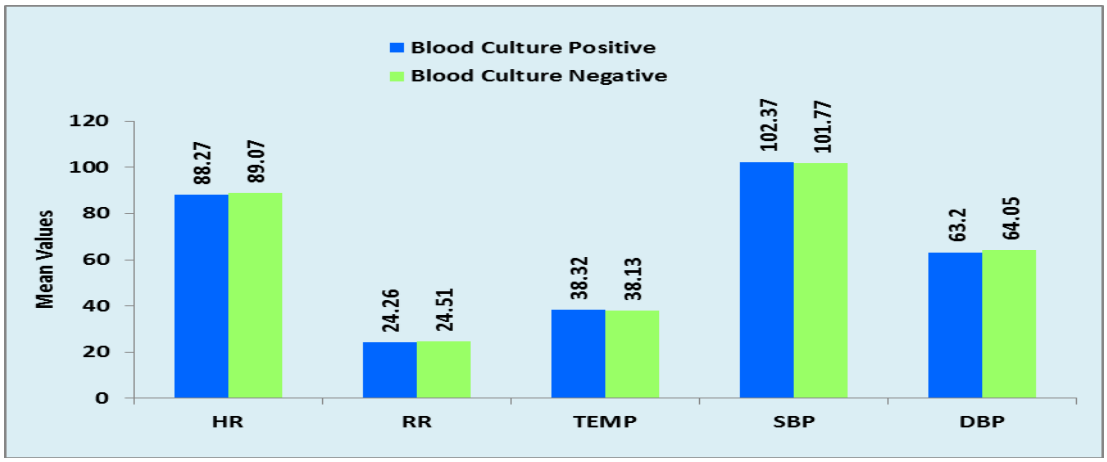

Fig 3: Correlation of vitals in diagnosis of culture positive enteric fever

Blood culture positive enteric fever was significantly associated with coated tongue (p-0.007), hepatomegaly (p-<0.001), splenomegaly (p-<0.001) and abdomen tenderness (p-<0.001).

Table 4: Correlation of clinical signs with diagnosis of culture positive enteric fever

	BLOOD CULTURE				P Value
	POSITIVE (n=113)		NEGATIVE (n=88)		
	Frequency	%	Frequency	%	
Coated Tongue	40	35.4%	16	18.2%	0.007
Skin Rash	0	0.0%	1	1.1%	0.438
Hepatomegaly	63	55.8%	20	22.7%	<0.001
Splenomegaly	50	44.2%	13	14.8%	<0.001
Abdominal Distension	1	0.9%	0	0.0%	1.000
Abdominal Tenderness	49	43.4%	15	17.0%	<0.001

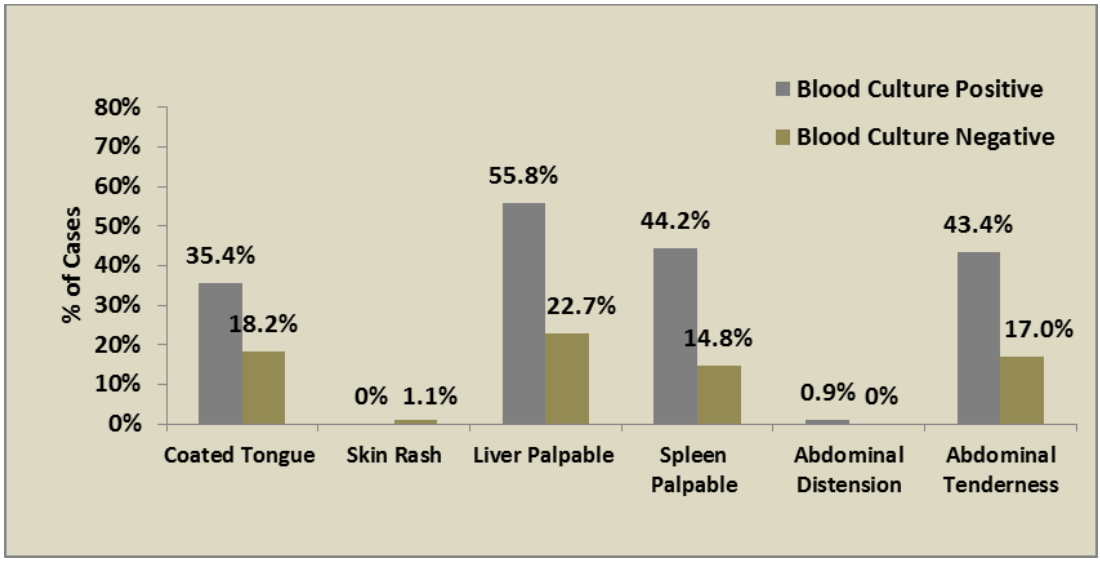

Fig 4: Correlation of clinical signs with diagnosis of culture positive enteric fever

The mean value of hemoglobin was lower in culture positive fever (11.2±1.48) compared to culture negative group with a mean hemoglobin of 11.79 ± 2.04 (p-0.004). Eosinopenia (<1%) was found in 92.9% of blood culture positive Enteric fever that significantly higher compared to culture negative patients. (p<0.001)

Table 5: Correlation of laboratory markers with diagnosis of enteric fever

	BLOOD CULTURE +VE (n=113)		BLOOD CULTURE -VE (n=88)		P Value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Hb	11.22 ± 1.48	11.20 (10.55 - 11.95)	11.79 ± 2.04	11.85 (10.83 - 12.98)	0.004
TLC	8508.06 ± 3361.04	7900.00 (6250.00 - 9850.00)	10365.91 ± 8104.40	8450.00 (5650.00 - 12650.00)	0.455
Neutrophil	62.13 ± 12.38	64.00 (53.90 - 70.60)	59.73 ± 17.15	60.15 (48.13 - 72.30)	0.331
Lymphocyte	30.04 ± 12.20	27.70 (21.70 - 37.80)	32.84 ± 16.43	32.40 (20.95 - 46.33)	0.242
Eosinophil	0.23 ± 0.58	0.00 (0.00 - 0.10)	1.59 ± 6.51	0.10 (0.00 - 1.45)	0.001
Monocyte	4.59 ± 2.99	4.60 (3.50 - 5.40)	4.36 ± 1.56	4.60 (3.80 - 5.40)	0.896
Plateletes Count	2.61 ± 0.89	2.41 (2.13 - 2.88)	2.77 ± 1.12	2.54 (2.07 - 3.04)	0.671

Table 6: Significance of Lab markers in diagnosis of blood culture positive enteric fever

Lab markers	BLOOD CULTURE				P Value
	POSITIVE (n=113)		NEGATIVE (n=88)		
	Frequency	%	Frequency	%	
Eosinopenia					
0 - 1%	105	92.9%	66	75.0%	<0.001
>1%	8	7.1%	22	25.0%	
CRP					
>1	106	93.8%	73	83.0%	0.015
<=1	7	6.2%	15	17.0%	
WIDAL					
Positive	70	61.9%	16	18.2%	<0.001
Negative	43	38.1%	72	81.8%	
TYPHIDOT					
Yes	70	61.9%	28	31.8%	<0.001
No	43	38.1%	60	68.2%	

Table 7: Diagnostic value of Lab markers

	Sensitivity	Specificity	PPV	NPV	Accuracy
Eosinopenia	92.9%	25.0%	61.4%	73.3%	63.2%
CRP	93.8%	17.0%	59.2%	68.2%	60.2%
WIDAL Test	61.9%	81.8%	81.4%	62.6%	70.6%
Typhidot	61.9%	68.2%	71.4%	58.3%	64.7%

ROC curves comparing the diagnostic value of various tests was suggestive of The AUC for widal was 0.719 (95% CI 0.647-0.790), typhidot was0.651 (95% CI 0.574-0.727), eosinophilia0.590 (95% CI 0.509-0.670), CRP0.554 (95% CI 0.473-0.635) . Best AUC was observed for Widal test.

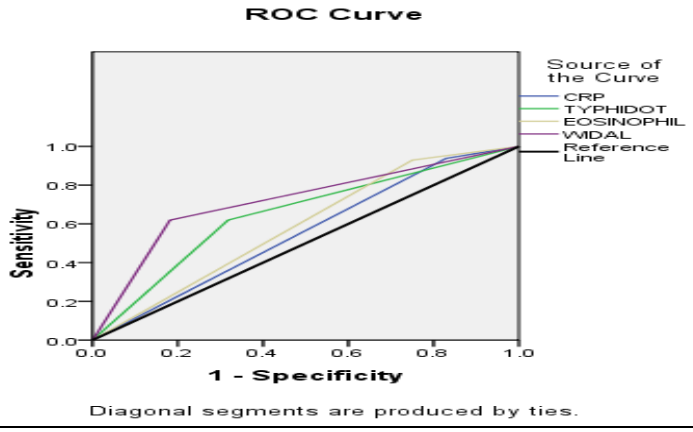

Fig 5: ROC Curve

Table 8: Area under curve

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error[a]	p value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
WIDAL	.719	.036	<0.001	.647	.790
TYPHIDOT	.651	.039	<0.001	.574	.727
EOSINOPHIL	.590	.041	.029	.509	.670
CRP	.554	.041	.187	.473	.635

Discussion

This study was done to compare the utility of clinical and laboratory markers in diagnosis of culture positive Enteric fever in children. Data from this study suggests that children with complaints of fever ≥5days, with blood culture positive for Enteric fever had hepatomegaly, splenomegaly, abdominal tenderness, eosinopenia, raised CRP, positive Widal & Typhi dot, which was statistically significant.

Mean duration of fever in patients with culture positive enteric fever was 6.81±1.72days and in patients with culture negative enteric fever was 6.60 ± 2.12 days. There was no significant difference in duration of fever in the two groups. This is probably due to the early visit to the medical facility by the parents these patients.

Our study showed that the presence of cough was against the diagnosis of enteric fever with P value of <0.001, which is statistically significant. Cough is probably not a major symptom in enteric fever and its presence was more in favour of another etiology, likely a respiratory cause of fever.

In our study, frequency of abdominal pain, vomiting and loose stools were important symptoms which were also statistically significant in culture positive patients.

Correlation of clinical signs with diagnosis of enteric fever

Despite relative bradycardia being a known sign of enteric fever, but we did not observe this finding in our study. Similarly, respiratory rate variation was also not a significant finding in our enrolled patients in either group. We observed statistically significant high grade fever in culture positive enteric fever patients.

Our study shows coated tongue is more frequent in blood culture positive enteric fever, i.e. in 40(35.4%) patients as compared to blood culture negative enteric fever, i.e. 16(18.2%) (p≤0.007). Our result was against a study done by Kuvandik C et al [8] that showed no significant result with coated tongue in enteric fever. Though the results were in concordance to Kuvandik et al [8] study with statistically significant hepatomegaly and splenomegaly.

Abdominal tenderness was found in 49(43.4%) patients of blood culture positive enteric fever and 15(17%) patients of blood culture negative enteric fever, which is statistically significant (p<0.001). Tender hepatomegaly was noticed in 80% of patients with enteric fever in a study by Britto et al [11].

Correlation of laboratory parameters in enteric fever

In our study, haemoglobin was lower in blood culture positive enteric fever compared to blood culture negative fever with p value of ≤0.004. A study by Farmakiotis et al[12] showed a median hemoglobin of 12.9 (11.43–13.65) g/dL.

We found eosinopenia in 92% of patients with culture positive fever with significant difference between the two groups p value -<0.001. Similar results were found in a study by Jog et al [13], Davies et al [14] and Pandey et al [15].

In our study, we found that CRP was higher in blood culture positive enteric fever as compared to blood culture negative enteric fever, which is statistically significant with p≤0.001. Our results were comparable to another study that showed raised CRP in culture positive typhoid fever with a mean of 4.3 [1.2-15] mg/dl Choo KE et al [16].

We found widal positive (>1:160) in 61.9% of patients with culture positive enteric fever and in 18.2% in culture negative patients (p value <0.001).Davies et al(22) found in their study that Widal test was positive (defined as S. typhi O antigen >120 and either S. typhi H or S. paratyphi H antigen titres>120) in 24 out of 64 patients (48.4%). Results for sensitivity and specificity for WIDAL were consistent

with the findings of Hosoglu et al[17], Wijedoruet al[18] and El-Sayedet al[19].

Our study showed Typhidot was positive in 61.9% patients with culture positive enteric fever compared to 31.8% in culture negative fever ($p \leq 0.001$). In our study, Typhi dot sensitivity and specificity results were comparable to study by Naheed et al[20], Olsen et al[21] and Khoharo et al[22].

Area under ROC for Widal were 0.719(95% CI 0.647-0.790); Typhidot 0.651 (95% CI 0.574-0.727); Eosinopenia 0.590(95% CI 0.509-0.670); CRP 0.554 (95% CI 0.473-0.635). CRP is a non-specific marker of infection and can be elevated in any infection. So, in the clinical context of suspicion of Enteric fever, Widal test is probably the best diagnostic marker for enteric fever. However, individual sensitivity and specificity of each of them including Widal test, are modest only. So, these tests are best used complementary to each other.

Limitations of Study

1. Sample size of the study was small so it is not possible to generalize the results.
2. This study did not evaluate the timing of the blood sampling of the patient.
3. Clinical signs and symptoms are not very specific which may occur in other infectious diseases.
4. Seasonal variation of Enteric fever as a confounding factor was not removed.
5. Socio-economic status as a confounding variable was not removed
6. Antibiotics taken prior to enrollment as a confounding factor was not removed.

Recommendations

1. All patients admitted with fever ≥ 5 days should be screened for Enteric fever.
2. Standard guidelines should be developed in our country regarding apporach to enteric fever on the basis of fever ≥ 5 days with hepato-splenomegaly, abdominal tenderness, coated tongue, eosinopenia, raised CRP, positive Widal and typhidot positive.
3. Role and efficacy of eosinopenia, raised CRP, Widal, typhidot needs to be evaluated in randomized control trial in large study population.
4. The timing of sampling of widal and typhidot should be evaluated.
5. Blood culture is gold standard for diagnosis of Enteric fever

In conclusion, clinical and laboratory findings can help the clinician to diagnose enteric fever in the absence of microbiological confirmation. Complications are rare in Enteric fever especially in cities where health care facility is easily accessible.

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