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CROSS SECTIONAL STUDY TO STUDY CLINICAL PROFILE OF BLOOD CULTURE POSITIVE TYPHOID FEVER PATIENTS

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ABSTRACT

Introduction: Typhoid fever is highly prevalent in India with hight rate of morbidity and mortality. There is paucity of data from India on the clinical and investigational profile of proven typhoid fever patients. Thus this study has been taken up to study these aspects of typhoid fever.
Aims and objectives: To study clinical profile of blood culture positive typhoid fever patients.
Materials and Methods: Study was carried out in the Department of Pediatrics, Northern Railways Central Hospital, New Delhi. 100 patients with fever of more than 3 days duration were taken. Detailed history and examination of these patients were done and noted on a proforma .Investigations like Typhidot-M, Blood culture & S. Widal were done. Blood culture was done in second week of fever. Other tests for evaluation of other causes of fever were also done.
Results: Clinical and investigative profile of typhoid fever patients had shown that distribution in male gender, hepatomegaly and raised ESR were associated with blood culture positive patients.
Conclusion: .In our study we found that clinical profile of blood culture positive patients were found to have comparable symptoms and signs when compared to blood culture negative patients. Distribution of male patients, hepatomegaly and raised ESR were found to be significantly associated with blood culture positivity.

INTRODUCTION

According to the World Health Organization (WHO), Confirmed case of typhoid fever is defined, as a patient with fever (> 38°C) that has lasted for at least three days, with a laboratory confirmed positive culture of S. typhi (Rapid Diagnosis of Typhoid Fever, 2006). Probable case of typhoid fever is a patient with fever (> 38°C) that has lasted for > 3 days, with a positive serodiagnosis or antigen detection test but without S. typhi isolation (Rapid Diagnosis of Typhoid Fever, 2006). Enteric fever is endemic in India with a rate of incidence ranging from 102 to 2219 per 100,000 in the population (Jog, 2008). An incidence of 980/100000 was recorded in late 1990's in a five year community based study of children in Delhi (Sinha *et al*., 1999; Ananthanarayan, 2009).

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Enteric fever can involve various organs leading to a wide range of presentations from uncomplicated to complicated typhoid fever involving multiple organs (Abro *et al*., 2009). Blood culture is generally recognized as the most useful diagnostic test for detecting S. typhi. However, a single blood culture is estimated to be only 50% to 80% sensitive (Farooqui *et al*., 1991). History, physical findings and fever pattern are suggestive but can neither confirm nor exclude typhoid (Farooqui *et al*., 1991). The disease is predominantly a disease of school going children and young adults and is reported to be milder in infants and young children (Palacios *et al*., 1981; Baver *et al*., Baver *et al*., 1951). Various organs have been involved in the course of typhoid fever, resulting in wide array of presentation (Hoffman *et al*., 1975).

SETTING

The study was carried out in the Department of Pediatrics , Northern Railway Central Hospital, New Delhi.

Patients of age group 1-14years of both sexes with history of fever of more than 38^0 C for more than three days duration were included in this study. Patients with prior history of intake of antibiotics and who had local infections were excluded from the study.

SAMPLE SIZE

Parents of patients were told about the nature of study and consent was taken. Ehical committee clearance was taken. Proforma of 100 patients from opd and indoor admission with fever of greater than 3 days duration was filled with detailed clinical history and examination was filled .Blood culture and other panel of tests for fever were sent. Serum widal was sent in 2nd week of fever by tube method.

Sample collection

Blood and Serum samples were collected for, blood culture, hemogram, ESR, peripheral smear for malarial parasite ,Indirect coombs test for Plasmodium, liver and kidney function tests. S. Widal was sent in second week of fever by tube method. Urine routine microscopy and urine culture sensitivity were also sent.

BLOOD CULTURE (BACT/ALERT- PF)

These culture bottles are used with BacT/ALERT Microbial Detection System. Its a quantitative procedure for enhanced recovery and detection of bacteria (aerobic and facultative anaerobic) microorganisms from blood. It determines if microorganisms are present in blood taken from a patient suspected of having bacteremia.

PRINCIPLE OF THE TEST

The method utilizes a colorimetric sensor and reflected light to monitor the presence and production of carbondioxide dissolved in the culture medium. If microorganisms are present in the test. Carbondioxide is produced as the organisms metabolize the substrates in the culture medium.When growth of the microorganisms produces CO2, the color of the gas permeable sensor installed in the bottom of the each culture bottle changes from blue green to yellow.The lighter color results in an increase of reflectance units monitored by the system. Bottle reflectance is monitored and recorded by the instrument every 10 minutes.

Contents

16 ml of complex media and 4ml of charcoal suspension. Media consists of Soyabean casein digest, Brain heart infusion solids, Sodium polyanethole sulfonate, Pyridoxine, Menadione, Hemin,L –cysteine, Amino acids Carbohydrate substrates in purified water. Bottle has an atmosphere of CO2 in oxygen and nitrogen under vaccum.

Specimen Collection and Prepration

Proper skin disinfection is an essential requirement to reduce the incidence of contamination..Culture bottle is labeled. Upto 4 ml of sample obtained and transferred to the bottle under aseptic precautions. The blood culture bottle should be transported to the main laboratory at15-40 degree C temp. In the laboratory blood culture bottles are incubated at 37 degrees C and checked for growth at1,2,3, and 7 days.

Fig1. BacT/ALERT culture bottle showing positive growth.Blood culture bottles kept in the incubator

For days1,2and 3,only bottles showing signs of positive growth are cultured on agar plates. On day 7 all bottles are subcultured before being discarded as negative (WHO, ?).

After bact-alert (blood culture) positivity for growth of bacteria,subcultures are made.

Colony characteristics: On blood agar,S.typhi and S.paratyphi produce non hemolytic smooth white colonies.Salmonella produce lactose non fermenting smooth colonies on MacConkey agar:

Biochemical tests were done to diagnose growth of salmonella typhi by recommended standard protocol (Mishra, 1991). During examination of patients liver span was measured and span higher for corresponding age was taken as hepatomegaly (Ananthanarayan *et al*., 2009). Splenomegaly was measured along the axis towards umbilicus from left coastal margin. Leucopenia was taken as TLC less than 4000 and Thrombocytopenia as Platelet count less than 1.5 lakh. Data of patients was collected on a proforma and filled on excel sheet.2x2 contingency tables were made. Chi square test, Fisher's exact test and Student t tests were applied to calculate significance and p value <0.05 was considered statistically significant. Demographic, clinical data, laboratory Parameter details were noted and analysed using SPSS software version 17.

OBSERVATIONS AND RESULTS

Demographic, clinical data, laboratory Parameter details were noted and analysed using SPSS software version 17(SPSS Inc., Chicago, IL, USA).

Fig. 2. BacT/Alert incubator and computerized result showing positive growth in culture bottle

In our study patients in age group 5-8yrs were maximally affected by typhoid fever followed by 9-12 yr age group. In our study age ranged from 1.5 yrs to14 yrs with mean age of 8.2 yrs +/-3.3SD.Age group 6-11 years was affected most. 50% of patients belonged to this group .In this age group males were affected more .In our study population of 100 patients, 46 patients were positive for blood culture. When we compared blood culture results in both genders then blood culture positivity in male gender is found to be statistically significant ($p<0.05$). When we had compared the blood culture results in various age groups then we found that there was no statistical significance($p>.05$).Blood culture positivity ranged from 1.5 yrs to 14 yrs with mean age 7.880+-3.24SD and its association with age distribution is found to be statistically not significant($p>0.05$). When we plotted the distribution of Blood culture results in various age groups , then maximum positivity is seen in age group 5-8yrs followed by 9-12yrs.

Table7 Comparison of Symptoms and Signs in Blood culture positive and negative patients. and their respective p value

DISCUSSION

Out of 100 patients 57%patients were male and 43%were female. 40%patients belonged to age group5-8 years followed by 35% in age group 9-12 yrs and 14% were <5yrs. with range of 1.5-14 yrs and mean age of presentation 8.2+/-3.3SD . Age distribution of definite and probable cases of typhoid fever was maximum in 5-8 yrs followed by 9-12 yrs. Similar results are seen in earlier studies that typhoid fever is more prevalent in boys (Escamilla *et al*., 1986) and in school going children and is milder in infants and young children (Palacios *et al*., 1981 Ashcroft, 1964; Baver *et al*., 1951). In our study, 15.2% of all patients with typhoid fever were under 5 years, which is close to the figure in some series (Ahmet Yaramis, 2001; Johnson, 1981; Oh, 1997).

Blood culture was positive in 46% of cases which is comparable to other studies by Bhutta *et al*. (1999), Dheer *et al*. (2012), Mishra *et al*. (1991) and this may be attributable to the difficulties of obtaining large enough blood volumes for cultures from children and it is a low bacteremic illness. The common signs and symptoms present in patients (both adults and children) with culture-proven typhoid fever from nine published studies are compared and summarised in Table 8. The signs that are most commonly reported are fever followed by diarrhoea, vomiting, abdominal pain, headache, splenomegaly, anorexia and hepatomegaly. Our patients with blood culture positivity for S. typhi also showed the similar clinical features .In our study we found that presence of hepatomegaly in culture positive patients is statistically significant ($p=0.001$). The Indonesian study, however, concluded that no symptom and sign combination performed adequately to be useful in clinical practice for identifying typhoid (Vollaard *et al*. 2005).We can also conclude from our study that no clinical signs and symptoms can be combined to diagnose typhoid fever as there was no statistical significance of distribution of clinical symptoms and signs in blood culture positive and negative patients.

Significance of Clinical features in Blood culture positive patients

In the current study, S. typhi were responsible for a total of 46% cases of enteric fever. In the earlier literature it is seen that S.typhi was responsible for nearly same % of cases of enteric fever (WHO, 2003). Amongst the definitive cases of typhoid fever ie.blood culture positive for S, typhi 39% belonged to5-8yr age group followed 37%in9-12 yr age group and 15.2% in <5year old age group. After the age of 20, there is a reduction in the incidence, which is probably due to immunity acquired from clinical or subclinical infection with increasing age. In our study 56.1%males were blood culture proven typhoid fever patients and this finding is highly significant statistically. Our findings are comparable to other studies which also show that more cases are reported among males than females, probably as the result of more exposure to infection (Park, 2005). Table 9: Comparison of clinical features of our study with a large study conducted at India (Mishra, 1991) Pakistan (Karachi) (Cleary *et al*., 2004) and Bangladesh (Ahmet Yaramis *et al*., 2001). Fever was the most consistent complaint (100%) which is also seen in other studies (Mishra, 1991; Cleary *et al*., 2004; Ahmet Yaramis, 2001).

Table1.Summary of age distribution characteristics

AGE							
N	Minimum	Maximum	Range	Mean	Std. Deviation	Median	Std. Error of Mean
100	1.5	14.0	12.5	8.210	3.3425	8.000	.3343

Table 2. Age group distribution

Age	Male	Female	Total
1-5yrs	11	11	22
6-10yrs	28	22	50
11-14yrs	16	12	28

Sociodemographic profile distribution in blood culture positive patients

Table 3. p value calculation for gender association in blood culture positive patients

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	5.487[a]	1	.019		
Continuity Correction[b]	4.579	1	.032		
Likelihood Ratio	5.565	1	.018		
Fisher's Exact Test				.026	.016
N of Valid Cases[b]	100				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 19.78.
b. Computed only for a 2x2 table

Table 4. Blood culture test results in various age groups

			AGE GROUP				Total
			< 5	5-8	9-12	13-14	
BLOOD CULTURE	POSITIVE	Count	7	18	17	4	46
		% within BLOOD CULTURE	15.2%	39.1%	37.0%	8.7%	100.0%
	NEGATIVE	Count	7	22	18	7	54
		% within BLOOD CULTURE	13.0%	40.7%	33.3%	13.0%	100.0%
Total		Count	14	40	35	11	100
		% within BLOOD CULTURE	14.0%	40.0%	35.0%	11.0%	100.0%

Table 5.p value calculation for age distribution in blood culture positive cases

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.611[a]	3	.894
Likelihood Ratio	.617	3	.892
Linear-by-Linear Association	.169	1	.681
N of Valid Cases	100		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.06.

Table 6. Clinical profile in blood culture positive typhoid fever patients

Symptoms	No.of patients	Percentage in blood culture positive cases
Blood Culture	46	
Fever	46	100
Malaise and lethargy	38	82.61
Anorexia	34	73.91
Abdominal pain	31	67.39
Nausea	30	65.22
Vomiting	27	58.70
Diarrhea	11	23.91
Headache	16	34.78
Cough	13	28.26
Constipation	9	19.57
Burning micturition	7	15.22
Jaundice	3	6.52
Ileus	1	2.17
Obtundation	1	2.17
Intestinal perforation	1	2.17
Signs		
Hepatomegaly	31	67.39
Pallor	29	63.04
Coated tongue	22	47.83
Splenomegaly	13	28.26
Skin rash(rose spots)	0	0.00

Table 7. Comparison of Symptoms and Signs in Blood culture positive and negative patients. and their respective p value

Symptoms	Blood culture positive	Blood culture negative	P value
Cough	12(26.1%)	20(37%)	.242
Nausea	30(65.2%)	34(63%)	.815
Vomiting	27(58.7)	25(46.3%)	.216
Diarrhea	11(23.9%)	13(24.1%)	.985
Constipation	9(19.6%)	16(29.6%)	.247
Anorexia	34(73.9%)	34(63%)	.242
Abdo pain	31(67.4%)	29(53.7%)	.164
Headache	16(34.8%)	21(38.9%)	.672
Jaundice	3(6.5%)	4(7.4%)	.863
Malaise/lethargy	37(80.4%)	40(74.1%)	.451
Burning micturition	7(15.2%)	10(18.5%)	.661
Obtundation	1(2.2%)	0(0%)	.276
Ileus	1(2.2%)	0(0%)	.276
Intestinal perforation	1(2.2%)	0(0%)	.276
Pallor	29(63%)	32(59.3%)	.699
Rose spots	0(0%)	1(1.9%)	.354
Coated tongue	21(45.7%)	15(27.8%)	.063
Hepatomegaly	31(67.4%)	20(37%)	.002
Splenomegaly	13(28.3%)	16(29.6)	.880
Hb<11gm%	22(47.8%)	29(53.7%)	.558
Leucopenia(TLC<4000)	3(6.5%)	3(5.6%)	.598
Lymphocytosis(TLC>11000)	5(10.9%)	3(5.6%)	.598
Eosinophil count(<1%)	3(6.5%)	2(3.7%)	.763
Thrombocytopenia(Plt<1.5lac)	10(21.7%)	10(18.55)	.688
ESR>20	24(52.2%)	39(72.2%)	.038

Table 8.Comparison of Prominent clinical features in culture proven typhoid fever patients in various studies

	Ammah et al. 1999	Nsutebu et al.2003	Walia et al 2005	Mathura et al. 2005	Kumar et al. 2005	Papaevang elouet al. 2004	Ispahani et al. 2000	Sinha et al 1999	Siddiqui et al 2006	Our study 2012
Fever	+	+	+	+	+	+	+	+	+	+
Anorexia	+	+	−	−	−	−	−	−	+	+
Vomiting	+	+	+	+	−	+	+	+	+	+
Hepatomegaly	−	−	+	−	+	−	+	−	−	+
Diarrhoea	+	+	+	+	+	+	+	+	+	+
Abdominal pain	+	+	+	+	−	−	+	−	+	+
Splenomegaly	−	−	+	+	+	−	+	+	−	+
constipation	+	−	−	+	+	−	−	−	+	+
Headache	+	+	−	+	−	−	+	−	+	+
Intestinal perforation	−	−	−	−	+	−	−	−	−	+
Myalgia	+	−	−	−	−	−	−	−	−	-

Table 9. Comparison of clinical features of our study with a large study conducted at India 19Pakistan (Karachi) and Bangladesh

Clinical symptoms and signs	% in our study	%in a study KSCH,New delhi(drug sensitive,resistant cases%)	%in a study of Bangladesh.	%in Pakistan, Karachi study(2000 patients)
Blood culture positive	46	50	65	
Fever	100	100,100	100	95
Malaise and lethargy	82		50.76	
Anorexia	73		78.46	70
Abdominal pain	67	45.5,28.2	3.07	21
Hepatomegaly	67	81.8,92.3	16.92	37
Nausea	65			
Pallor	63		36.92	76
Coated tongue	58		32.3	20
Vomiting	47	36.3,33.3	20	39
Head ache	34		75.38	4
Splenomegaly	28	36.3,66.7	23.07	17
Cough	28	27.3,35.9	35.38	
Diarrhea	23	18.1,43.6	27.69	36
Constipation	19	0,17.9	23.07	4
Burning micturition	15		1.53	
Jaundice	6	0,5.1	9.18	2
Intestinal perforation	1			0.5
Obtundation	1		9.8	2
Ileus	1			1
Rose spots	0		3.07	

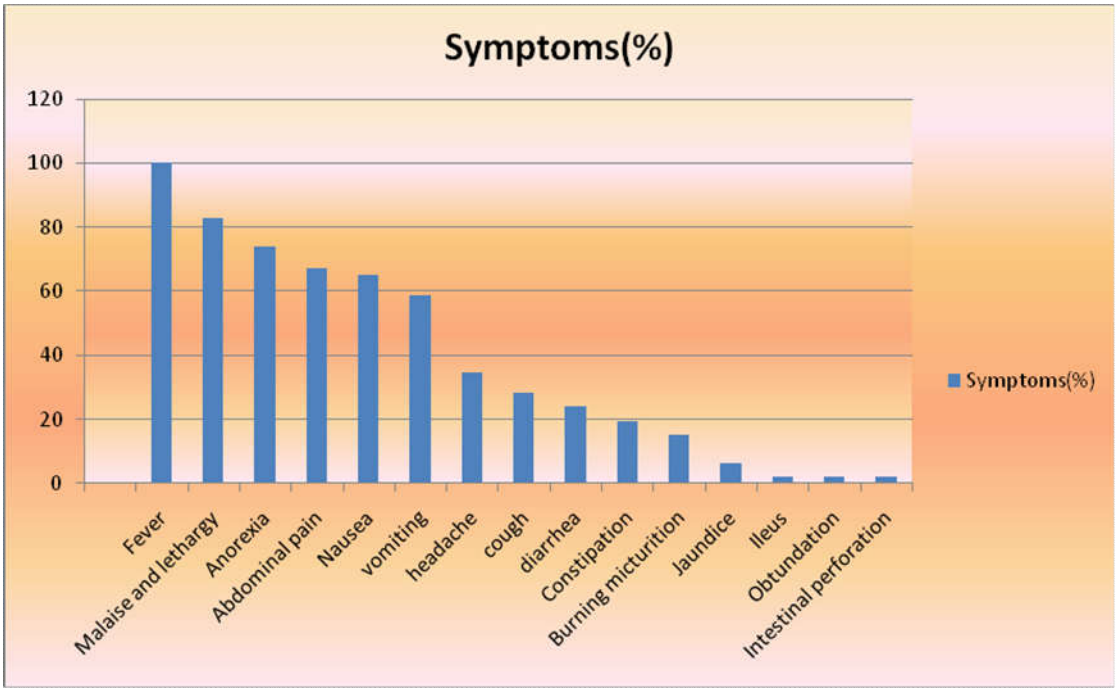

Fig. 1. Distribution of clinical profile (Symptoms%) in blood culture positive typhoid fever patients

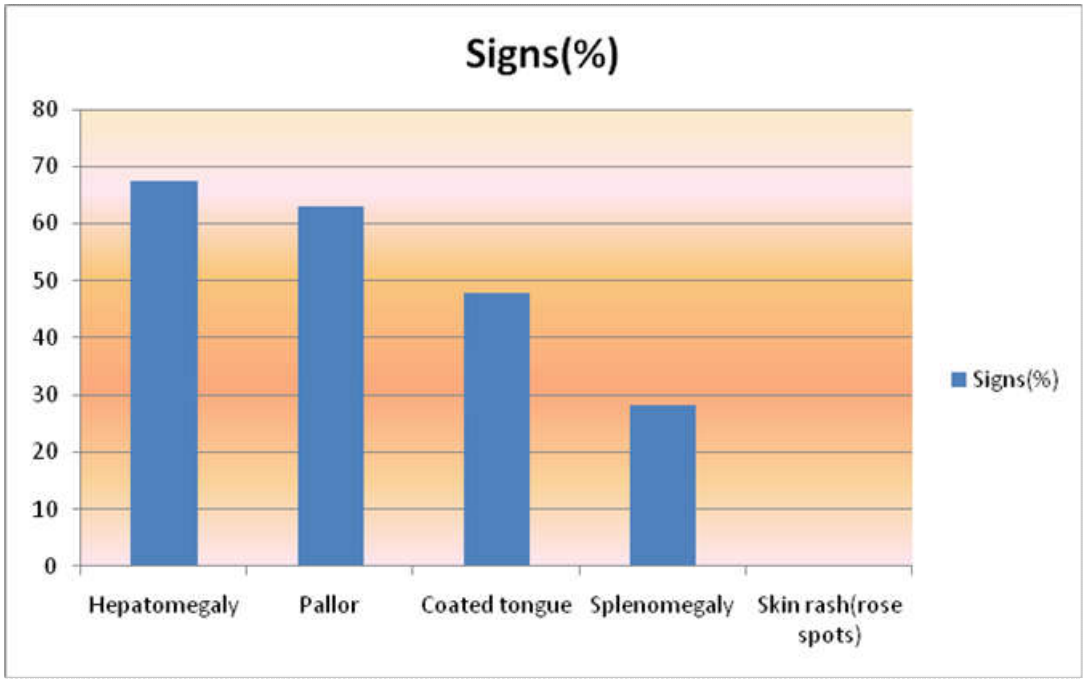

Fig. 2. Distribution of clinical profile (Signs%) in blood culture positive typhoid fever patients

Children in this series commonly presented with fever, anorexia, malaise, gastrointestinal symptoms, diarrhea and headache were which more common than constipation in this study, which is in accordance with the results from other studies (Oh, 1997; Laditan, 1981; Yap *et al*., 1998; Ahmet Yaramis *et al*., 2001; Rasaily, 1994; Secmeer *et al*., 1995). Hepatomegaly (67%) and splenomegaly (28%) were the major physical findings in our study. Seçmeer *et al*. reported that, in a large series in children with enteric fever, besides, 68.5% had elevated liver enzymes, while only 44.4% had hepatomegaly with or without splenomegaly (Secmeer, 1995). Hepatomegaly was observed 2.3 times more frequently than splenomegaly in our study.

Oh *et al*. and Laditan reported that, in their series, hepatomegaly was almost twice as frequently observed as splenomegaly (Laditan, 1981; Yaramis, 2001; Oh, 1997). Splenomegaly is found in 28.2 % of patientsin our study and most studies have reported it in 30-61% of young children (Mishra, 1991; Ahmet Yaramis, 2001; Mulligan, 1971; Kapoor *et al*., 1985; Duggan, 1975; Scagg, 1969). Rose spots were seen in 1% of blood culture negative patients. Rose spots are seen in minority of patients and are difficult to recognize in dark skinned individuals. Cutaneous involvement with S.typhi is common, including characteristic skin lesion associated with typhoid fever described as rose spots and is seen in 3% of patients in a study from Bangladesh (Ahmet Yaramis, 2001;

Cohen *et al*., 2006). Constipation was present in19.5% of cases. 1% of our patient has shown to have intestinal perforation. Late diagnosis or failure to respond to treatment may lead to serious complications, including gastrointestinal hemorrhage, perforation of the gut, and shock. Hb<11gm% was seen in47.8% of definite cases of typhoid fever. It is seen that Hb is normal in the initial stages but drops with progressing illness. Severe anemia is unusual and should make one suspect intestinal haemorrhage or hemolysis or an alternative diagnosis like malaria (IAP Guidelines, 2006). Only 6.5% of our blood culture positive patients had leucopenia, in contrast to 20-25% that is reported (IAP Guidelines, 2006). 10.9% patients had leucocytosis, a laboratory finding that is believed to cast a doubt and makes the diagnosis less probable. Eosinopenia is seen in 6.5% of patients of definitive typhoid fever. It is seen that eosinopenia often absolute may be present in 70-80% of cases. Presence of absolute eosinopenia offers a clue to diagnosis but does not differentiate it from other acute bacterial or viral infections.[42] Thrombocytopenia is seen in 21.7% of blood culture positive patients of typhoid fever. It is seen that overall prevalence of thrombocytopenia is around 10-15% (IAP Guidelines, 2006). ESR is high in 52.2% of blood culture positive and 72.2% in blood culture negative patients.

Conclusion

None of clinical symptoms and signs in typhoid fever have statistical association in proven blood culture positive patients with typhoid fever except Hepatomegaly and ESR positivity. Thus to diagnose typhoid fever one has to rely on specific blood tests as most of the clinical symptoms and signs are non specific.

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