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The utility of serological test in diagnosis of typhoid fever in children

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Abstract

Enteric fever or typhoid fever is a life-threatening multi-system infection common in underdeveloped nations. Blood cultures give unequivocal proof of infection and are the cornerstone of laboratory diagnosis. RDTs detect IgM within 2–3 days after infection. IgM indicates a recent infection, while IgG indicates a distant infection. Study goal: To examine the role of serological tests as a first test while waiting for blood culture results and to demonstrate IgM and IgG accuracy in recognizing typhoid illness in children. Cross-sectional research with analytic component done at the Karbala Children's Teaching Hospital. The research included 81 children with typhoid-like symptoms, including fever, headache, vomiting, and stomach discomfort. The investigation yielded hematological, biochemical, and serological outcomes. A blood culture was performed to verify the diagnosis. Most study participants (78/96.3%) had positive anti-salmonella IgM findings, whereas 32/39.5% did. Blood cultures diagnosed 47 (58%) study individuals with typhoid fever (Salmonella infection). Positive blood cultures provide 43 (91.5%) ciprofloxacin-susceptible isolates. Anti-salmonella IgM has 95.7% sensitivity and 5.6% specificity. 70.8% anti-salmonella IgM accuracy. Anti-salmonella IgG had 38.3% sensitivity and 61.1% specificity. Anti-salmonella IgG had 44.6% accuracy. The major sign of enteric fever is a high body temperature, along with anorexia, vomiting, stomach discomfort, and headache. The main risk factor is water availability. Serological tests with a positive IgM result serve a significant role in diagnosing typhoid fever and commencing antibiotic treatment early while waiting for blood culture results.

Keywords: Girls, Women, Premenstrual dysphoric disorder, Environmental factors

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Introduction

Salmonella typhi and Salmonella paratyphi cause enteric fever, often known as typhoid fever (TF), one of the most severe life-threatening illnesses widespread in developing countries and caused by Salmonella typhi and Salmonella paratyphi (1). High population density disadvantaged and impoverished places, insufficient sanitization, lack of pure drinking water, and poor socioeconomic status are potential contributors to the prevalence of sickness. Although the disease and its consequences have been recognized since the nineteenth century, the burden of TF has not changed (2). The chief causes of this disadvantage are inadequate diagnostic techniques and the emergence of drug-resistant infections (2). The most reliable diagnostic procedures are blood, bone marrow, and faecal cultures (3). Cultures provide solid evidence of the infection and antibiotic sensitivity information about the isolate (4). Etiology and propagation: Typhoid fever is caused by the Gram-negative bacteria Salmonella enterica subsp. enterica serovar Typhi. On the basis of the Multi-Locus Sequence Typing (MLST) subtyping system, the two most prevalent sequence types of S. Typhi are ST1 and ST2, which are now found worldwide (5, 6).

The evolution of untreated typhoid fever is often split into three separate phases, each lasting around one week. Throughout these periods, the patient grows weary and malnourished (7). In the first week, fever swings with bradycardia, lethargy, headache, and cough. Epistaxis and abdominal pain are prevalent. Leukopenia, eosinopenia, and lymphocytosis; Typhi-positive blood cultures (7). During the second week, the individual is often too exhausted to rise, has a temperature plateauing at 40 degrees Celsius, and has bradycardia with a dicrotic pulse wave. Delirium can generate serenity and agitation. Typhoid is referred to as "nervous fever" because to the delirium it causes. One-third of people have rose-colored spots on their lower breast and stomach (8). Third week: patient is poisonous, anorexic, and losing weight. Increasing bowel perforation risks aggravate abdominal distension and peritonitis.

Auscultation reveals tachypnea and lung base crackles. Metastatic signs appear (9). Typhoid patients need clinical treatment. Patients in locations with inadequate sanitation or unclean drinking water or who have travelled to endemic areas and have a three-day fever with GI symptoms (pain, constipation, or diarrhoea) are extremely suspect. First-week diagnosis is challenging, but lab tests help (10). Blood culture is fundamental to TF diagnosis. It is the most common exam. Blood cultures are more successful with larger sample volumes. Blood cultures for secondary bacteremia are more reliable, but 30% to 50% may be falsely negative, depending on method and timing (8). In the bacteremic phase, stool culture is less successful. Second and third-week stool culture is diagnostic.

Inflammation of intraluminal dendritic cells may make it positive for S typhi days after consumption. Later in the disease, stool cultures show gallbladder bacteria (11). Bone marrow is used to diagnose typhoid. Aspirated bone marrow is grown in agar. Due to more microorganisms in bone marrow, it's more sensitive than blood cultures (12). PCR has inconsistent effectiveness diagnosing typhoid illness. It can identify H and O antigen genes based on DNA (13).

Serological tests. Widal test: It was the mainstay of typhoid fever diagnosis for decades. The enteric fever serological test finds antibodies to O (surface) and H (flagellar) antigens. In this test, the serum is combined with a salmonella slurry containing particular antigens (14). Rapid diagnostic tests (RDTs): Typhidot and Tubex TF are among the most widely used RDTs within the more recently developed diagnostic devices for TF. There are a number of other tests available such as the Typhidot-M, the Multi-Test Dip-S-Ticks, Bioline, and Mega Salmonella however little data on their performance is available (15).

Typhidot test: It is an immune-chromatographic assay designed for the qualitative detection and differentiation of specific IgM and IgG antibodies against specific Salmonella typhi outer membrane protein (OMP) antigen in human serum or plasma. It is intended to be used as in vitro diagnostic of TF. Tubex test: A serological test kit (TUBEX™, IDL Biotech, Sweden) developed for the diagnosis of TF detects antibodies to the Salmonella enterica serovar Typhi lipopolysaccharide O9 antigen (16, 17). Enzyme-Linked Immunosorbent Assay (ELISA): ELISA identifies antibodies to the capsular polysaccharide Vi antigens, which is useful for identifying carriers but seldom helpful in acute illness (18,19). The objectives of this study are to examine the role of serological testing in the diagnosis of typhoid fever as an initial test while awaiting blood culture findings and to demonstrate the accuracy of IgM and IgG in children with confirmed typhoid fever.

Patients and methods

Study design, setting, and data collection time

This was a cross-sectional study with an analytic component conducted at Karbala Teaching for Children during a period of one year from Jan. 2019 to Jan. 2020.

Study Population and sample size

There are 120 children with suspicion of typhoid fever collected to participate in the study.

Inclusion criteria

The study included 81 children according to clinical features suggestive of typhoid fever such as fever of more than 3 days, headache, abdominal pain, nausea, and vomiting attended the hospital and were admitted to the Pediatric ward.

Exclusion criteria

39 children were removed from the research because they were taking antibiotics throughout their febrile illness, which might have affected the development of microorganisms in blood cultures and therefore the results. for data collection: The data were gathered by the distribution of a well-designed questionnaire (included as an appendix to the research after the citations) that was edited, evaluated, amended, and approved by a designated panel. It includes the subsequent:

- Demographic information (Age, gender, and residence).
- Possible source of infection.
- Clinical features.
- Duration of hospitalization.
- Investigation results included hematological, biochemical, and serological (CBC, CRP, LFT, ESR, GUE, and CSF). Blood culture was done to confirm the diagnosis.
- Management options and complications.

Serological tests (Anti-salmonella IgM and IgG)

Done by strip stick (Typhoid IgG/IgM Rapid Test Device) (Manufactured by CTK Biotech Located in San Diego County, California).

For whole blood, serum, and plasma specimens, hold the dropper vertically and administer 2 drops of the specimen (about 50 L) to the specimen well (S) of the test device, followed by 1 drop of buffer and the start of the timer. The results were analyzed after 10 minutes, and the entire experiment took 15 minutes. A blood culture was performed to isolate the pathogen in accordance with conventional methods, using two samples from two places taken one hour apart using an antiseptic technique. Needs microscopic examination, culture with 4 agars (XLD, MacConkey, Blood, Chocolate agar), and biochemical for testing bacterial characteristics. By which can detect salmonella but not its subspecies.

Statistical analysis

Version 26 of Statistical Package for the Social Sciences (SPSS) was used to analyze the data. Mean, standard deviation and ranges are shown for the data. The presentation of categorical data by frequencies and percentages. Determined were the sensitivity and specificity of serological tests.

Results

The total number of study patients was 81. All of them were children suspected to have typhoid fever by clinical picture and evaluated for the role of serological tests to confirm the diagnosis.

Socio-demographic characteristics

The ages of the study participants ranged from 1 to 15 years, with a mean of 8.44 years and a standard deviation (SD) of 3.9 years. The majority of research participants were younger than 10 years 41 (50.6%). Regarding gender, the ratio of males to females was 1.18:1, with 44 males (54.3% of the total) to 37 females (45.7% of the total). Regarding domicile, 59 (72.8%) of the study's participants resided in urban areas.

Clinical information

The distribution of study patients by clinical information is shown in table (1). All the children with suspected typhoid fever presented with fever 81 (100%), 38 (46.9%) of them had fever duration for 7 – 14 days before admission and 33 (40.7%) of them were hospitalized for duration from 6 – 10 days.

Regarding clinical features, the most common associated clinical feature was anorexia 70 (86.4%) followed by vomiting 61 (75.3%).

Table 1.

Distribution of study patients by clinical information

Variable	No. (n= 81)	Percentage (%)
Clinical features		
Fever	81	100.0
Anorexia	70	86.4
Vomiting	61	75.3
Abdominal pain	57	70.4
Ill looking	46	56.8
Headache	45	55.6
Diarrhea	31	38.3
Chills	28	34.6
Hepatomegaly	10	12.3
Constipation	7	8.6
Splenomegaly	8	9.9
Toxicity	3	3.7
Hemorrhage	2	2.5
Jaundice	2	2.5
Obtundation	1	1.2
Duration of fever before admission (Day)		
< 7	36	44.4
7 – 14	38	46.9
> 14	7	8.6
Duration of hospitalization (Day)		
< 5	28	34.6
5 – 10	33	40.7
> 10	20	24.7

Investigation

In this study, means of Hb (10.27 g/dl); WBC (7.69 *10^3/ml); lymphocyte (35.08%); neutrophil (53.46%); monocyte (10.1%); PLT (239.58 *10^3/ml); TSB (1.74 mg/dl); SGPT (104.97 U/l); SGOT (133.75 U/l); CRP (43.74 mg/dl); and ESR (38.7 mm/h) as shown in table (2).

Table 2.

Investigation results

Variable	Mean ± SD	Range
CBC		
Hb (g/dl)	10.27 ± 2.0	4.0 – 13.4
WBC (* 10^3/ml)	7.69 ± 3.4	2.8 – 24.5
Lymphocyte (%)	35.08 ± 15.5	2.95 – 71.1
Neutrophil (%)	53.46 ± 20.2	2.2 – 87.9
Monocyte (%)	10.1 ± 5.1	4.0 – 24.6
Platelet count (* 10^3/ml)	239.58 ± 134.7	17.0 – 592.0
Retics (%)	1.19 ± 0.43	0.71 – 1.87
LFT		
TSB (mg/dl)	1.74 ± 5.2	0.13 – 27.0
Direct	0.34 ± 0.77	0 – 3.39
SGPT (U/l)	104.97 ± 235.98	9.4 – 1510.0
SGOT (U/l)	133.75 ± 156.6	18.0 – 795.0
CRP (mg/dl)	43.74 ± 46.2	0.32 – 201.0
ESR (mm/h)	38.7 ± 30.3	8.0 – 95.0

Serological tests

Figure 1 shows the distribution of study patients by serological test results for salmonella infection. Most of study patients showed positive anti-salmonella IgM results 78 (96.3%); while 32 (39.5%) of them showed positive anti-salmonella IgG results.

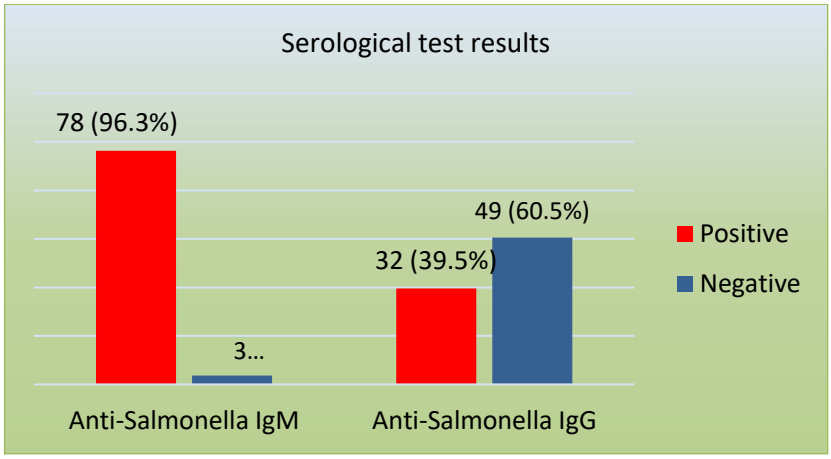

Figure 1.

Serological test results for salmonella infection

Blood culture results (Diagnosis)

Tables 3 show the blood culture results. In this study, 47 (58%) of study patients were diagnosed with typhoid fever (salmonella infection).

Table 3.

Distribution of study patients by blood culture results

Blood culture results	No. (n= 81)	Percentage (%)
Positive	47	58.0
Negative	18	22.2
Not done	11	13.6
Contaminated	5	6.2

Sensitivity, specificity, and accuracy of serological tests

Anti-salmonella IgM

Table 4 shows the sensitivity, specificity, and accuracy of anti-salmonella IgM result. The sensitivity of anti-salmonella IgM was 95.7%, while the specificity was 5.6%. Accuracy of anti-salmonella IgM was 70.8%

Table 4.

Sensitivity, specificity, and accuracy of anti-salmonella IgM result

Anti-salmonella IgM result	Blood culture result		
	Positive	Negative	Total
Positive	45	17	62
Negative	2	1	3
Total	47	18	65
Sensitivity and specificity	95.7%	5.6%	70.8%
	Sensitivity	Specificity	Accuracy

Anti-salmonella IgG

Table 5 shows the sensitivity, specificity, and accuracy of anti-salmonella IgG result. The sensitivity of anti-salmonella IgG was 38.3%, while the specificity was 61.1%. Accuracy of anti-salmonella IgG was 44.6%.

Table 5.

Sensitivity, specificity and accuracy of anti-salmonella IgG result

Anti-salmonella IgG result	Blood culture result		
	Positive	Negative	Total
Positive	18	7	25
Negative	29	11	40
Total	47	18	65
Sensitivity and Specificity	38.3%	61.1%	44.6%
	Sensitivity	Specificity	Accuracy

Both anti-salmonella IgM and anti-salmonella IgG

Table 6 shows the sensitivity, specificity, and accuracy of both anti-salmonella IgM and IgG results. The sensitivity of both anti-salmonella IgM and IgG was 38.3%, while the specificity was 61.1%. Accuracy of both anti-salmonella IgM and IgG was 44.6%.

Table 6.

Sensitivity, specificity, and accuracy of both anti-salmonella IgM and IgG results

Both anti-salmonella IgM and IgG result	Blood culture result		
	Positive	Negative	Total
Positive	18	7	25
Negative	29	11	40
Total	47	18	65
Sensitivity and specificity	38.3%	61.1%	44.6%
	Sensitivity	Specificity	Accuracy

Discussion

In the present work, patients' age mean was 8.44± 3.9 years (ranging from 1 to 15 years). The highest proportion of patients was aged ≥ 10 years 41 (50.6%). Regarding gender, proportion of males was slightly higher than females 44 (54.3%) versus 37 (45.7%) with a male to female ratio of 1.18:1. About residence, 59 (72.8%) of study patients were living in urban area. Ninety six patients with culture proved typhoid fever were enrolled in Tyib et al study in 2017, 55 (57.2%) of them were males and 41 (43.8%) females, about 73% of them were from urban and 27% from rural area.

The age of the patients enrolled in this study were from 1 month -14 years with an average of 6.8 years (20). In comparison to a study conducted in 2016 by Kumar and colleagues, enrolled were 197 children with acute febrile illness and clinical symptoms associated with typhoid fever. The average age of the people under investigation was 7.431 years. The research comprised 101 (51.2%) female children and 96 (48.8%) male children, with a female to male ratio of 1.05:1 (21). Moore et al. observed a different outcome in their 2014 research of 500 children with fever. The median (IQR; range) age of the children was 2.7 years (1.1–8.0 years; 1 month to 15 years), and 264 (53%) of the children were boys, with a male to female ratio of 1.1:1 (22).

The differences are related to a variety of causes, as the life style, in which the general hygiene in food and drink they consume inside homes or outdoors and to the socioeconomic status of the enrolled families. Additional, the educational level of the parents determined their attendance for health center for management and follow-up and to provide adequate clean life indoor. This study revealed that all the children with suspected typhoid fever presented with fever 81 (100%), 38 (46.9%) of them had fever duration for 7 – 14 days before admission and 33 (40.7%) of them were hospitalized for duration from 6 – 10 days.

Regarding clinical features, the most common associated clinical feature was anorexia 70 (86.4%) followed by vomiting 61 (75.3%). By comparison, Tyib TH and others found in a study done in 2017, The length of fever prior to receiving medical attention ranged from 2 to 19 days, with a mean of around 7 days. The mean number of days required for fever to reduce ranged from 2 to 10 days. Aside from fever, headache was the most prevalent symptom (67.7%), followed by stomach discomfort (56.2%), and finally diarrhoea (31%) among the patients. The symptoms seen least frequently were disorientation (5%) and constipation (1%) (20).

In Mohammed et al study in 2014, all patients suspected to have typhoid fever had fever (100%), which was the commonest presenting sign, followed by headache in 59.5%, and vomiting in 58%, with the constipation been the lowest presenting clinical feature (21%) (23). Different finding reported by Moore and colleagues in their study in 2014, as found that temperature more than 39 oC was observed in 60% for 5-7 days. The commonest presentation was abdominal pain in 80%, vomiting and headache in 50% of them (22). A variety of factors determined the differences observed above, of these factors were study design, sample size, documentation of fever, maturity and general condition of the child, the severity and duration of the disease, presence of comorbid condition, use of antibiotics and other supportive measures.

Most of patients in this study showed positive anti-salmonella IgM results 78 (96.3%); while 32 (39.5%) of them showed positive anti-salmonella IgG results. By using ELISA assay, results in Majeed et al study in 2018, showed that the acute incidence of typhoid fever based on IgM antibody was 32.6%, while chronic incidence of IgG antibody was 2.7%, Both types of antibodies was positive 12% in patients (24). Another lower results noticed in Nirmala et al study in 2015, in which 71.9% of patients diagnosed with typhoid fever had positive IgM test, 11.5% of them had positive IgG test with 16.5% of others had both positive anti-salmonella IgM and IgG results (25). Differently, in total of 500 children with fever enrolled in Moore et al study in 2014, 106 (21.2%) patients had a positive IgM test (22).

Finally, Sultanna and colleagues in study in 2012 reported that among 150 blood samples from the suspected cases of typhoid fever, 106 (70.7%) were positive for IgM of Salmonella typhi by immunochromatographic test (26). This may suggest that the differences may return to difference in the area and the season of study, stage of disease, variation of individual immune response, the cultural and health level, and samples size in each study.

In fact, lateral flow immunoassay test is rapid, easy, reliable and is better test needed for the diagnosis of typhoid fever. In this study, sensitivity of anti-salmonella IgM was 95.7%, while specificity was 5.6%. Accuracy of anti-salmonella IgM was 70.8%. Also, sensitivity of IgG was 38.3%, specificity was 61.1% and accuracy 44.6%. Additionally, sensitivity,

specificity and accuracy of both IgM and IgG was 38.3%, 61.1% and 44.6% respectively. The current finding compared to Kumar et al study in 2016, According to their findings, typhidot IgM has a sensitivity of 96.43 percent and a specificity of 54.44 percent (21). Compared to Moore et al 2014 .'s study, in which IgM sensitivity was 59.4% (95% confidence range = 41–76) and specificity was 97.8% (95% confidence interval = 96–99), the current study's IgM sensitivity is 98% (95% confidence interval = 96–99) and specificity is 99.2%. In addition, they discovered that IgG produced more varied findings with decreased sensitivity and specificity (3.57 and 31.95 percent, respectively) (22).

In a 2012 study by Sultana et al., sensitivity and specificity of IgM were found to be 83.3% and 92%, respectively. The researchers concluded that IgM is quick, easy to conduct, field-applicable, and highly sensitive and specific for detecting antibodies in typhoid illness (26). In 2009, Narayanappa et al. did a research that yielded different results. IgM had a sensitivity of 92.6% and a specificity of 37.5%, respectively (27). The IgM was utilized differently depending on the duration of sickness prior to testing. Due to an allegedly growing IgM antibody response, the test was more sensitive when the length of sickness was more than 5 days. In addition, the high endemicity and incidence of typhoid fever in some nations may impact the tests' sensitivity and specificity (28).

As some studies have indicated, it is possible that fast diagnostic techniques are more sensitive than blood culture. Consequently, a result that looks to be a false-positive test in comparison to a blood culture may actually be a true-positive. This theory requires more testing. Alternatively, a false-positive result may be due to a previous infection with serotype typhi or another non-typhoid pathogen. Salmonella (29).

Conclusions

The major sign of enteric fever is a high body temperature, along with anorexia, vomiting, stomach discomfort, and headache. The main risk factor is water availability. Serological tests with a positive IgM result serve a significant role in diagnosing typhoid fever and commencing antibiotic treatment early while waiting for blood culture results. Ciprofloxacin is more effective against salmonella infections.

Ethical approval

The study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008. No formal ethical clearance was sought for conducting the study.

Conflicts of Interest

The authors declare that they have no competing interests.

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None

Study registration

Not required.

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