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ASSESSMENT OF CURRENT DIAGNOSTIC TESTS FOR THE DIAGNOSIS OF TYPHOID FEVER

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Abstract:

Introduction: *Typhoid fever is a potentially fatal multi-system disease caused mainly by the subspecies Salmonella enterica (S enterica) enterica serovar typhi and, to a lesser extent, by the related paratyphi A, B and C serotypes and others.*

Objectives: *To evaluate various methods of diagnosing typhoid fever in hospitalized patients and to determine which is the best for diagnosis.*

Study Type: *Retrospective cross-sectional study.*

Patients and Methods: *A total of 100 patients were selected from the Medicine department of District Headquarter Hospital, Haripur for the diagnosis of typhoid fever from April 2019 to April 2020. About 50 of them were tested for the Vidal test and the rest were performed for them blood culture.*

Results: *The widal test showed positive results in 14% of patients, the rest were negative. There was a significant difference between the two groups (p = 0.002), while blood cultures were negative in 86% of the cases and the remaining 14% were positive for other bacteria such as E. coli, Pseudomonas and Staphylococcus spp. There were significant differences between the two groups (p = 1).*

Conclusion: *The widal test is not useful in diagnosing the disease, and the blood culture was negative due to inadequate blood collection time.*

Key words: *Typhoid, Fever, Salmonella, Diagnosing*

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INTRODUCTION:

Typhus is a multi-system disease caused mainly by the subspecies Salmonella enterica (S. enterica) enterica serovar typhi and, to a lesser extent, by the related Para typhi A, B and C serotypes and others. It causes fever, malaise, diffuse abdominal pain and constipation. If left untreated, typhoid fever leads to delirium, intestinal hemorrhage, and intestinal perforation. Survivors can be left behind with long-term carriers[1-2]. Human beings are the only reservoir host for this disease. The diagnosis of this disease can be made using the Widal test, which is a diagnostic test that has been important for many years and consists in the determination of agglutinating antibodies against the H (flagella) and O (somatic) antigens of Salmonella typhi[3-4]. However, the major disadvantage of the Vidal test is its cross-reactivity with some other bacteria of the same type or with other pathogens. Other diagnostic tests are also used, such as blood culture, fecal culture for gallbladder bacterial excretion, urine culture, and bone marrow culture. The extensive test has been performed since the 1950s[5-6]. Currently, molecular methods are used to detect specific DNA sequences in clinical samples from patients. The food industry has been using PCR technology for several decades and guidelines for the quantitative PCR detection of Salmonella in food are published[7-8]. The aim of the study was to evaluate various methods of diagnosing typhoid fever in hospitalized patients and to determine which of them is the best for diagnosis.

PATIENTS AND METHODS:

This is a retrospective cross-sectional study of 100 patients consulted at the Medicine department of District Headquarter Hospital, Haripur for the diagnosis of typhoid fever from April 2019 to April 2020. Competent consent was obtained from patients. Data was collected that included demographic information such as age, gender, marital status, occupation, residence status, if available in hospital records. Inclusion criteria were patients with fever and leukopenia, while the exclusion criteria were other bacterial and viral diseases that cause fever. About 50 of them were tested for the Vidal test and the rest were taken for blood culture.

Blood culture

The skin was disinfected with 2% iodine solution, 10% iodine polyvidone, 70% alcohol or 0.5% chlorhexidine in 70% alcohol. The disinfectant should evaporate from the skin surface prior to blood sampling. Approximately 10 ml of blood was collected by venipuncture and then added to the blood culture bottles of the BacT / ALERT machine (which is an automated system for rapid microbial detection). Ideally there were 2 bottles: BacT / ALERT FA (green label) which is intended for aerobic breeding and BacT / ALERT FN (orange label) which is intended for anaerobic breeding should be used for each set of cultures drawn. After the bottles are inoculated with the sample, the patient name and date are labeled on the sample, then immediately loaded into an automatic analyzer and incubated for up to 7 days for Salmonella. Each bottle of BacT / ALERT® contains sterile culture medium and is equipped with a colorimetric sensor that turns from gray to yellow in the presence of CO2 produced by growing microorganisms. After the bottles are loaded, the colorimetric sensors are scanned every 10 minutes. Upon detection of growth, the system generates an audible and visual alarm and the sample data is recorded. After positive growth was detected, a subculture was performed using a sterile syringe in which a portion of the blood from the positive bottle was poured onto agar media (chocolate, blood, Salmonella Shigella and MacConkey) and spread over the agar using a sterile loop. After 24 hours, we tested the plate for Salmonella on MacConkey agar: smooth colonies were observed that did not ferment lactose, and smooth white non-hemolytic colonies were observed on blood agar.

Extensive test

Reagent and samples were brought to room temperature. Approximately 50 µL of a serum sample should be tested and one drop of each control placed in separate circles for the slide test. Vigorously vortex the antigen or vortex before use. Add 1 drop of antigen to each circle next to the test sample. Mix with a disposable mixer and spread over the entire surface closed with a circle. Rotate the slide gently for 1 minute and watch for agglutination.

Slide agglutination method (titration)

This is done for samples that showed positive agglutination in the qualitative test. Using a micropipette, add 80 µL, 40 µL, 20 µL, 10 µL and 5 µL of the undiluted serum to separate test slide circles. Place 1 drop (50 µl) of antigen in each circle next to the test sample. Mix with a disposable mixer and spread over the entire surface closed with a circle. Rock the slide gently back and forth and observe macroscopically for agglutination for 1 minute.

Reading and interpretation

Examine macroscopically for the presence or absence of lumps within 1 minute after removing the slide from the rotator, comparing the test results with a control serum. The reactions obtained by titrating the glass slides are roughly equivalent to those that would occur in a tube with serum dilutions of 1/20, 1/40, 1/80, 1/160, and 1/320, respectively. If a reaction is found, it is

recommended to confirm the reaction and determine the titer with a test tube.

Statistical analysis

The data was statistically analyzed using:

• Descriptive statistics: percentages are calculated

• Inference Statistics: Chi-square Tests and Fisher's Exact Test All of these activities were performed with Minitab version 13.20. The value of $p \leq 0.05$ was considered statistically significant.

RESULTS:

A total of 100 patients were assessed for the diagnosis of typhoid fever. They complained of an enlarged spleen and the complete blood count showed leukopenia. They were sent for a Vidal examination and blood culture to assess their benefits in diagnosis. A total of 50 of them were tested with the Vidal test. About 50 (50%) of them are men and the rest are women (50%). The remaining 50 patients were screened for blood culture, 48% of them were male and the remaining 52% were female (Figures 1 and 2).

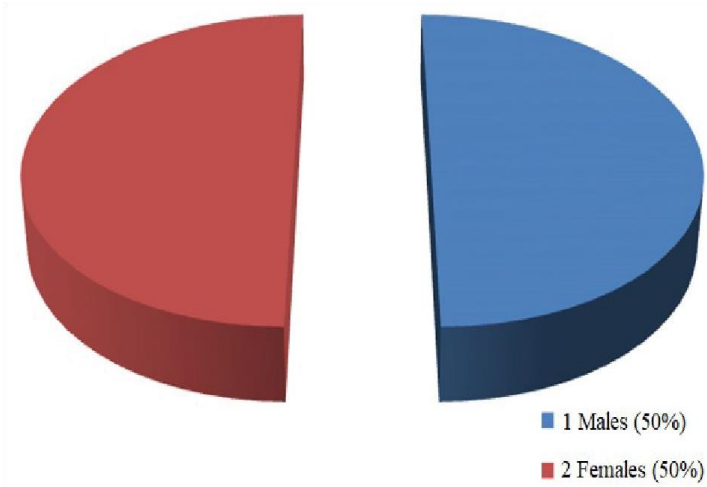

Figure 1 Percentages of males and females' patients that had done Widal test

The widal test showed positive results in 14% of the patients and the rest were negative as shown in Table 1.

Table 1 Results of the Widal test

Results of the Widal test	***S. Typhi* O**	***S. Typhi* H**	***S. paratyphi* AO**	***S. paratyphi* Ah**	***S. paratyphi* BO**	***S. paratyphi* BH**	**p-value**
	No (%)	**No (%)**	**No (%)**	**No (%)**	**No (%)**	**No (%)**	
Positive	7 (14%)	5 (10%)	1 (2%)	0 (0%)	5 (10%)	5 (10%)	0.002
Negative	43 (86%)	45 (90%)	49 (98%)	50 (100%)	45 (90%)	45 (90%)	

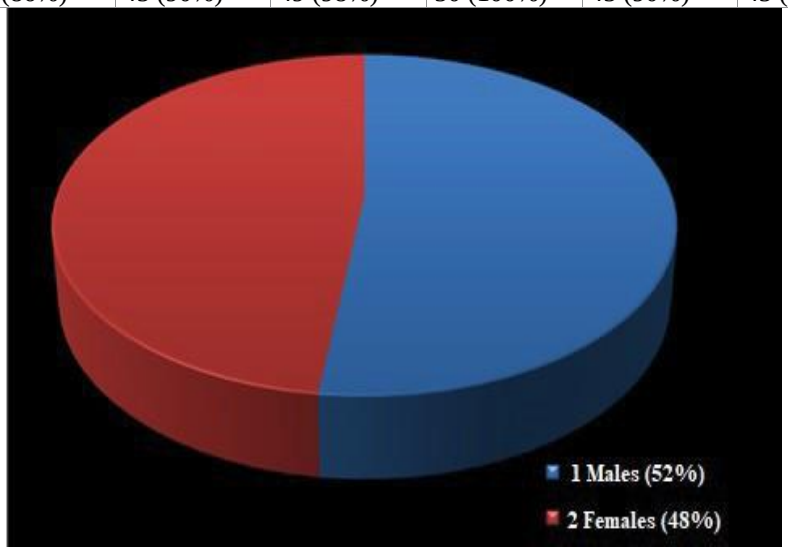

Figure 2 Percentages of males and females' patients that had done a blood culture test

There was a significant difference between the two groups ($p = 0.002$) while the blood culture results were negative in 86% of the cases and the remaining 14% were positive for other bacteria such as E. coli, Pseudomonas spp. and Staphylococcus spp. There were no significant differences between the two groups ($p = 1$) as shown in Table 2.

Table 2 Results of blood culture

Results of blood culture	Number of patients N (%)	p- value
No growth	43 (86%)	1
Growth	7 (14%)	
Total	50 (100%)	

DISCUSSION:

Typhus is a serious systemic infectious disease with stunning effects on children and adults in crowded, poorly sanitary populations. There is a high prevalence of Salmonella typhi in the world, despite the adequate availability of therapeutic drugs. This may be due to antibiotic resistance. Distinguishing infection with typhoid fever (Salmonella typhi) and paratyphoid (Salmonella paratyphi A, B) from other causes of fever in endemic areas is a diagnostic challenge. While the commercially widespread enteric fever test is available as an alternative to the current standard reference test for blood or bone marrow culture, their diagnostic accuracy is unclear. If accurate, they could potentially replace a blood culture, as the World Health Organization (WHO) has recommended a major diagnostic test for intestinal fever. The broad agglutination test is perhaps the most frequently used laboratory test for the diagnosis of typhoid fever, especially in developing countries where blood culture is often unavailable[10]. However, the interpretation of the test remains a controversial topic, especially in the context of endemic regions, as the agglutination test is often positive in differential and higher titers among a large percentage of the healthy population. Paired Widal tests are often not feasible, so one unpaired test should be used for screening and diagnosis. Even specific chemotherapy is often administered on the basis of a single Widal test. In this study, we were unable to diagnose this disease because the timing of the test was inadequate, and this test gave many false-positive results because it gave false-positive results in any febrile state, which is why it is called the fever agglutination test[11]. Thus, this test is a putative serological test in which antigens of S. typhi bacteria are mixed with the patient's serum, which may contain specific antibodies against S. typhi. Positive tests indicate agglutination or clumping of the mixture visible to the naked eye. Basic laboratory tests with the Vidal test had many limitations in terms of both sensitivity and specificity. However, the Widal method is both fast and relatively inexpensive compared to urine, faecal, blood culture or bone marrow culture methods. The bone marrow method is considered possibly the best method of laboratory confirmation, although it is often unavailable in some parts of the world due to technical limitations[12]. It is therefore very important to establish a baseline value for the Widal's test and re-evaluate at regular intervals to ensure that the standard cut-offs are as accurate and up-to-date as possible on a particular demographic basis. It was shown that the significant baseline Anti TO, TH, AO, AH, BO agglutinin titers among the participants were 1:80 for each of them, respectively. A titer of 1:40 was observed for the BH antigen. It turned out that for a single Widal test, the baseline values for the normal range should be revised and set 1:80 for all antigens (TO, TH, AO, AH, BO, BH) except for BH for which it should be 1 40[13]. In our country, the diagnostic titer was 1: 160. As for the blood culture, we were unable to isolate these bacteria from the blood because the timing of the blood collection was inadequate. Blood cultures are used as the final diagnosis of typhoid fever, but this takes time and is not routinely available in a timely manner[14]. The study was conducted by Suwarto et al, who found that out of 187 people, 27 had Salmonella typhi and 12 had S. Para typhi in blood cultures[15]. So, another reason is the small number that was taken in this study, which also contributes to a negative blood culture, inappropriate timing of blood collection, or the possibility of the patient taking an antibiotic.

CONCLUSION AND RECOMMENDATION:

Clinical examination and sampling timing are important. Serial Widal should be performed after and before treatment and during patient observation.

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