Section: Microbiology

Research

CONTRIBUTION OF ENTERIC FEVER IN FEBRILE ILLNESS

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Abstract

Background: Enteric fever is one of the common febrile diseases of humans. The objectives of this study were to:1) Estimate the prevalence of enteric fever among febrile patients visiting tertiary care hospital;2) comparison for efficacy of Typhi Dot test over Widal test;3) Gender wise estimation of enteric fever; 4) Estimation of enteric fever in patients having age group less than 15 years and 5) comparison of share of Enteric fever in ICU patients over OPD patients. **Materials and Methods:** Blood samples were collected from 194 febrile patients with symptoms clinically similar to enteric fever. Widal test was used for testing sera using standard method. Only febrile patients having fever for more than a week time were included in the study. The known patients already on antibiotic therapy were excluded. Chi-Square test and Logistic Regression analysis were used to analyze the data. **Result:** Out of 108 samples put under Typhi dot 48 found positive which is 44.44% meaning there by almost half of the samples are found positive by Typhi dot. On the other hand only 20 samples found positive out of 194 samples put to Widal test. Only 10.31% samples are positive by Widal test. Out of 48 positive samples declared by Typhidot again tested by Widal test, only 06 (27.27%) are positive. 16 samples (72.72%) found negative. 26 patients opted out from Widal test. It means the efficacy of typhi dot test is 27.27% over Widal test. We don't recommend typhi dot test for diagnosis of enteric fever. It is observed from this study that female patients have 12.84% attacking rate whereas male patients have only 7.05% attacking rate. The maximum positive samples are found in age group of 16-30 years (14.81%) whereas lowest positive cases are found in age group less than 15 years (3.57%). It is significant to note that maximum positive cases are in age group of 16-45 years which is 15 out of 20 positive cases. More positive cases (12.28%) are found from the patients kept in ICU. OPD patients have recorded only 9.48% positive samples. **Conclusion:** The contribution of enteric fever amongst the patients of febrile fever is 10.31% in the present study. It means one among 10 febrile patients are suffering with salmonella typhi infection in the region. Female patients have more attacking rate than male patients. In ICU patients, enteric fever cases found more than OPD patients.

INTRODUCTION

To undertake study to know positive cases of Enteric fever among patients brought to hospital, on various parameters of age and sex etc.

Enteric fever, referring to typhoid fever and paratyphoid fever, is a common bacterial disease with high morbidity and mortality rates in low- to middle-income countries in Asia, Africa, and South America, associated with limited proper sanitation and safe drinking water supply.[1,2] Typhoid fever has been estimated to cause about 26 million (typhoid) and five million (paratyphoid A) illnesses, with 190,000 enteric fever deaths in 2010 globally.[3]

Economically developing nations face the disease as a major public health problem, particularly low-income countries of Asia and sub-Saharan Africa, where majority of the population strives for safe water, limited sanitation and hygiene infrastructure as well. Usually, children below 15 years of age are more susceptible to the disease probably due to the

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fact that adults develop immunity from recurrent infection and subclinical cases.[4]

Typhoid or enteric fever is mainly caused by Salmonella enterica serovar Typhi and also to a lesser extent by S. Paratyphi A. Humans are the only reservoir for these organisms. The main sources of infection are the stool and urine of infected persons, with the important vehicles being contaminated water, food and flies. The causative agent is either waterborne or foodborne for this gastrointestinal infection. The onset and severity of the disease mainly depends on the virulence of the organism and the infective dose.[5]

In India, data from hospital- and community-based studies are limited. A systematic literature review of studies on enteric fevers in India showed only a few community-based studies and only seven hospital-based studies in the last 10 years which estimated the incidence of typhoid.[6] A large-scale community study conducted in India in an urban slum setting has described the incidence of the disease as high as 2/1000 population/year under five year of age and 5.1/1000 populations/year under 10 year of age.[7] A similar study from north India has reported that most of the cases occurred in children aged 5-12 year, wherein 24.8 per cent of cases were in children up to five years of age.[8] Unfortunately, the absence of nation-wide estimates of burden of the disease has minimized the effective prevention and control efforts of enteric fever.

In 2020, the number of typhoid cases across Delhi was estimated to be over 11.4 thousand, down from approximately 17.21 thousand typhoid cases in 2019. The highest number of cases of about 48 thousand was recorded in the state in 2012.[9]

There have been two large scale studies in India on the incidence of Blood culture confirmed typhoid fever, one among individuals under 40 years old and another among children 6 to 17 years old,[10,11] but as yet, none on paratyphoid fever. Thus, the actual burden of paratyphoid fever in India and its incidence and characteristics relative to typhoid fever are poorly understood. In a study conducted in Punjab that examined 340 enteric fever cases, 334 S Typhi and 6 Paratyphi A isolates were identified.[12] This scenario, however, has changed as recent studies have highlighted the increasing occurrence of paratyphoid fever.[13,14,15,16,17] Typhoid fever incidence varies substantially in Asia. Very high typhoid fever incidence has been found in India and Pakistan.[18] In comparison, typhoid fever frequency was moderate in Vietnam and China and intermediate in Indonesia.[19]

Primary strategies for typhoid fever control involve safe water supply, adequate sanitation facilities and proper hygienic practices. However, these require sustainable investments, huge financial outlays and long-term political commitment. The introduction of WASH program has helped to improve the WASH situation in India although there still remains a significant gap in achievements. Several other issues have created a hindrance in disease burden control as well.

The key bottleneck is the non-availability of robust country-wide surveillance data in India. Additionally, the need for improved POC diagnostics which will be rapid, simple and accurate yet affordable remains a plausible challenge. Treatment of typhoid fever cases poses a veritable challenge. MDR S. Typhi strains leading to drug-resistant typhoid have become a major concern. Thus, preventive intervention measures turn out to be the key to control of the disease. Other than provision of safe water and sanitation, vaccination of high-risk populations is universally accepted as the most promising short-term strategy with respect to the control of typhoid fever. To make the best use of the control measures in such resource-poor endemic settings, there is a need to develop disease burden extrapolation models to choose the sites that need to be prioritized for routine intervention. The surveillance data need to be roped in to create the coordinated plans to translate into tangible actions, which is deployment of these interventions to the targeted population.[20]

Epidemiology of Enteric Fever in India

India is a huge country with considerable geographic, social and religious diversity. However, enteric fever is endemic throughout the country and places a heavy burden on government and private healthcare facilities alike. The incidence varies both geographically – from 140 episodes per 100 000 person years in Kolkata, East India 21 to 273 per 100 000 person years in Delhi– and by age.[21,22] A study conducted by the International Vaccine Institute found the incidence of culture-proven S. typhi to be 340 per 100 000 population-year among children aged 2–5 years, 493/100 000 population-year in children aged 5–15 years and 120/100 000 population-year in adults older than 15 years.[23] When surveying countries across Asia, their data suggest an inverse correlation between typhoid incidence and the mean age of typhoid cases. Incidence also varies by season with yearly peaks occurring between July and October, coinciding with the monsoon.[24,25] closely reflecting the pattern seen with other waterborne diseases. Baseline endemicity is punctuated by intermittent epidemics that may occur at any time of the year. These can be enormous; one epidemic in Maharashtra, West India, involved more than 9000 cases of S. typhi in 12 weeks in a population of 135000.[26] Investigations into this and other outbreaks have found that they are point-source epidemics caused by faecal contamination of drinking water by typhoid carriers.[27,28] Two to five per cent of those infected develop chronic carriage, excreting S. typhi in their stool and posing an infection risk to others.[29]

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MATERIALS AND METHODS

The present study has been carried out on the patients either visited as OPD patients in different specialties of the hospital or hospitalized patients including ICU patients in Rama Medical College Hospital and Research Centre Hapur, after taking their informed consent and approval of protocol by ethics committee of college. The history of the patients was febrile since almost a week period. The samples are collected and brought to Microbiology lab of the hospital and tested. Some of the samples were tested by Typhi Dot initially and samples positive by Typhi Dot were again put to Widal test for confirmation of enteric fever. The inclusion criteria were to include all patients suffering with fever since more than one week. The patients who were already known for taking antibiotic therapy were excluded from the study group. The present study is planned to conduct cross sectional, intend to know positive cases gender -wise and also age-wise. The efforts are being made to know the accuracy of Typhi Dot test over Widal test. The observation has also been made to know the attack rate of ICU patients over general ward OPD patients.

A reliable, easy and affordable rapid diagnostic test is a need for our clinicians, many of whom consider Typhidot to be promising. Typhidot has been used as the only tool to diagnose typhoid fever by general practitioners and consultants despite its low sensitivity and specificity causing misdiagnosis and treatment. The sensitivity of Typhidot was found to be 26.7% and the specificity was 61.5% in one of the important study .The Positive Predictive Value (PPV) was 7.4% and the Negative Predictive Value (NPV) was 87.9% in this study .Even though Typhidot is rapid, easy and affordable, its use should be discouraged due to low sensitivity and specificity and insignificant (p=0.067) association to the disease as propounded in this study.[30] Typhidot is a simple test and requires no training of staff for specialized equipment. Hence it is widely used in all third world countries as a reliable and affordable means of detecting typhoid.

Typhidot is done on a dot ELISA kit that detects IgM and IgG antibodies against the outer membrane protein (OMP) of the Salmonella typhi. The Typhidot test is expected to become positive within 2–3 days of infection. The test is based on the presence of specific IgM and IgG antibodies. IgM shows recent infection whereas IgG signifies remote infection. Typhidot was 67% sensitive and 54% specific, with 85% positive and 81% NPVs.[31] In a study in Egypt in which Typhidot was compared with a new ELISA not yet commercially available, the sensitivity and specificity were again very low.[32]

The Widal test detects agglutinating antibodies against the O and H antigens of S. Typhi. The Widal test was developed over a century ago and remains one of the world's most widely used diagnostic tests but suffers from significant limitations in its sensitivity and specificity, as well as reliability. Like most serologic tests, a false-negative Widal test may occur early in the course of illness, and a false-positive Widal test may result from past infection or from previous exposure to cross-reactive antigens or vaccination. There are no universal standards that define the cutoff dilution of agglutinating antibodies to indicate a positive Widal test.

Widal test -The Widal test procedure is carried out in two steps

1. Qualitative Widal Test
2. A quantitative Widal test: It is a semi-procedure test, which means we will check for O if O is positive, H if H is positive, and both if both are positive.

Interpretation of Widal Test-Slide Method

After mixing the serum and reagent properly and rotating the slide, wait for the results to show. The result will be positive if it shows positive in more than 100 in the O circle and 200 in the case of H. In other words, it is a positive Widal test if the titre is above 100 in O and 200 in H. However, the results can be negative due to antibiotics, malaria, dengue, or the fever has affected the patients for more than a few days, etc.

We have interpretated test results in the following ways:

Negative if S. Typhi is smaller than or equal to 1:80 and positive if S. Typhi is more than or equal to 1:160.

Tube Widal Test

Apart from qualitative and quantitative Widal tests, there is another test method; the standard tube method. Here, eight tubes are taken, diluted and observed. The first test can screen for typhoid fever; however, a tube Widal test effectively confirms a fever.

Nowadays, 3 x 0.5 ml Kahn tubes are used for both O and H agglutination.

Interpretation of Widal Test-Tube Method

If patients have typhoid fever and there is some agglutination, we will see that the 9th tube (positive control) will look similar to one of the eight other tubes. If there is no enteric fever, there will be no change in the normal range of the eight tubes and widal test.

If the tube that showed agglutination has a titre of more than 1:100 in case of O and 1: 200 in H, it will be Widal test positive (active infection). Other than this, rest titers are considered the normal range of a Widal test.

Limitations of Widal Test

No doubt, the Widal test is a quick and effective way to diagnose typhoid fever, but it has some limitations as well, including:

1. The results of the Widal test can be falsely positive in the case of past vaccination or S. Typhi infection.
2. The Widal test is time-consuming; until a diagnosis is made, it becomes too late to start the treatment.

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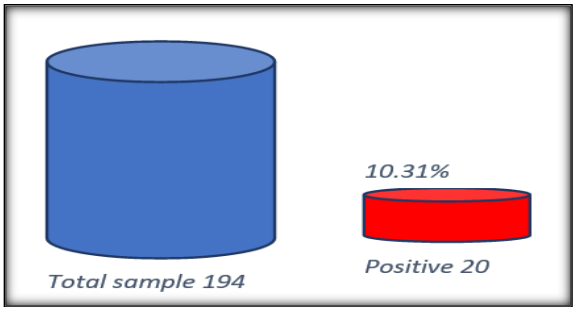
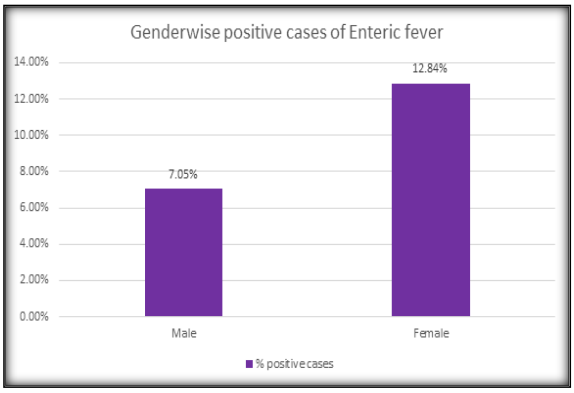
3. A Widal test cannot distinguish between a patient's past infection, current infection, or a S. Typhi vaccination.
4. The test results can be falsely positive in typhus, acute falciparum malaria, chronic liver disease, rheumatoid arthritis, nephrotic syndrome and myelomatosis.

The Widal test had a positive predictive value of <10%, but in a high prevalence setting the negative predictive value was high at 95.6%. Thus it is used in this capacity in many hospitals.24 The Widal test remains the most widely available and frequently used test in the community for diagnosis ofenteric fever[33]. Although its limitations are well-known, it is simple, quick and inexpensive.

RESULTS





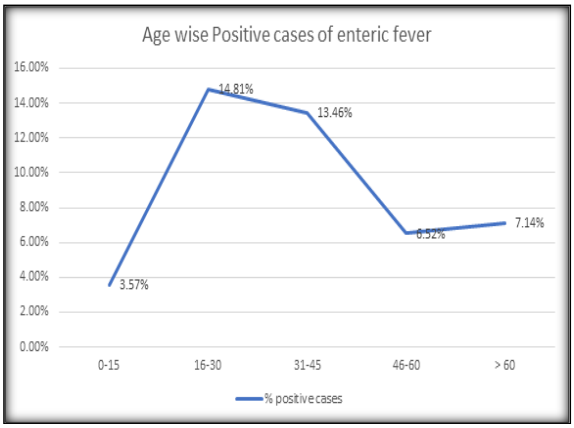


Table 1: Positive cases as per type of Test

Type of Test	Total sample tested (No.)	Positive sample (No.)	% Positive sample
Typhi Dot	108	48	44.44
Widal	194	20	10.31

Observation: Out of 108 samples put under Typhi dot 48 found positive which is 44.44% meaning there by almost half of the sample are found positive. On the other hand only 20 samples found positive out of 194 samples put to test by Widal. Only 10.31% samples are positive by Widal test.

Table 2: Positive sample by Typhi Dot test put to Widal test.

Typhi Dot positive sample (No.) -A	Positive sample (no) by Widal test	% Positivity
22	06	27.27
Remark- out of 48 positive by typhi dot 16 found negative by Widal and 26 patients opted out		

Observation: Out of 48 positive samples declared by Typhi dot again tested by Widal test, only 06 (27.27%) are positive. 16 samples (72.72%) found negative. 26 patients opted out from Widal test. It means the efficacy of typhi dot test is 27.27% over Widal test. We don't recommend typhi dot test for diagnosis of enteric fever.

Table 3: Gender wise positive samples by Widal test.

Gender	No. of total sample tested	Positive sample(no)	% positive sample
Male	85	06	7.05
Female	109	14	12.84
Total	194	20	10.31

Observation: It is observed from this study that female patients have 12.84% attacking rate whereas male patients have only 7.05% attacking rate.

Table 4: Age wise positive sample by Widal test.

Age bracket (years)	Total sample tested (no)	Positive sample(no.)	% Positive cases
0-15	28	01	3.57
16-30	54	08	14.81
31-45	52	07	13.46
46-60	46	03	6.52
60	14	01	7.14
Total	194	20	10.31

Observation: The maximum positive samples are found in age group of 16-30 years (14.81%) whereas lowest positive cases are found in age group less than 15 years (3.57%). It is significant to note that maximum positive cases are in age group of 16-45 years which is 15 out of 20 positive cases.

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Table 5: Positive sample from ICU and Wards by Widal Test.

ICU Sample tested (no.)	Positive sample (no.)	% positive sample	Different wards sample tested (no.)	Positive sample (no.)	% Positive sample
57	07	12.28%	137	13	9.48%

Observation: More positive cases (12.28%) are found from the patients kept in ICU. OPD patients have recorded only 9.48% positive samples.

DISCUSSION

The present study is basically cross-sectional prospective study. The samples are collected for the duration of two and half months from the patients mostly from rural area or semi urban area of population in this tertiary care hospital. In this study, total 194 samples brought from ICU patients and from patients of different wards which are put to widal test. 20(10.31%) are found positive. All the patients were febrile and suspected for enteric fever. Initially 108 samples are tested with Typhi Dot which gave 48 samples as positive. For confirmation of enteric fever, 22 positive (by Typhi Dot) are again tested by Widal. Only 6 samples (27.27%) were actually found positive. 16 (72.72%) are negative. 26 patients opted out to further Widal test.

Out of 194 samples put to Widal test, 6(7.05%) out of 85 male patients and 14(12.84%) out of 109 samples from female patients found positive. It indicate that enteric fever is more prevalent in female patients comparing to male patients. In one study carried out in July 2022 in north India, the attack rate was found 16.1% and 17.4% among men and women, respectively. [34]

Whereas in one other study, more males (52%) than females (48%) were infected by Salmonella. The ratio of typhoid patients was greater in young people having ages between 24-38 years.[35] In the present study , maximum positive case 14.81% are in the age bracket of 16-30years and 13.46% in 31-45years age .The positive cases in the age up to 15 years is just 3.57% in the present study which is contrary to the other studies where The incidences of typhoid and paratyphoid fevers were 608.1 (95% confidence interval, 481.1-768.7) and 111.7 (59.5-191.1) per 100 000 PY, respectively, highest among children aged 10-15 years.[36]

Enteric fever is a common but serious disease that affects mostly children and adolescents in the developing countries. Salmonella enterica serovar Typhi remains responsible for most of the disease episodes.[37]

In the present study, it is observed that the attack rate on ICU patients are more i.e 12.28% in comparison to patients of all other wards which was recorded 9.48% in the study.

CONCLUSION

Enteric fever is an important cause of morbidity in India and will continue to do so as long as the socioeconomic conditions viz a viz cleanliness of water and observing proper hygiene which predispose to the disease prevail. There are other issues with inaccurate diagnosis, inadequate treatment and worsening drug resistance that are a threat to India. Only a combined approach of vaccination, improved living conditions and control of antibiotic resistance is likely to yield sustained reductions in the incidence of this disease. From July to September every year just after mansoon , febrile diseases like malaria , Chikungunya, Dengue and enteric fever create heavy burden in India. The solution appears to be progressive on supply of clean drinking water and over all hygiene.

The present study highlights more enteric fever cases in female patients drawn from rural or semi urban area which indicate adulterated drinking water and Hygiene habits in habitats. The other outcome of this study is that the maximum cases of enteric fever are prevailing in adults of earning age group which affect the livelihood. The contribution of enteric fever amongst the patients of febrile fever is 10.31% in the present study. It means one among 10 febrile patients are suffering with salmonella infection in the region.

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