|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
PubMed (National Library of Medicine ID: 101738825)
Index Copernicus Value 2018: 75.71
Original Research Article
Volume 4, Issue 8; August: 2020; Page No. 96-101

ASSESSMENT OF CLINICAL AND LABORATORY PARAMETERS IN TYPHOID FEVER IN PEDIATRIC CASES ADMITTED TO NMCH, PATNA

Dr. Samiksha Sharma[1], Dr. Girijanand Jha[2], Dr. Binod Kr Singh[3], Dr. Saroj Kumar[4]
[1]Senior Resident, Department of Pediatrics, Nalanda Medical College and Hospital Patna, Bihar, India
[2]Senior Resident, Department of Pediatrics, Nalanda Medical College and Hospital Patna, Bihar, India
[3]Professor and HOD, Department of Pediatrics, Nalanda Medical College and Hospital Patna, Bihar, India
[4]Assistant Professor, Department of Pediatrics, Nalanda Medical College and Hospital Patna, Bihar, India

Article Info: Received 25 July 2020; Accepted 26 August 2020
DOI: https://doi.org/10.32553/ijmbs.v4i8.1376
Corresponding author: Dr. Samiksha Sharma
Conflict of interest: No conflict of interest.

Abstract

India has a very high disease burden (214.2 per 1,00,000 individuals/year), primarily affecting children 5 to 15 years. Recently, there have been concerns of increasing proportion of infections in very young children, rising paratyphoid infections, and emerging drug resistance. Also, there are challenges in diagnosis and management of enteric fever due to lack of laboratory-based investigations. While blood culture remains the gold standard of diagnosis, the mainstays in developing countries are serological tests, which are suboptimal due to lack of standardization and uniformity. Hence based on above condition the present study was planned for Assessment of Clinical and Laboratory Parameters in Typhoid Fever in Pediatric Cases Admitted to NMCH, Patna.

The present study was planned in Department of Pediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India. The study was planned from January 2018 to November 2018. In the present study 50 childrens of age up to 18 years having fever more than 7 days were enrolled. These cases were enrolled based on the Widal positive or positive culture were enrolled in the present study.

The data generated from present study concludes that Typhoid fever manifestations are diverse. The most common symptoms apart from fever were anorexia, vomiting, pain abdomen, diarrhoea followed by headache and cough. Also the Serum parameters are also seen changed in the Thyphoid affected patients. Typhoid fever remains a major public health problem in the developing countries predominantly seen in school going children among pediatric age group.

Keywords: Clinical, Laboratory Parameters, Typhoid Fever, Pediatric Cases, etc.

Introduction

Typhoid fever, also known as enteric fever, is a potentially fatal multisystemic illness caused primarily by Salmonella enterica serotype typhi and, to a lesser extent, S enterica serotypes paratyphi A, B, and C. The terms typhoid and enteric fever are commonly used to describe both major serotypes.

Typhoid fever has a wide variety of presentations that range from an overwhelming multisystemic illness to relatively minor cases of diarrhea with low-grade fever. The classic presentation is fever, malaise, diffuse abdominal pain, and constipation. Untreated typhoid fever may progress to delirium, obtundation, intestinal hemorrhage, bowel perforation, and death within 1 month of onset. Survivors may be left with long-term or permanent neuropsychiatric complications.

S typhi has been a major human pathogen for thousands of years, thriving in conditions of poor sanitation, crowding, and social chaos. It may have responsible for the Great Plague of Athens at the end of the Pelopennesian War. [1] The name S typhi is derived from the ancient Greek typhos, an ethereal smoke or cloud that was believed to cause disease and madness. In the advanced stages of typhoid fever, the patient's level of consciousness is truly clouded. Although antibiotics have markedly reduced the frequency of typhoid fever in the developed world, it remains endemic in developing countries. [2] Infections with S paratyphi may be surpassing those caused by S typhi, in part because of immunological naivete among the population and incomplete coverage by vaccines that target typhi.

Note that some writers refer to the typhoid and paratyphoid fever as distinct syndromes caused by the typhi versus paratyphi serovars, while others use the term typhoid fever for a disease caused by either one. We use the latter terminology. We refer to these serovars collectively as typhoidal salmonella.

All pathogenic Salmonella species, when present in the gut are engulfed by phagocytic cells, which then pass them through the mucosa and present them to the macrophages in the lamina propria. Nontyphoidal salmonellae are

phagocytized throughout the distal ileum and colon. With toll-like receptor (TLR)–5 and TLR-4/MD2/CD-14 complex, macrophages recognize pathogen-associated molecular patterns (PAMPs) such as flagella and lipopolysaccharides. Macrophages and intestinal epithelial cells then attract T cells and neutrophils with interleukin 8 (IL-8), causing inflammation and suppressing the infection. [3, 4]

In contrast to the nontyphoidal salmonellae, S typhi and paratyphi enter the host's system primarily through the distal ileum. They have specialized fimbriae that adhere to the epithelium over clusters of lymphoid tissue in the ileum (Peyer patches), the main relay point for macrophages traveling from the gut into the lymphatic system. The bacteria then induce their host macrophages to attract more macrophages. [3]

S typhi has a Vi capsular antigen that masks PAMPs, avoiding neutrophil-based inflammation, while the most common paratyphi serovar, paratyphi A, does not. This may explain the greater infectivity of typhi compared with most of its cousins. [5]

Typhoidal salmonella co-opt the macrophages' cellular machinery for their own reproduction [6] as they are carried through the mesenteric lymph nodes to the thoracic duct and the lymphatics and then through to the reticuloendothelial tissues of the liver, spleen, bone marrow, and lymph nodes. Once there, they pause and continue to multiply until some critical density is reached. Afterward, the bacteria induce macrophage apoptosis, breaking out into the bloodstream to invade the rest of the body. [4]

The bacteria then infect the gallbladder via either bacteremia or direct extension of infected bile. The result is that the organism re-enters the gastrointestinal tract in the bile and reinfects Peyer patches. Bacteria that do not reinfect the host are typically shed in the stool and are then available to infect other hosts. [2, 4]

Chronic carriers are responsible for much of the transmission of the organism. While asymptomatic, they may continue to shed bacteria in their stool for decades. The organisms sequester themselves either as a biofilm on gallstones or gallbladder epithelium or, perhaps, intracellularly, within the epithelium itself. [7] The bacteria excreted by a single carrier may have multiple genotypes, making it difficult to trace an outbreak to its origin. [8]

Typhoidal salmonella have no nonhuman vectors. An inoculum as small as 100,000 organisms of typhi causes infection in more than 50% of healthy volunteers. [9] Paratyphi requires a much higher inoculum to infect, and it is less endemic in rural areas. Hence, the patterns of transmission are slightly different.

The following are modes of transmission of typhoidal salmonella: Oral transmission via food or beverages handled by an often asymptomatic individual—a carrier—who chronically sheds the bacteria through stool or, less commonly, urine. Hand-to-mouth transmission after using a contaminated toilet and neglecting hand hygiene. Oral transmission via sewage-contaminated water or shellfish (especially in the developing world). [10, 11, 12]

Paratyphi is more commonly transmitted in food from street vendors. It is believed that some such foods provide a friendly environment for the microbe. Paratyphi is more common among newcomers to urban areas, probably because they tend to be immunologically naïve to it. Also, travellers get little or no protection against paratyphi from the current typhoid vaccines, all of which target typhi. [13, 14]

Typhoidal salmonella are able to survive a stomach pH as low as 1.5. Antacids, histamine-2 receptor antagonists (H2 blockers), proton pump inhibitors, gastrectomy, and achlorhydria decrease stomach acidity and facilitate S typhi infection. [4]

HIV/AIDS is clearly associated with an increased risk of nontyphoidal Salmonella infection; however, the data and opinions in the literature as to whether this is true for S typhi or paratyphi infection are conflicting. If an association exists, it is probably minor. [15, 16, 17, 18]

Other risk factors for typhoid fever include various genetic polymorphisms. These risk factors often also predispose to other intracellular pathogens. For instance, PARK2 and PACGR code for a protein aggregate that is essential for breaking down the bacterial signaling molecules that dampen the macrophage response. Polymorphisms in their shared regulatory region are found disproportionately in persons infected with Mycobacterium leprae and S typhi. [11]

On the other hand, protective host mutations also exist. The fimbriae of S typhi bind in vitro to cystic fibrosis transmembrane conductance receptor (CFTR), which is expressed on the gut membrane. Two to 5% of white persons are heterozygous for the CFTR mutation F508del, which is associated with a decreased susceptibility to typhoid fever, as well as to cholera and tuberculosis. The homozygous F508del mutation in CFTR is associated with cystic fibrosis. Thus, typhoid fever may contribute to evolutionary pressure that maintains a steady occurrence of cystic fibrosis, just as malaria maintains sickle cell disease in Africa. [19, 20]

As the middle class in south Asia grows, some hospitals there are seeing a large number of typhoid fever cases among relatively well-off university students who live in group households with poor hygiene. [21] American clinicians should keep this in mind, as students from these areas often come to the United States for further education. [22]

The clinical syndromes associated with S typhi and paratyphi are indistinguishable. Typhoid fever begins 7-14 days after ingestion of the organism . The fever pattern is stepwise, characterized by a rising temperature over the course of each day that drops by the subsequent morning. The peaks and troughs rise progressively over time.

Over the course of the first week of illness, the notorious gastrointestinal manifestations of the disease develop. These include diffuse abdominal pain and tenderness and, in some cases, fierce colicky right upper quadrant pain. Monocytic infiltration inflames Peyer patches and narrows the bowel lumen, causing constipation that lasts the duration of the illness. The individual then develops a dry cough, dull frontal headache, delirium, and an increasingly stuporous malaise. [2]

At approximately the end of the first week of illness, the fever plateaus at 103-104°F (39-40°C). The patient develops rose spots, which are salmon-colored, blanching, truncal, maculopapules usually 1-4 cm wide and fewer than 5 in number; these generally resolve within 2-5 days. [2] These are bacterial emboli to the dermis and occasionally develop in persons with shigellosis or nontyphoidal salmonellosis.

During the second week of illness, the signs and symptoms listed above progress. The abdomen becomes distended, and soft splenomegaly is common. Relative bradycardia and dicrotic pulse (double beat, the second beat weaker than the first) may develop.

In the third week, the still febrile individual grows more toxic and anorexic with significant weight loss. The conjunctivae are infected, and the patient is tachypneic with a thready pulse and crackles over the lung bases. Abdominal distension is severe. Some patients experience foul, green-yellow, liquid diarrhea (pea soup diarrhea). The individual may descend into the typhoid state, which is characterized by apathy, confusion, and even psychosis. Necrotic Peyer patches may cause bowel perforation and peritonitis. This complication is often unheralded and may be masked by corticosteroids. At this point, overwhelming toxemia, myocarditis, or intestinal hemorrhage may cause death.

If the individual survives to the fourth week, the fever, mental state, and abdominal distension slowly improve over a few days. Intestinal and neurologic complications may still occur in surviving untreated individuals. Weight loss and debilitating weakness last months. Some survivors become asymptomatic S typhi carriers and have the potential to transmit the bacteria indefinitely. [21, 2, 4]

India has a very high disease burden (214.2 per 1,00,000 individuals/year), primarily affecting children 5 to 15 years. Recently, there have been concerns of increasing proportion of infections in very young children, rising paratyphoid infections, and emerging drug resistance. Also, there are challenges in diagnosis and management of enteric fever due to lack of laboratory-based investigations. While blood culture remains the gold standard of diagnosis, the mainstay in developing countries are serological tests, which are suboptimal due to lack of standardization and uniformity. Hence based on above condition the present study was planned for Assessment of Clinical and Laboratory Parameters in Typhoid Fever in Pediatric Cases Admitted to NMCH, Patna.

Methodology:

The present study was planned in Department of Pediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India. The study was planned from January 2018 to November 2018. In the present study 50 childrens of age up to 18 years having fever more than 7 days were enrolled. These cases were enrolled based on the Widal positive or positive cultures were enrolled in the present study.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria: Positive blood culture for Salmonella typhi and/ or Salmonella paratyphi organisms. Significant Widal titre. A repeat fourfold rise in Widal test titer.

Exclusion criteria:. Patients with respiratory tract infection (tuberculosis, pneumonia); Patients with urinary tract infections;. Patients with malaria; Immunocompromised patients (AIDS); Patients who had already vaccinated with typhoid vaccine.

Results & Discussion:

Diagnosis of enteric fever is fraught with problems. History, physical findings and fever pattern are suggestive but can neither confirm nor exclude typhoid. Blood culture is the 'gold standard' for diagnosis and also gives information about antibiotic sensitivity of the isolate; however the cost of cultures and administration of prior antibiotics are hindrance in this diagnostic approach.

Assessment of a child presenting with fever without an obvious focus is a challenge to most of us. To determine the etiology and plan the management in the first few days is always difficult and yet imperative. In view of the anxiety of the parents, most pediatricians have the tendency to start some antibiotics before any real clue about the etiology irrespective of the act that most of these fevers might just be of viral etiology. In enteric fever this initial antibiotic might modify the course of the disease and pose significant difficulty in interpretation of lab investigations. Typhoid fever also known as “Enteric fever”, is a collective

term that refers to both typhoid and paratyphoid fever. It is one of the most common causes of fever in children with variable presentations and significant difference in the signs and symptoms compared to adults. [23] It is a common infectious disease presenting as acute multisystem febrile illness caused by gram negative organism several serovar-S. enterica serotype typhi (formerly S. typhi).

Enteric fever, a systemic infection by Salmonella enterica serotype Typhi (S. Typhi) or Salmonella enterica serotype Paratyphi A (S. Paratyphi A), affects around 11-21 million individuals globally with a high mortality. [23-26]. India has a very high disease burden (214.2 per 1,00,000 individuals/year) [26], primarily affecting children 5 to 15 years. Recently, there have been concerns of increasing proportion of infections in very young children, rising paratyphoid infections, and emerging drug resistance. [26-27] Also, there are challenges in diagnosis and management of enteric fever due to lack of laboratory-based investigations. [28-29] While blood culture remains the gold standard of diagnosis, the mainstay in developing countries are serological tests, which are suboptimal due to lack of standardization and uniformity0. [29]

Typhoid fever imposes a serious global burden amounting to 26.9 million cases (symptomatic infection with Salmonella typhi) of typhoid fever reported in 2010 and apparently 5.74 lakh deaths worldwide. [30] Inspite of provision of safe water and sanitation, better treatment and vaccination, burden of the disease in certain areas of the Globe is however remaining quite high and moreover the disease is becoming more complex in certain areas of World like some parts of African Subcontinent. [31]

There has been intense study regarding the genomics of S.typhi and the genetic mechanism behind its unique human-adaptiveness. There has been exciting new genetic technological innovation to demonstrate that the same genes in S.typhi and S.typhimurium may have different regulatory pathways and different function. This understanding may help for developing newer target for vaccine development and new antibacterial drug for S.typhi in endemic areas. [31]

Table 1: Basic Details

Parameters	No. of Cases
Sex:	
Males	31
Females	19
Age:	
Less than 1 year	11
1 – 5 years	14
6 – 10 years	9
11 – 15 years	6
Hospital Stay:	
1 – 3 days	12
3 – 7 days	32
More than 7 days	6

Table 2: Symptoms & Physical Findings

Symptoms	Observed in No. of Cases
Fever	50
Anorexia	31
Vomitting	22
Pain Abdomen	10
Diarrhea	8
Headache	6
Cough	5
Physical Findings	**Observed in No. of Cases**
Toxic look	35
Coated tongue	25
Hepatomegaly	22
Splenomegaly	10
Hepatosplenomegaly	8
Pallor	5

Table 3: Laboratory Parameters

Laboratory Parameters	Observed in No. of Cases
Hemoglobin:	
Anemia (Hb <11g%)	8
Total leukocyte count:	
Leucocytosis (>11000cells/mm3)	7
Leucopenia (<4000 cells/mm3)	17
Polymorphs:	
Neutropenia	20
Neutrophilia	16
Eosinophils:	
Eosinophilia	4
Eosinopenia	19
Platelets:	
Thrombocytopenia	7
SGOT: Elevated	4
SGPT: Elevated	6
Widal titres:	
TO >1:100	45
TH >1: 200	41
Blood culture positive: Salmonella	12

Our findings are similar to most of the studies who have reported typhoid fever being more common beyond 5 years of age. [32] The higher incidence in school going children can be explained from the fact that school children are at high risk of consuming contaminated drinking water. They are also exposed to various food items from street vendors. These factors make them more vulnerable to exposure to typhoid bacilli. Hoverer the study of Sinha A et al found almost equal incidence in the two age groups. This however can be attributed to the fact that they carried out their study in a low-income urban area of Delhi, with active surveillance for case detection. [33] Variability in diagnosis among younger children could be related to the high incidence of other illnesses in this age group, difficulty in obtaining adequate volumes of blood for culture, lower rates of exposure, and protective effect of breastfeeding. Also, we didn‟t find any sex predilection in this study, Different researchers [34-36] have also reported variable sex incidences. In this study, fever was the presenting symptom in all the patients which

was more of remittent or intermittent type, classical stepladder rise of temperature was not seen.

Chow et al investigated usefulness of widal test in diagnosing typhoid fever in endemic areas in children. They found widal test to be positive in 88% of typhoid fever cases on 1st occasion when the test was done. [37] Parry et al also reported that 83% of blood culture positive cases of typhoid fever had a positive widal test. [38]

Few studies have been conducted on hematological profile of typhoid fever patients with no reported study in our region. Akgun et al reported leucopenia in 20% of patients. [39] Yaramis A et al [40] reported leucopenia in 18% & thrombocytopenia in 10% of cases in their study on pediatric population. They reported a left shift in 78% of cases. Leucocyte count is usually not less than 2500/mm3 and severe leucopenia (less than 2000/mm3) is very rare. [37] Leucocytosis is commonly seen in children in first 10 days of illness & in cases of hemorrhage. P K Yap & C T Chua [41] observed anemia in 13%, leucopenia in 16 % & thrombocytopenia in 32% of cases in their study. Malik A S & Malik R H [42] found thrombocytopenia in 26% of typhoid fever cases in Malasian children. Ifeanyi O E reported reduced PCV, reduced neutrophil count and relatively raised lymphocyte count in typhoid patients. [44]

Thrombocytopenia is generally seen as a complication of typhoid fever. However it can also be encountered as a presenting symptom. [43]

The main limitation of this study is hospital-based nature of data, which may not reflect the actual situation in the community. The clinical history and examination conducted by different team members at different time periods might have lacked uniformity. The use of antibiotics prior to hospitalization was based on a solicited history, and lacked documentation of specific drug in few cases. Discretionary use of hepatic enzymes and serological tests limited the number available for analysis. Minimum inhibitory concentration (MICs) and genomic sequencing of the isolates could have provided more insights into the emerging antimicrobial resistance, but were not available in this study. The retrospective nature of data and small sample size for trend comparison were other potential limitations.

Conclusion:

The data generated from present study concludes that Typhoid fever manifestations are diverse. The most common symptoms apart from fever were anorexia, vomiting, pain abdomen, diarrhoea followed by headache and cough. The Serum parameters are also seen changed in the Typhoid affected patients. Typhoid fever remains a major public health problem in the developing countries predominantly seen in school going children among pediatric age group.

References:

1. Papagrigorakis MJ, Synodinos PN, Yapijakis C. Ancient typhoid epidemic reveals possible ancestral strain of Salmonella enterica serovar Typhi. Infect Genet Evol. 2007 Jan. 7(1):126-7.
2. Christie AB. Infectious Diseases: Epidemiology and Clinical Practice. 4th ed. Edinburgh, Scotland: Churchill Livingstone; 1987.
3. Raffatellu M, Chessa D, Wilson RP, Tükel C, Akçelik M, Bäumler AJ. Capsule-mediated immune evasion: a new hypothesis explaining aspects of typhoid fever pathogenesis. Infect Immun. 2006 Jan. 74(1):19-27.
4. Parry CM, Hien TT, Dougan G, et al. Typhoid fever. N Engl J Med. 2002 Nov 28. 347(22):1770-82.
5. de Jong HK, Parry CM, van der Poll T, Wiersinga WJ. Host-pathogen interaction in invasive Salmonellosis. PLoS Pathog. 2012. 8(10):e1002933.
6. Ramsden AE, Mota LJ, Münter S, Shorte SL, Holden DW. The SPI-2 type III secretion system restricts motility of Salmonella-containing vacuoles. Cell Microbiol. 2007 Oct. 9(10):2517-29.
7. Gonzalez-Escobedo G, Gunn JS. Gallbladder epithelium as a niche for chronic Salmonella carriage. Infect Immun. 2013 Aug. 81(8):2920-30.
8. Chiou CS, Wei HL, Mu JJ, Liao YS, Liang SY, Liao CH, et al. Salmonella enterica serovar Typhi variants in long-term carriers. J Clin Microbiol. 2013 Feb. 51(2):669-72.
9. Levine MM, Tacket CO, Sztein MB. Host-Salmonella interaction: human trials. Microbes Infect. 2001 Nov-Dec. 3(14-15):1271-9.
10. Earampamoorthy S, Koff RS. Health hazards of bivalve-mollusk ingestion. Ann Intern Med. 1975 Jul. 83(1):107-10.
11. Ali S, Vollaard AM, Widjaja S, Surjadi C, van de Vosse E, van Dissel JT. PARK2/PACRG polymorphisms and susceptibility to typhoid and paratyphoid fever. Clin Exp Immunol. 2006 Jun. 144(3):425-31.
12. Ram PK, Naheed A, Brooks WA, Hossain MA, Mintz ED, Breiman RF. Risk factors for typhoid fever in a slum in Dhaka, Bangladesh. Epidemiol Infect. 2007 Apr. 135(3):458-65.
13. Karkey A, Thompson CN, Tran Vu Thieu N, Dongol S, Le Thi Phuong T, Voong Vinh P, et al. Differential epidemiology of Salmonella Typhi and Paratyphi A in Kathmandu, Nepal: a matched case control investigation in a highly endemic enteric fever setting. PLoS Negl Trop Dis. 2013. 7(8):e2391.
14. Vollaard AM, Ali S, van Asten HA, Widjaja S, Visser LG, Surjadi C, et al. Risk factors for typhoid and paratyphoid fever in Jakarta, Indonesia. JAMA. 2004 Jun 2. 291(21):2607-15.
15. Gotuzzo E, Frisancho O, Sanchez J, Liendo G, Carrillo C, Black RE, et al. Association between the acquired immunodeficiency syndrome and infection with Salmonella typhi or Salmonella paratyphi in an endemic typhoid area. Arch Intern Med. 1991 Feb. 151(2):381-2.
16. Manfredi R, Chiodo F. Salmonella typhi disease in HIV-infected patients: case reports and literature review. Infez Med. 1999. 7(1):49-53.
17. Gordon MA, Graham SM, Walsh AL, Wilson L, Phiri A, Molyneux E, et al. Epidemics of invasive Salmonella enterica serovar enteritidis and S. enterica Serovar typhimurium infection associated with multidrug resistance among adults and children in Malawi. Clin Infect Dis. 2008 Apr 1. 46(7):963-9.
18. Monack DM, Mueller A, Falkow S. Persistent bacterial infections: the interface of the pathogen and the host immune system. Nat Rev Microbiol. 2004 Sep. 2(9):747-65.
19. van de Vosse E, Ali S, de Visser AW, Surjadi C, Widjaja S, Vollaard AM, et al. Susceptibility to typhoid fever is associated with a polymorphism in the cystic fibrosis transmembrane conductance regulator (CFTR). Hum Genet. 2005 Oct. 118(1):138-40.
20. Poolman EM, Galvani AP. Evaluating candidate agents of selective pressure for cystic fibrosis. J R Soc Interface. 2007 Feb 22. 4(12):91-8.
21. Dutta TK, Beeresha, Ghotekar LH. Atypical manifestations of typhoid fever. J Postgrad Med. 2001 Oct-Dec. 47(4):248-51.

22. Arndt MB, Mosites EM, Tian M, Forouzanfar MH, Mokhdad AH, Meller M, et al. Estimating the burden of paratyphoid a in Asia and Africa. PLoS Negl Trop Dis. 2014 Jun. 8 (6):e2925.

23. Mogasale V, Maskery B, Ochiai RL, Lee JS, Mogasale VV, Ramani E, et al. Burden of typhoid fever in low-income and middle-income countries: A systematic literature-based update with risk-factor adjustment. Lancet Glob Health. 2014;2: e570-80.

24. W2. World Health Organization. Typhoid Vaccines: WHO Position Paper – March 2018. Weekly Epidemiological Record. 2018;13:153-72.

25. Meiring JE, Gibani M, Basnyat B, Bentsi-Enchill AD, Clemens J, Darton TC, et al. The Typhoid Vaccine Acceleration Consortium (TyVAC): Vaccine Effectiveness Study Designs: Accelerating the introduction of typhoid conjugate vaccines and reducing the global burden of enteric fever. Report from a Meeting held on 26–27 October 2016, Oxford, UK. Vaccine. 2017;35:5081-8.

26. Ochiai RL, Acosta CJ, Danovaro-Holliday M, Baiqing D, Bhattacharya SK, Agtini MD et al. A study of typhoid fever in five Asian countries: Disease burden and implications for controls. Bull World Health Organ. 2008;86:260-8.

27. Feasey NA, Gaskell K, Wong V, Msefula C, Selemani G, Kumwenda S, et al. Rapid emergence of multidrug resistant, H58-lineage Salmonella typhi in Blantyre, Malawi. PLoS Negl Trop Dis. 2015;9:e0003748.

28. Parry CM, Wijedoru L, Arjyal A, Baker S. The utility of diagnostic tests for enteric fever in endemic locations. Expert Rev Anti Infect Ther. 2011;9:711-25.

29. Sanjeev H, Nayak S, Pai AKB, Rai R, Karnaker V, Ganesh HR. A systematic evaluation of Rapid Dot-EIA, blood culture and Widal test in the diagnosis of typhoid fever. Nitte University J Health Science. 2013;3:21-4.

30. Buckle GC, Walker CL, Black RE. Typhoid fever and paratyphoid fever: systematic review to estimate global morbidity and mortality for 2010. J Glob Health 2012; 2: 10401.

31. Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL. Typhoid fever.Lancet. 2015 Mar 21;385(9973):1136-45. doi: 10.1016/S0140-6736(13)62708-7. Epub 2014 Oct 21.

32. Kumar A, Pandit V, Shetty S, Rao CR, Pattanshetty S, Samarasinghe CM. Study of Clinical Profile and Antibiotic Sensitivity Pattern in Culture-positive Typhoid Fever Cases. Indian J Community Med 2012;37:256-8

33. Sinha A, Sazawal S, Kumar R, Sood S, P Reddaiah VP, Singh B et al. Typhoid fever in children aged less than 5 years. The Lancet. 1999; 354 (9180):734-7.

34. Garg K, Mangal N, Mathur HC. Clinical profile of multi drug resistant typhoid fever in Jaipur City. Indian Pediatr 1994 Feb;31:191-3.

35. Mathura KC, Chaudhary D, Simkhada R, Pradhan M, Shrestha P, Gurubacharya DL. Study of clinical profile and antibiotic sensitivity pattern in culture positive typhoid fever cases. Kathmandu University Medical Journal 2005;3:376-9.

36. Chowta MN, Chowta NK. Study of clinical profile and antibiotic response in typhoid fever. Indian J Med Microbiol 2005;23:125-7.

37. Chow CB, Wang PS, Cheung MW, Yan WW, Leung NK. Diagnostic value of the Widal test in childhood typhoid fever. Pediatr Infect Dis J. 1987 Oct;6(10):914-7. [PubMed]

38. Parry CM, Hoa NT, Diep TS, Wain J, Chinh NT, Vinh H, Hien TT, White NJ, Farrar JJ. Value of a single-tube widal test in diagnosis of typhoid fever in Vietnam. J Clin Microbiol. 1999 Sep;37(9):2882-6. [PubMed]

39. Akgun Y, Bac B, Boylu S, Aban N, Tacyildiz I. Typhoid enteric perforation. Br J Surg. 1995 Nov;82(11):1512-5.

40. Yaramis A, Yildirim I, Katar S, Ozbek MN, Yalcin I, Tas M et al. Clinical and Laboratory Presentation of Typhoid fever. International Pediatrics.2001;16(4): 227 – 231.

41. Yap PK, Chua CT. The haemogram in the diagnosis of acute typhoid fever--with special reference to thrombocytopenia. Singapore Med J. 1983 Jun;24(3):161-2. [PubMed]

42. Malik AS, Malik RH. Typhoid fever in Malaysian children. Med J Malaysia. 2001 Dec;56(4):478-90. [PubMed]

43. Serefhanoglu K, Kaya E, Sevinc A, Aydogdu I, Kuku I, Ersoy Y. Isolated thrombocytopenia: the presenting finding of typhoid fever. Clin Lab Haematol. 2003 Feb;25(1):63-5.

44. Ifeanyi OE. Changes in some haematological parameters in typhoid patients attending University Health Services Department of Michael Okpara University of Agriculture, Nigeria. Int. J.Crr. Microbiol. App. Sci 2014; 3(1):670 -674.