International Journal of General Medicine
and Pharmacy (IJGMP)
ISSN(P): 2319-3999; ISSN(E): 2319-4006
Vol. 5, Issue 3, Apr - May 2016, 1-12

International Academy of Science,
Engineering and Technology
Connecting Researchers; Nurturing Innovations

ENTERIC FEVER-REVISITED

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ABSTRACT

Enteric fever is systemic infection with the bacterium *salmonella enterica* serotype typhi and it continues to be a worldwide major health problem. Today enteric fever is causing diagnostic and therapeutic challenge for physicians in Indian subcontinent and south-east Asia due to its changing mode of presentation as well as the occurrence of multidrug resistance. This review focuses on recent atypical clinical presentation, newer diagnostic test and changing pattern of multidrug resistant enteric fever (MDREF) and its therapeutic options.

KEYWORDS: Atypical Presentation, Diagnostic and Therapeutic Challenge, Enteric Fever, Multidrug Resistance Enteric Fever, *Salmonella Typhi*

INTRODUCTION

Enteric fever is a systemic infection caused by the bacterium *salmonella enterica* serotype *typhi*. It is derived from the Greek word '*typhos*' meaning smoke/cloud, which refers to the apathy and confusion being the prominent features of a fully developed and untreated disease. Enteric fever continues to be a global health problem. The burden of the disease is extensive in the developing countries where basic sanitary conditions remain poor.

In India, the disease is endemic with a morbidity rate varying from 102 to 2219 per 100,000 populations. Today enteric fever is causing diagnostic and therapeutic challenge for physicians in Indian subcontinent and south-east Asia due to its changing mode of presentation as well as the occurrence of multidrug resistance. Simultaneously, the clinical symptoms are often obfuscated by various diseases presenting with fever like malaria, dengue fever, leptospirosis, rickettsioses. Chloramphenicol was the Gold standard treatment of enteric fever for long, but widespread and indiscriminate use of this drug lead to the resistant strains of salmonella. Resistance to commonly used antibiotics like chloramphenicol, ampicillin, amoxicillin, cotrimoxazole, ciprofloxacin and cefotaxime, has been reported from different parts of India in last two decades, which has further complicated the treatment of enteric fever.

This review focuses on recent atypical clinical presentation, newer diagnostic test and changing pattern of multidrug resistance enteric fever (MDREF) and its therapeutic options.

TERMINOLOGY

Enteric fever is a systemic clinical syndrome produced by certain salmonella organisms. It encompasses the terms typhoid fever, caused by *S. typhi* and paratyphoid fever caused by *S. paratyphi* A, *S. paratyphi* C. and occasionally other salmonella serotypes[6]. In practice, the terms enteric fever and typhoid fever (Cloudy fever) are used synonymously.

CAUSITIVE ORGANISM

Salmonella is a gram –ve enterobacteriaceae. It has two species- *salmonella enterica* (six sub species) and *salmonella bongori*. *Salmonella typhi* and *paratyphi* are sub species of *salmonella enterica*. It is non-spore forming facultative anaerobic bacilli of size 2-3 µm x 0.4-0.6 µm.

EPIDEMIOLOGY

Despite various health measures, the prevalence of enteric fever is rising and the burden of the disease lies on the developing countries because of poor sanitary conditions[1], rapid population growth, increased urbanization, inadequate human waste treatment, limited water supply and overburdened health care system. In 2000, it was estimated that over 2.16 million episodes of typhoid occurred worldwide, resulting in 216000 deaths affecting all ages[7]. The annual incidence is highest (> 100 cases/100000 population) in south central and southeast Asia; medium (10-100 cases/100000 population) in rest of Asia, Africa, Latin America, Oceania (excluding Australia and New Zealand); low (<10/100000 population) in rest parts of the world. In India, the disease is endemic with a morbidity rate varying from 102 to 2219 per 100,000 population[3, 4, 5]. Reported data for the year 2013 shows 1.53 million cases and 361 deaths from typhoid in India[59].The reasons are many. In endemic areas, the identified risk factors for the disease include eating food prepared outside the home, such as ice cream or flavored iced drinks from street vendors[8,9], drinking water contaminated[10] with faces and urine occurring despite preventive health measures, having a close contact or relative with recent typhoid fever[8], poor housing with inadequate facilities for personal hygiene[11]. Human Immunodeficiency Virus (HIV) infected patient also have an increased incidence of *S. typhi* infection in industrialized countries[12] of the world where typhoid is not a big problem. Infection from laboratories does occur. Carriers are often responsible for epidemic outbreak[13].

CLINICAL PRESENTATION

The clinical presentation is variable in nearly up to 50% of cases and the classical clinical feature may not be seen in all the patients and the disease may present in atypical form. Table-1 gives an account of such classical and atypical presentation of Enteric Fever.

Table 1: Clinical Presentation

Classical Presentation	Atypical Presentation
FEVER[14,15] High grade continuous "Step Ladder" rise without chills and rigor	High grade, continuous or intermittent with chills & rigor
HEPATOMEGALY[16] **:** - Hepatomegaly with splenomegaly (soft) - Nontender	- Hepatomegaly alone or associated with splenomegaly (soft to firm) - Tender
RESPIRATORY SYMPTOMS: Less common	More common (cough, audible crackles on chest examination)
PARALYTIC ILEUS : Common	Low incidence
INTESTINAL PERFORATION AND BLEEDING :	
Common	Less common
ACUTE NEPHRITIS : Common	Less common
CLINICAL JAUNDICE[17] (Typhoid Hepatitis): Common	Rare: (Only mild alteration in SGOT/PT and ALK.

	Phosphates suggestive of hepatic involvement)
ARTHRITIS AND ARTHRALGIA WITH JOINT EFFUSION :	
Less common	More common
CARDIOVASCULAR[18,19] : Rare	Frequent (Myocarditis, Endocarditis, Pericarditis – Rare)
NEUROPSYCHIATRIC MANIFESTATION[15,19] :	
Less common	More common. (Delirium, Psychosis, Seizure, Encephalopathy, Typhoid Meningitis, Cerebritis, Peripheral Neuritis, Guillain-Barre syndrome, Bell's palsy, Parkinsonism, Encephalomyelitis, Transverse myelitis, Pseudo bulbar palsy, Palatal palsy, chorea etc.)
CHLORAMPHENICOL RESISTANCE[20] :	
Not seen	Common-Since 1972 (India) (Kerala, New Delhi, Calcutta, Mumbai, Pondicherry, Rajasthan, Pune, Srinagar, Punjab).
MULTI DRUG RESISTANCE : Not present **FLUOROQUINOLONE RESISTANCE [21,22,23]:** Not present	Incidence increasing Incidence increasing

INVESTIGATIONS

Certain relevant investigations clinch early diagnosis and help cut-short the period of illness.

Diagnostic Test

Bacterial Culture

Blood Culture

Blood Culture gives positive results in 44-83% of cases[24, 25]. The sensitivity decreases after the first week of disease[58]. The yield may improve when blood samples are drawn from three different sites at one time. Blood culture is the mainstay of the diagnosis of this disease[58]. The volume of blood culture[26] and the ratio of blood to broth determines blood culture yield. 10-15 ml should be taken from school children and adult in order to achieve optimal isolation rate where as 2-4 ml are required from toddlers and preschool children, this is because children have higher levels of bacteremia than adults. A failure to isolate the organism may be caused by several factors i) the limitation of laboratory media, ii) the presence of antibiotics, iii) the volume of the specimen cultured or iv) the time of collection.

Bone Marrow

Bone marrow culture has proved to be a very sensitive diagnostic test[31]. Culture gives positive result in >80%[57] of cases. However, bone marrow aspiration and culture may not be feasible in all clinically suspected cases in endemic area as it is a painful procedure and requires trained staff for specimen collection.

Stool and Urine culture

Stool and urine culture can also be used for diagnosis of enteric fever but they are less sensitive than blood culture[58]. For stool culture 3-10grams of stool is taken in an "enteric kit" (bottle with Cary Blair medium with 0.16% agar)

[57]. Rectal swabs are not preferred. Urine culture has very poor diagnostic yield of 7%[60]

Widal Agglutination Test

This is most commonly used serological test for the diagnosis of enteric fever. The test detects the presence of agglutinating antibodies in the serum of infected / exposed patients against lipopolysaccharides (LPS;O) and flagella (H) antigens of *Salmonella typhi*[26].These antibodies are present at 6-8 days and 10-12 days respectively. A progressive fourfold rise of titer in paired sera is considered significant[27,28]. Nowadays, the widal test, of single serum from a recently admitted patients showing a titre of 160 or more antigen (somatic, O) is considered diagnostically significant. Clinically, it is obvious that a single widal test in an unvaccinated or unexposed patient may have some diagnostic relevance. However, the result of such a single test has no diagnostic significance in an endemic region because of following regions[28]. i) the inherent variability's of the test, ii) difficulty in establishing a steady-state baseline titre for the population, iii) repeated exposures to S. typhi in endemic regions, iv) cross reactivates with other non-salmonella organisms (malaria, dengue, milliary tuberculosis, chronic liver disease etc.) and iv) lack of reproducibility of the test result. The false positivity in widal test in fever of viral aetiology and malaria[29], can be significantly reduced by the use of modified widal test[30], where in inactivating (by 2 mercaptoethanol) IgM antibodies (specific for somatic antigen, O) the agglutination would be brought about only by specific IgG while in the conventional Widal test agglutination is due to specific IgG and IgM (specific for flagellar antigen, H). The difference in the titres indicates specific IgM class of antibodies which is the hallmark of recent infection.

Newer Diagnostic Tests

***DNA Probe*[31]**

Ruben et al constructed a DNA probe cloned from *Citrobacter freundii* which has similar Vi antigen as that of the ViaB region of chromosome of *Salmonella typhi*. It was found to be highly specific for the DNA of S. typhi but low sensitivity. It could detect only 76% cases with positive blood cultures and 44% in bone marrow positive cultures. More so, it requires high technical expertise and it is not cost effective when performed on an individual basis. The process is time consuming.

***Polymerase Chain Reaction (PCR)* [31]**

This method is specific and more sensitive than blood culture. The widely researched target genes for *Salmonella typhi* PCR based assays include *fliC-d, viaB, invA, hilA a*nd others. It is positive even in presence of low level of bacteremia in enteric fever. But it is expensive and often, technical expertise is not available. Contamination of specimen may yield false positive result.

***Co-Agglutination (Coag) and Latex Agglutination (LA) Test*[32]**

These are rapid diagnostic method for diagnosing enteric fever by detecting Barber Protein (BP) and Vi-antigen of S. typhi in patient's sera (table-2). These tests have advantages over blood culture and the Widal test, as results are rapidly available there is no requirement for paired sera, results are unaltered by prior antibiotic therapy and cheaper so that they can be applied on masses.

Table 2: Summaries of the Sensitivity and Specificity of These Tests in Blood Culture Positive and Widal Test Positive Subjects

Test	Sensitivities (%)	Specificities (%)
LA Test	Vi = 93.3	100.0
	BP = 91.7	98.5
Coag Test	Vi = 83.3	98.5
	BP = 86.7	98.5

Adenosine Deaminase (ADA) Activity[33]

Adenosine deaminase is an enzyme that catalyses the irreversible hydrolytic deamination of adenosine into inosine and ammonia, is considered as marker of cell medicated immunity. A recent publication has concluded that the peak ADA level was observed in the later part of the first week and may remain elevated up to four weeks. The low ADA levels at diagnosis in enteric fever reflects poor cell mediated immunity and these patients tend to develop complications. The specificity of this test needs verification.

Typhidot [34, 26]

Typhidot test is an enzyme linked immunosorbant assay (ELISA) in the dot test format, which detects IgM and IgG antibodies against Outer Membrane Protein (OMP) of Samonella Typhi with specificity of 80 percent and sensitivity of 100 percent[35] on stored sample. Test becomes positive in the 1st week of infection. It is easy and rapid to perform and to read. The detection of IgM reveals acute typhoid in the early phase of infection, while the detection of both IgG and IgM suggest acute typhoid in the middle phase of infection. In case of reinfection there is a secondary immune response with a significant boosting of IgG over IgM and in order to increase the diagnostic accuracy in these situations the original Typhidot test was modified (Typhidot-M) by inactivating total IgG in the serum sample. Typhidot-M can replace the widal test when used in conjuction with the culture method for the rapid and accurate diagnosis of typhoid fever. The high negative predictive value of the test suggests that Typhidot-M would be useful in areas of high endemicity.

TREATMENT

Case Definition

CONFIRMED CASE	A patient with persistent fever (38°c or more) lasting 3 or more days, with laboratory confirmed *S. typhi* organisms (blood, bone marrow, bowel fluids).
PROBABLE CASE	A patient with persistent fever (38°c or more) lasting 3 or more days, with a positive serodiagnosis or antigen detection test but no *S. typhi* isolation.
CHRONIC CARRIER	An individual excreting *S. typhi* in the stool or urine for longer than 1 year after the onset of acute typhoid fever.

Evolutionary Concept

In pre-chloramphenicol days, dietary modification was the only method of treatment of enteric fever available. It consisted mainly of liquid foods especially milk and juices. Diet restriction was resorted to and sometimes this reached to the brink of semi starvation. Today diet apparently does not play any important role but adequate caloric intake and supply of sufficient fluids and electrolytes is ensured so as to compensate for their loss during the course of illness. From 1960 onward, a variety of drugs were offered as 'cure', the main plank being antibiotics. Chloramphenicol was the first. It was the Gold standard treatment of enteric fever for long. But widespread and indiscriminate use of this drug for the treatment

of diarrhoeal diseases and other infections led to "failed response". This was mainly due to appearance of drug resistant strains of salmonella[36].

Drugs

- Chloramphenicol used as a first line drug treatment of enteric fever before seventies.
- Ampicillin and amoxicillin: these two drugs were supposed to be good drugs for the treatment of enteric fever. These were chosen to treat resistant cases during the seventies.
- In 1980s, cotrimoxazole became the drug of choice for treatment of enteric fever. It was useful in patients with organism's resistance to chloramphenicol.
- Since 1990s *Salmonella typhi* developed resistance simultaneously to all of the drugs used in first line treatment (chloramphenicol, contrimoxazole and ampicillin) and are known as Multi Drug Resistant Enteric Fever (MDRTF) [37]. Fluroquinolones and cephalosporins were added to the list in 1990s. Selected fluroquinolones eg. Ciprofloxacin, ofloxacin etc, were useful for cases where the disease was due to Multi Drug Resistant Enteric Fever (MDREF). Lately these drugs became the first line in the treatment of enteric fever, as they were cheap and very effective. Later on some strains of S. typhi also showed reduced susceptibility to the fluroquinolones[38, 39, 40, and 21]. These organisms when tested by disc testing with nalidixic acid showed resistance. So in other words resistance to nalidixic acid is a surrogate marker which predicts the fluroquinolones failure and can be used to guide antibiotic therapy. The nalidixic acid resistant *S. typhi* (NARST) is a marker of reduced susceptibility to Fluroquinolones. Clinical safety of ciprofloxacin in children is controversial because of fear of acute arthropathy (joint pains, restriction of joint movement, and/or joint swelling) as though it is completely reversible. The arthropathic side effects are seen in animals with high dose when used for prolonged period. But most of the studies[41, 42, and 43] done so far in children have not documented any skeletal toxicity.
- Cerfuroxine axetil[44] is considered to be safe and very effective in adults. Several newer third generation cephalosporins including ceftriaxone, cefotaxime and cefoperazone have been used in the treatment of enteric fever. Certriaxone so far has been used most widely and it is considered to be safest for the use in the children.
- Cephalosporins are expensive drugs and should be used discretely. Indications for their use are[45]:-
  - Ciprofloxacin-resistant typhoid
  - Typhoid meningitis
  - Typhoid fever in pregnancy and G6PD deficiency, where quinolones are contraindicated.
  - When quinolone therapy produces or aggravates psychosis.
- Gentamycin and Netilmycin are the two aminoglycosides used in enteric fever. Netilmycin, along with third generation cephalosporins, is considered as a drug of choice in S. typhi meningitis[46].
- Steroids in addition to antibiotics are used in severe or complicated cases with severe toxaemia with prolonged altered state of consciousness, shock and DIC. Its use is based on the assumption that adrenocortical functions are impaired due to gram negative endotoxaemia. The dose recommended is 3 mg/kg of intravenous dexamethasone over 30 minutes initially, followed by 1 mg/kg every 6 hours[47], along with H_2 receptor blockers.

- Recently, azithromycin[26] is being used as an alternative agent for treatment of uncomplicated cases; aztreonam and imipenem[1] are also potential second line drugs which are used in severe cases.

MULTI DRUG RESISTANT ENTERIC FEVER (MDREF)

Multidrug resistant enteric fever is a major problem in the recent arena. Epidemiological studies tended to define MDREF as strains of Salmonella that are resistant to two or more antibiotics in vitro[61]. Clinically the term MDREF denotes to those strains which are resistant to all the three first line antibiotics: Chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole[62]. The MDREF is plasmid mediated and the incidence of MDREF is rapidly increasing in India and has become a global problem too. First report of chloramphenicol resistant strain came from England in 1950[43]. First epidemic caused by chloramphenicol resistant strain was that which occurred in Mexico[63] in 1972. In 1987, MDREF was reported from South East Asia[48]. Since 1989 outbreaks caused by strains of S. typhi resistant to chloramphenicol, ampicillin & trimethoprim and with additional resistance to streptomycin, sulfonamide and tetracyclines have been reported in Pakistan and India[64]. Table 3 depicts the scene of drug resistance in India.

Table 3: Drug Resistance in India

Year	Religion	Author	Drug	Resistance (%)
1972	Kerala	Paniker & Vimala[49]	CH, CO, AMP	2.5
1988	Mumbai	Rodrigues et al[50]	CH, CO, AMP	1.6
1989	Mumbai	Deshpande et al[44]	CH, CO, AMP	6.2
1989	Mumbai	Deshpande et al[44]	CH, CO, AMP	23.2
1990	Mumbai	Rodrigues et al[50]	CH, CO, AMP	31.0
1990	Mumbai	Deshpande et al[44]	CH, CO, AMP	35.0
1990	Calcutta	Anand et al[51]	AMP, CH, CO	49.1-89.1
1991	New Delhi	Gupta & Meena[14]	CEF, CH, AMP, GEN, AM, NET, CO	8.33-87.5
1992	Pondicherry	Chandra et al[52]	CH, AMP, CO, FUR, CIP	71.0
1996	Rajasthan	Maheshwari & Agrawal[53]	AMX, CH, AM, GEN, AMP, CO	33.0-70.0

(CH-Chloramphenicol, CO=Cotrimoxazole, AMP=Ampicillin, AMX = Amoxicillin, CIP=Ciprofloxacin, GEN=Gentamycin, AM=Amikacin, FUR=Furezolidene, CEF=Cefotaxine, NET=Netilmicin)

TREATMENT OF MDREF

Multidrug resistant enteric fever (MDREF) has become a therapeutic challenge for physicians in the Indian subcontinent and Southeast Asia. By 1999, it was recommended triple therapy will have to be instituted using a ceftriaxone, quinolone and aminoglycoside for effective therapy[54, 55, 56]. The options available to a physician for treatment of MDREF are namely:

- Triple therapy with third generation cephalosporin, quinolone and aminoglycoside.
- Cetriaxone and
- Ceftibuten.

The last two options should be preserved to situations where other options have failed. With triple therapy defervescence occurs between 6-8 days in most patients.

Table 4 and 5 outlines the treatment strategies for both uncomplicated and severe Enteric Fever with different

sensitivity patterns.

Table 4: Treatment of Uncomplicated Enteric Fever[26]

	1st Line Oral Drugs			2nd Line Oral Drugs		
Susceptibility	**Antibiotic**	**Daily Dose mg/kg**	**Days**	**Antibiotic**	**Daily Dose mg/kg**	**Days**
Fully sensitive	Fluroquinolone e.g. ofloxacin or ciprofloxacin	15	5 – 7	Chloramphenicol Amoxicillin Cotrimoxazole	50-75 75-100 8-40	14 – 21 14 14
Multidrugs Resistance	Fluroquinolone Or cefixime	15 15-20	5-7 7-14	Azithromycin Cefixime	10-20 15-20	7 7-14
Fluroquinolone Resistance	Azithromycin or Cefixime	8-10 15-20	7 10-14	Cefixime	20	7-14

Table 5: Treatment of Severe Enteric Fever[26]

	1st Line Parenteral Drugs			2nd Line Parenteral Drugs		
Susceptibility	**Antibiotic**	**Daily Dose mg/kg**	**Days**	**Antibiotic**	**Daily Dose mg/kg**	**Days**
Fully sensitive	Fluroquinolone e.g. ofloxacin	15	10-14	Chloramphenicol Amoxicillin Cotrimoxazole	100 100 8-40	14 – 21 14 14
Multidrugs Resistance	Fluroquinolone	15	10-14	Ceftriaxone or Cefotaxime	60 60	10-14
Fluroquinolone Resistance	Ceftriaxone or cefotaxime	60 80	10-14	Fluroquinolone	20	7-14

REFERENCES

1. Parry CM, Hien TT, Dougan G, white NJ, and Farrar JJ. Typhoid Fever. N. Engl. J. Med 2002; 347:1770-82
2. Ochiai RL, Acosta CJ, Danovaro-Holliday MC, Baiqing D, Bhattacharya SK, Agtini MD, et al; Domi Typhoid Study Group. A study of typhoid fever in Five Asian Countries: disease burden and implication for controls. *Bull World Health organ* 2008; 86:260-8
3. Park JE, Park K: Typhoid Fever. *Text Book of Preventive Social Medicine*. 13th ed. Banarasidas Bhanol 1991; 558-560.
4. Park K. Intestinal infections; Typhoid fever, In Park's *Text Book of Preventive and Social Medicine*, Jabalpur. 14th Ed. 1994.
5. Chowta MN, Chowta NK. Study of clinical profile & Antibiotic Response in Typhoid Fever. *Indian J Med Microbiol* 2005; 23(2) : 125-27
6. Ashkenazi S., Cleary TG. Ciprofloxacin Use: Acute Arthopathy and Long Term Follow-up. *Ind. Pediat* 1996; 33(1):910-916.
7. Crump JA, Luby SP, Mintz ED. The Global burden of typhoid fever. Bull World Health Organ 2004; 82:346-53.
8. Black RE, Cisneros L, Levine MM, Banfi A, Lobos H, Rodriquez H. Case-control study to identify risk factors for paediatric endemic typhoid fever in Santiago, Chile. *Bull World Health Organ* 1985; 63(5):899-904.

9. Luby SP, Faizan MK, Fisher-Hoch SP, Syed A, Mintz ED, Bhutta ZA, McCormick JB: Risk factors for typhoid fever in an endemic setting, Karachi, Pakistan. *Epidemiol infect* 1998; 120(2):129-38.
10. Mermin JH, Villar R, Carpenter J, Roberts L, Samaridden A, Gasanova L, Lomakina S, Bopp C, Hutwaqner L, Mead P, Ross B, Mintz ED. A massive epidemic of multidrug-resistant typhoid fever in Tajikistan associated with consumption of municipal water. *J infect Dis* 1999; 179: 1416-22.
11. Gasem MH, Dolmans WM, Kenter MM, Djokomoeljanto RR. Poor food hygiene and housing as risk factors for typhoid fever in Semarang, Indonesia. *Trop Med int Health* 2001; 6:484-90.
12. Manfredi R, Donzelli C, Talo S, Guzman SM, Chiodo F. Typhoid Fever and HIV infection: a rare disease associated in industrialized countries. Int J Infect Dis. 1998-1999 winter; 3(2) : 105-8.
13. Gorbach SL. Typhoid Fever In. *Cecil Text Book of Medicine*. Wingastoden and Smith Eds. 18th Ed. Saunders 1988; p. 1587.
14. Gupta S, Meena HS. Changing Profile of Enteric Fever-In-Summer-91. *J. Assoc. Physicians of India* 1992; 40(11):726-729.
15. Mehta PJ, Hakim A, Kamath S. The Changing Faces of Salmonellosis. *J. Assoc. Physicians of India* 1992; 40(11):713-714.
16. Adams EB. Typhoid and Para-typhoid Fevers. *Oxford Text Book of Medicine*. Weatherall, Ledingham Warrel, Oxford University Press, 2nd Ed 1987, 5:218-23.
17. Kundan AK. Typhoid Hepatitis *J. Assoc. Physicians of India* 2002;50:719-720.
18. Kamili MA, Gazanfar A, Samia R, Reshi GH, Allaqaband GQ. Salmonella infection mimicking Acute Rheumatic Fever. *J. Assoc. Physicians India* 1996; 44(8):579-580.
19. Gokhale YA, Malkan G, Bichile LS, Saraswati K, Deodhar L, Rajopadhyay M, Deodhar KP, Menon PS. Restrospective Treatment Analysis of Salmonella infections. *J. Assoc. Physicians of India* 1992; 40(11):733-735.
20. Chakravorty B, Jain N, Gupta B, Rajvanshi P, Sen MK, Krishna A. Chloramphenicol Resistant Enteric Fever. *J. Assoc. Physicians India* 1993; 91(1):10-13.
21. Ray P, Sharma J, Marak RSK, Garg RK. Predictive efficacy of nalidixic acid resistance as a marker of fluoroquinolone resistance in salmonella enterica var typhi. *Indian J Med Res* 2006; 124:105-108.
22. Kapil A, Das B. Nalidixic acid susceptibility to screen ciprofloxacin resistance in salmonella typhi. *Indian J Med Res* 2002; 115:49-54.
23. Wain J, Hoa TN, Chinh NT, et al. Quinolone resistant salmonella typhi in Vietnam : molecular basis of resistance and clinical response to treatment. *Clin infect Dis* 1997; 25: 1404-10.
24. Akoh JA. Relative Sensitive of blood and bone marrow culture in typhoid fever. *Trop. Doctor* 1991; 21:174-176.
25. Gilman RH, Terminel M, Levine MM, Hernandez-Mendoza P, Hornick RB. Relative efficacy of blood, urine, rectal swab and rose spot culture. *Lancet* 1975; 1211-1213.

26. World health organization. Background document: The diagnosis, treatment and prevention of typhoid fever. WHO/V&B/03.07. Geneva: *World Health Organization* 2003.
27. Sansone P, Saslaw MS, HenneKens CH. High titre widal reaction. *JAMA* 1972; 220:1615-6
28. Olopoenia LA, King AL. Widal agglutination test – 100 years later: still plagued by controversy. *Postgrad Med J* 2000; 76:80-84
29. Singh PS. Two hundred false widal positive cases from Eastern U.P.*J. Assoc. Phisicians India* 1996; 44(11):842.
30. Pai AP, Koppikar GV, Despande S. Role of modified Widal test in the diagnosis of enteric fever. *J. Assoc. Physicians of India* 2003; 51:9-11.
31. Chaudhry R, Shankar S, Nisar N, Dey AB. Recent Advances in the Diagnosis of Enteric Fever. *Trop. Gastro*1995; 16(3):8-12.
32. Pandya M, Pillai P, Deb M. Rapid Diagnosis of Typhoid Fever By Detection of Barber Protein and Vi Antigen OF Salmonella Serotype Typhi. *J. Med. Microbiol* 1995; 43:185-188.
33. Mishra OP, Gupta BL, Ali Z, Nath G, Chandra L. Adenosine Deaminase Activity in Typhoid Fever. *Ind. Pediat* 1994; 31:1379-1384.
34. Jesudasan MV, SivaKumar S. Prospective evaluation of rapid diagnostic test Typhidot for typhoid fever. *Indian J Med Res* 2006; 123:513-6
35. Jesudason M. Esther E, Mathai E. Typhidot test to detect IgM and IgG antibodies in typhoid fever. *Indian J Med Res* 2002; 116:70-2.
36. Agrawal KC, Panhotra BR, Mahanta J, Arya VK, Garg RK. Typhoid Fever due to Chloramphenicol Resistance S. typhi associated with R-plasmid. *Ind. J. Med* 1981; 73:484-488.
37. Kundu R, Ganguly N, Ghosh TK, Yewale VN, Shah RC, Shah NK; IAP Task Force Report : Management of Enteric Fever in Children. *Indian Pediatr* 2006; 43:884-7.
38. Gupta A, Swarnkar NK, Choudhary SP. Changing antibiotic sensitivity in enteric fever. *J Trop Ped* 2001; 47:369-371
39. Dutta P, Mitra U, Dutta S, De A, Chatterjee MK, Bhattacharya SK. Ceftriaxone therapy is ciprofloxacin treatment failure typhoid fever in children. *Indian J Med Res* 2001; 113:210-213
40. Kadhiravan T, Wig N, Kapil A, Kabra SK, Renuka K, Misra A. Clinical outcomes in typhoid fever : adverse impact of infection with nalidixic acid-resistant Salmonella typhi. *BMC infect Dis* 2005; 5(1):37
41. Mishra OP, Gupta BL, Nath G, Prakash J. Treatment of Multi Drug Resistant Typhoid Fever. *J. Tropical Pediatrics* 1996; 42(5):310-311.
42. Karande S, Kshirsagar NA. Ciprofloxacin Use : Acute Arthropathy and Long Term Follow-up. *Ind. Pediat* 1996; 33(11):910-916.
43. Sharma A., Gathwala G. Clinical profile and Outcome in Enteric Fever. *Ind. Pediat* 1993; 30:47-50.

44. Desphande AK, Joshi SR, Lal HM, Cooverji ND, Ajay S. Cefuroxime Axetil in the treatment of Salmonella typhi infection (Enteric Fever) in adults. *J. Assoc. Physicians of India* 1996; 44(11):786-789.
45. Kelkar PM, James E. Typhoid Fever. *J. Assoc. Physician India* 1997; 45:37-48.
46. Giri OP, Singh AN. CSF profile of S. typhi meningitis. *Journal Assoc. Physicians of India* 1992; 40:848.
47. Gerald TK. Salmonellosis. *Harrisons Principles and Practice of Internal Medicine*. Weatherall, Ledingham Warrel, Oxford University Press, 2nd Ed 1987; 5:218-23.
48. Mirza SH, Beeching NJ, Hart CA. Editorial-Multi Drug Resistant Typhoid: a global problem. *J. Med. Microbiol* 1996; 44:317-319.
49. Panikar CKJ, Vimala KN. Transferable Chloramphenicol Resistance in Salmonella Typhi. *Nature* 1972; 239:109-110.
50. Rodrigues C, Mehta A, Mehtar S, Blackmose PH, Hakimiyan A. Chloramphenicol Resistance in Salmonella Typhi Report from Bombay. *J. Assoc. Physicians of India* 1992; 40(11):729-731.
51. Anand AC, Kataria VK, Singh W, Chatterjee SK. Epidemic Multi Resistant Enteric Fever in Eastern India. *Lancet* 1990; 335 (1):352.
52. Chandra R, Srinivasan S, Nalini P, Rao RS. Multi Drug Resistant Enteric Fever. *J Trop Med Hyg* 1992; 95(4):284-287.
53. Maheswari VD, Aggarwal SK. Present status of Drug Resistance in cases of Enteric Fever in Rajasthan. *J. Assoc. Physicians of India* 1996; 44(9):618-619.
54. John M, Mani A. Changing trends in the treatment of enteric fever. *J. Assoc. Physician India* 2000; 40:112.
55. Hassan KM, Murthy D. Changing pattern of multidrug resistant enteric fever - A physician Dilema. *J. Assoc. Physician India* 2001; 49:1043.
56. Chogle AR. Multiple resistant salmonellosis - An Escalating problem. *J. Assoc. Physician India* 2002; 50:375-376.
57. Guidelines of management of Typhoid fever: ministry of health and family welfare Zimbabwe 2011.
58. Guidelines for the diagnosis, management, and prevention of typhoid fever : Ministry Of Health Fiji Islands 2010
59. Typhoid Fever: Park's Textbook of Preventive and Social Medicine 23/e
60. Gilman R.H, Terminel M., Levine M.M., Hernandez-Mendoza P., & Hornick R.B. (1975). Relative efficiency of blood, urine, rectal swab, bone-marrow, and rose-spot culture for recovery of typhoid Fever: Lancet 1975 May 31;1(7918):1211-3
61. Ryder RW, Blake PA, Murlin AL. increase in antibiotic resistant among isolates of Salmonella in the United States 1967-75. J infect Dis 1980; 142: 485-491
62. Smith SM, Palumbo PE, Edelson PJ. Salmonella strains resistant to multiple antibiotics: Therapeutics implications. Paediatr infect Dis 1984; 3:455-460.

63. Olarte J, Galind DE. Salmonella typhi resistant to chloramohenicol, ampicillin and other antimicrobial agents: strains isolated during an extensive typhoid fever epidemic in mexico. Antimicrob agent's chemother 1973; 4:597-601.

64. Rowe B, Ward LR, Threlfall EJ. Multidrug resistant Salmonella typhi: A worldwide epidemic clinical infectious diseases 1997; 24 (suppl I): S 106-9.