“A CROSS SECTIONAL STUDY OF CLINICAL AND BIOCHEMICAL PROFILE OF ENTERIC FEVER”

By

DR. PRIYAL PATEL

Dissertation submitted to

S.B.K.S. MEDICAL INSTITUTE & RESEARCH CENTRE

SUMANDEEP VIDYAPEETH, PIPARIA, VADODARA

In partial fulfillment

of the requirements for the degree of

DOCTOR OF MEDICINE

in

MEDICINE

Under the Guidance of

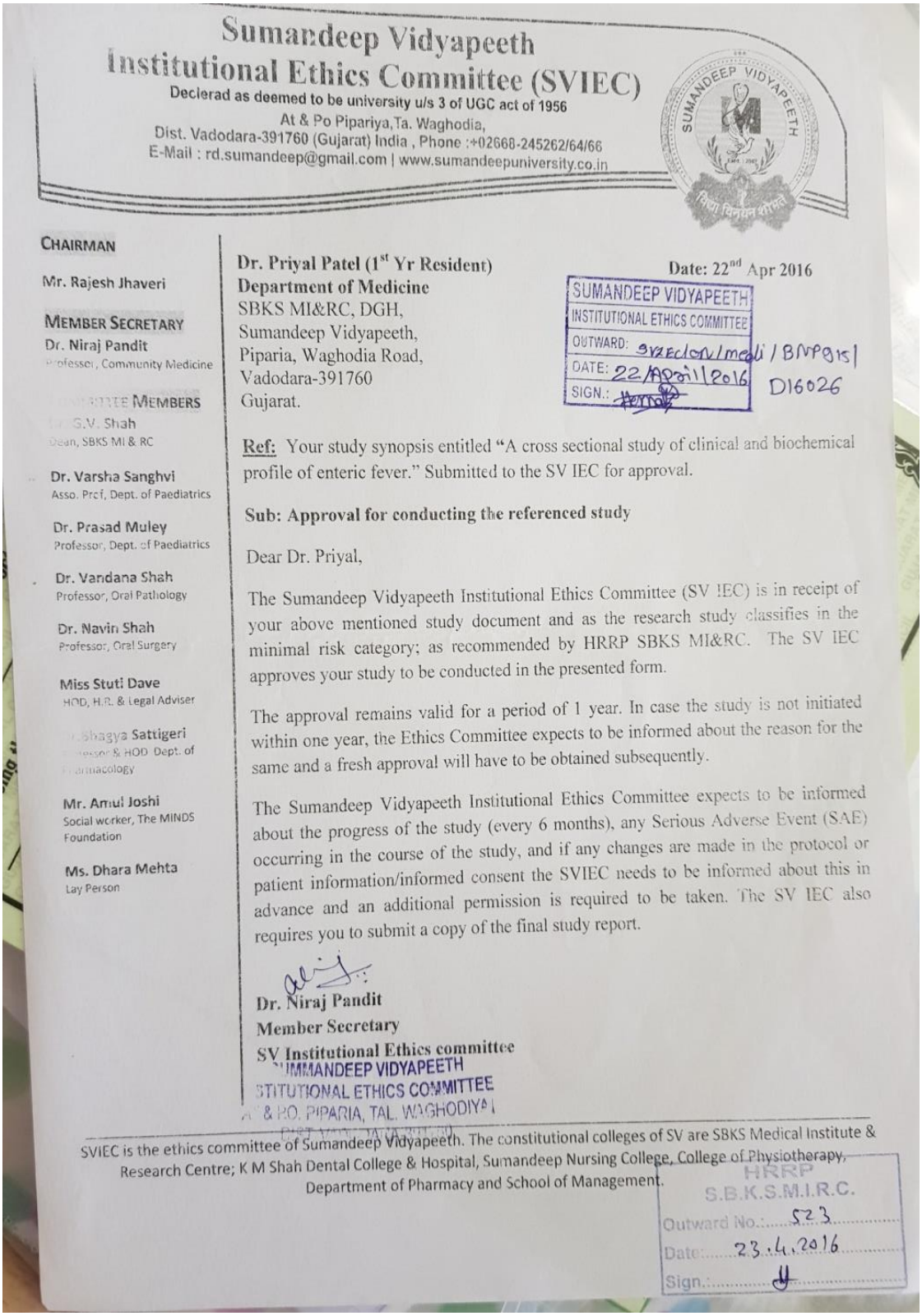
DR. HETAL PANDYA

(PROFESSOR & HEAD OF THE DEPARTMENT OF MEDICINE)

SBKS MEDICAL INSTITUTE & RESEARCH CENTRE,

PIPARIA, VADODARA

YEAR 2015-2018



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Sub: Approval for conducting the referenced study

Dear Dr. Priyal,

The Sumandeep Vidyapeeth Institutional Ethics Committee (SV IEC) is in receipt of your above mentioned study document and as the research study classifies in the minimal risk category; as recommended by HRRP SBKS MI&RC. The SV IEC approves your study to be conducted in the presented form.

The approval remains valid for a period of 1 year. In case the study is not initiated within one year, the Ethics Committee expects to be informed about the reason for the same and a fresh approval will have to be obtained subsequently.

The Sumandeep Vidyapeeth Institutional Ethics Committee expects to be informed about the progress of the study (every 6 months), any Serious Adverse Event (SAE) occurring in the course of the study, and if any changes are made in the protocol or patient information/informed consent the SVIEC needs to be informed about this in advance and an additional permission is required to be taken. The SV IEC also requires you to submit a copy of the final study report.

Dr. Niraj Pandit
Member Secretary
SV Institutional Ethics committee

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Date: 10th October 2017

STUDY COMPLETION CERTIFICATE

This is to certify that your study entitled: "A Cross Sectional Study of Clinical and Biochemical Profile of Enteric Fever" Research Project was done by **"Dr. Priyal Patel"** (PG Student, Dept of Medicine, S.B.K.S MI & RC, Dhiraj Hospital, Piparia, Waghodia road, Vadodara-391760, Gujarat) and it was conducted to the satisfaction of the Sumandeep Vidyapeeth Institutional Ethics committee.

Dr. Niraj Pandit
Member Secretary
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SUMANDEEP VIDYAPEETH

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"A CROSS SECTIONAL STUDY OF CLINICAL AND BIOCHEMICAL PROFILE OF ENTERIC FEVER" AT DHIRAJ GENERAL HOSPITAL, PIPARIA** is a bonafide and genuine research work carried out by me under the guidance of **DR. HETAL PANDYA, PROFESSOR & HEAD OF DEPARTMENT OF MEDICINE, SBKS Medical Institute & Research Centre, Piparia, Vadodara.**

Date: **Signature of the Candidate**

Place:PIPARIA **DR. PRIYAL PATEL**

SUMANDEEP VIDYAPEETH

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"A CROSS SECTIONAL STUDY OF CLINICAL AND BIOCHEMICAL PROFILE OF ENTERIC FEVER" AT DHIRAJ GENERAL HOSPITAL, PIPARIA** is a bonafide research work done by **DR. PRIYAL PATEL** under my guidance and in partial fulfillment of the requirement for the degree of **M.D. Medicine.**

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"To Almighty God, whose eternal blessing and divine presence helps us to fulfil all our goals"

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Last but not the last, I express my thanks to all my patients without whom this study would not have been possible.

Dr. PRIYAL PATEL

ABSTRACT

INTRODUCTION: Enteric fever is a systemic infection caused by Salmonella enterica, including S. enteric serotype typhi and serotype paratyphi. Enteric fever, being transmissible by faeco-oral route, is primarily a disease of regions where overcrowding, poor sanitation and untreated water.

AIM: To Assess The Current Pattern Of Clinical Presentation, Biochemical Findings And Complications Of Typhoid Fever.

METHODS: This study was carried out in Dhiraj Hospital affiliated with SBKS MIRC after IEC approval, 50 patients of clinical and biochemical profileof enteric fever were enrolled after obtained informed consent. Detailed history and clinical examination done in all patients. Serum widal level was done of all the patient at the time of admission.

Result 50 adult patients diagnosed as having enteric fever were enrolled in the study. Analysis of demographic profile, the mean age of the study group was 34, patient range from 18 year to 65 year. Almost two third patients 35(70%) were male. Male to female ratio was 2:1.

Classical pattern of enteric fever is stepladder type which was seen in 64% of study population. Other patterns observed are intermittent and continuous type. G.I. Tract is the most common involved system symptoms are vomiting, abdominal pain , diarrhoea ,and constipation. Most common biochemical abnormalities found were thrombocytopenia(40%) and hyperbillirubinemia (32%) On subanalysis, 38 patients with 1:320 ratio of widal titre 17(45%) patients was admitted to hospital, 1:180 ratio of widal titre in total 12 patients and out of them 7(58%) admitted and treatment

given, p value of admitted study population with widal titre ratio is 0.411, which is not significant so study population of admission is not correlated. No severe complication or mortality was noted in this study.

CONCLUSION: Typhoid fever is still an endemic disease in this region of India. For the prevention of disease in developing countries like India public education measures should be to encouraged regarding sanitation and hygiene. In the diagnosis of typhoid fever though none of the clinical symptoms and sign have very high accuracy, diagnostic criteria's may be helpful when combined with high index of suspicion and relevant laboratory investigation.

KEY WORDS: **Enteric fever, Widal test**

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INTRODUCTION

Enteric fever is a systemic infection caused by Salmonella enterica, including S. enteric serotype typhi and serotype paratyphi. Enteric fever, being transmissible by faeco-oral route, is primarily a disease of regions where overcrowding, poor sanitation and untreated water are the norm[1].High fever, toxaemia, constipation during the 1st week of fever complicated by encephalopathy and perforation during 3rd week of fever are the typical manifestation of the disease[2].Relative bradycardia at the peak of high fever is indicator of typhoid fever. Coated tongue, alteration of bowel habits varying from constipation in adults to diarrhea in children, tender abdomen, hepatomegaly, and splenomegaly are often present[3]. Agarwal et al in their study found clinical features of typhoid fever to be in conformity with earlier studies. [4,5,6].

Many reports from developing countries show that the clinical presentation of typhoid fever have significantly altered often leading to missed diagnosis, the consequence of which is immense in terms of scarce health resources and patients suffering. Therefore its clinical spectrum requires constant reappraisal to update our physicians with current knowledge about pattern of typhoid fever.The present study was intended to assess the current pattern of presentation of typhoid fever,its pathological and biochemical findings[7,8].Intestinal perforation and intestinal hemorrhages are two most feared complications of typhoid fever.[9]Neurologic complications[10,11] include myelitis (6%),cerebellitis (1.1%) meningitis (0.5%),and encephalitis (0.3%). Typhoid fever increases the risk of abortion, especially during the first trimester.[12,13]

AIM

- To assess the current pattern of clinical presentation, biochemical findings and complications of typhoid fever.

OBJECTIVES

The objectives are:

1. To study socio-demographic and epidemiologic features of enteric fever cases.
2. To study various clinical manifestations and biochemical profile of enteric fever.
3. To study complication profile, duration of hospital stay and outcome of enteric fever cases.

REVIEW OF LITERATURE

- Bacteria of the genus *Salmonella* are highly adapted for growth in both humans and animals and cause a wide spectrum of disease. The growth of serotypes *S. typhi* and *S. paratyphi* is restricted to human hosts, in whom these organisms cause enteric (typhoid) fever. The remaining serotypes (nontyphoidal *Salmonella*, or NTS) can colonize the gastrointestinal tracts of a broad range of animals, including mammals, reptiles, birds, and insects. More than 200 serotypes are pathogenic to humans, in whom they often cause gastroenteritis and can be associated with localized infections and/or bacteremia.[14.]

ETIOLOGY:

- This large genus of gram-negative bacilli within the family Enterobacteriaceae consists of two species: *S. enterica*, which contains six subspecies, and *S. bongori*. *S. enterica* subspecies I includes almost all the serotypes pathogenic for humans. According to the current *Salmonella* nomenclature system, the full taxonomic designation *S. enterica* subspecies *enterica* serotype *typhimurium* can be shortened to *Salmonella* serotype *typhimurium* or simply *S. typhimurium*.Members of the seven *Salmonella* subspecies are classified into >2500 serotypes (serovars) according to the somatic O antigen [lipopolysaccharide (LPS) cell-wall components], the surface Vi antigen (restricted to *S. typhi* and *S. paratyphi* C), and the flagellar H antigen. For simplicity, most *Salmonella* serotypes are named for the city where they were identified, and the serotype is often used as the species designation. Salmonellae are gram-negative, non-spore-forming, facultatively anaerobic bacilli that measure 2–3 by 0.4–0.6m. They are chemotrophs, obtaining their energy from oxidation and reduction reactions using organic sources. They are also facultative anaerobes, capable of surviving with or without oxygen[15].

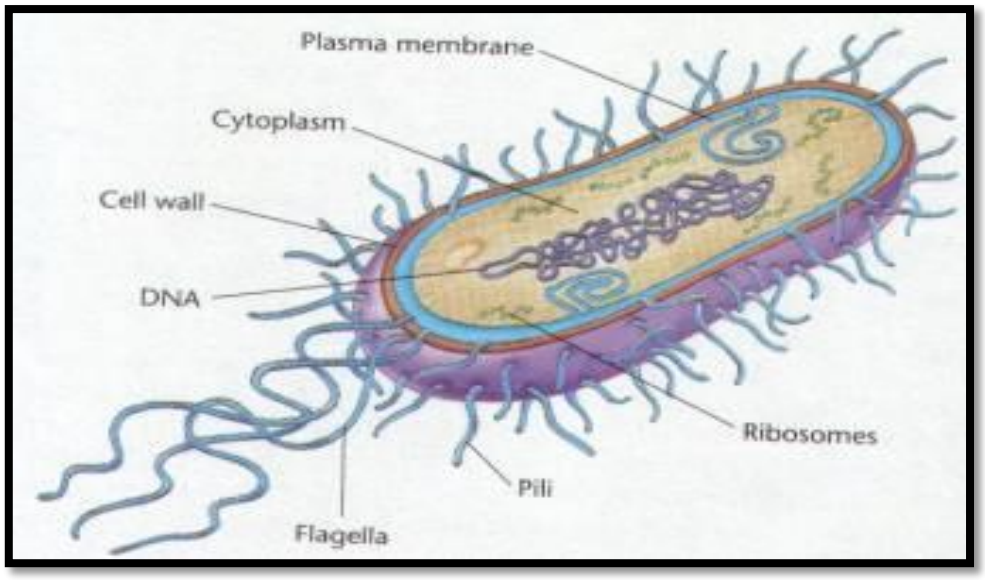


Fig 1: Salmonella Organism

TRNASMISSION:

The bacterium that causes typhoid fever may be spread through poor hygiene habits and public sanitation conditions, and sometimes also by flying insects feeding on feces. Public education campaigns encouraging people to wash their hands after defecating and before handling food are an important component in controlling spread of the disease. According to statistics from the United States Centers for Disease Control and Prevention (CDC), the chlorination of drinking water has led to dramatic decreases in the transmission of typhoid fever in the United States.[16]

HISTORY:

Salmonella was first visualized in 1880 by Karl Eberth in the Peyer's patches and spleens of typhoid patients.[17] Four years later in 1884 Georg Theodor Gaffky was able to successfully grow the pathogen in pure culture.[18] A year after that, medical research scientist Theobald Smith discovered what would be later known as *Salmonella enterica* (var. Choleraesuis). At the time, Smith was working as a research laboratory assistant in the Veterinary Division of the United States Department of Agriculture. The department was under the administration of Daniel Elmer Salmon, a veterinary pathologist.[19] Initially, *Salmonella* Choleraesuis was thought to be the causative agent of hog cholera, so Salmon and Smith named it "Hog-cholerabacillus". The name *Salmonella* was not used until 1900, when Joseph Leon Lignières proposed that the pathogen discovered by Daniel Salmon's group be called *Salmonella* in his honor.[20]

The Detection, culture, and growth conditions:

Most subspecies of *Salmonella* produce hydrogen sulfide,[21] which can readily be detected by growing them on media containing ferrous sulfate, such as is used in the triple sugar iron test. Most isolates exist in two phases: a motile phase I and a nonmotile phase II. Cultures that are nonmotile upon primary culture may be switched to the motile phase using a Craigie tube or ditch plate.[22]*Salmonella* can also be detected and subtyped using multiplex[23] or real-time polymerase chain reactions (PCR)[24 from extracted *Salmonella* DNA.

Mathematical models of *Salmonella* growth kinetics have been developed for chicken, pork, tomatoes, and melons.[25,26,27,28,29] *Salmonella* reproduce asexually with a cell division interval of 40 minutes.[20]*Salmonella* species lead predominantly host-

associated lifestyles, but the bacteria were found to be able to persist in a bathroom setting for weeks following contamination, and are frequently isolated from water sources, which act as bacterial reservoirs and may help to facilitate transmission between hosts.[30] The bacteria are not destroyed by freezing,[31,32] but UV light and heat accelerate their destruction. They perish after being heated to 55 °C (131 °F) for 90 min, or to 60 °C (140 °F) for 12 min.[33] To protect against *Salmonella* infection, heating food for at least 10 minutes to an internal temperature of 75 °C (167 °F) is recommended.[34,35] *Salmonella* species can be found in the digestive tracts of humans and animals, especially reptiles. *Salmonella* on the skin of reptiles or amphibians can be passed to people who handle the animals.[36] Food and water can also be contaminated with the bacteria if they come in contact with the feces of infected people or animals.[37] Although serotyping of all surface antigens can be used for formal identification, most laboratories perform a few simple agglutination reactions that define specific O-antigen serogroups, designated A, B, C_1, C_2, D, and E. Strains in these six serogroups cause 99% of *Salmonella* infections in humans and other warm-blooded animals. Molecular typing methods, including pulsed-field gel electrophoresis and polymerase chain reaction (PCR) fingerprinting, are used in epidemiologic investigations to differentiate *Salmonella* strains of a common serotype.[38 H2]

EPIDEMIOLOGY:

In contrast to other *Salmonella* serotypes, the etiologic agents of enteric fever—*S. typhi* and *S. paratyphi* serotypes A, B, and C—have no known hosts other than humans. Most commonly, food-borne or waterborne transmission results from fecal contamination by ill or asymptomatic chronic carriers. Sexual transmission between

male partners has been described. Health care workers occasionally acquire enteric fever after exposure to infected patients or during processing of clinical specimens and cultures. With improvements in food handling and water/sewage treatment, enteric fever has become rare in developed nations. Worldwide, however, there are an estimated 22 million cases of enteric fever, with 200,000 deaths annually. The incidence is highest (>100 cases per 100,000 population per year) in south central and Southeast Asia; medium (10–100 cases per 100,000) in the rest of Asia, Africa, Latin America, and Oceania (excluding Australia and New Zealand); and low in other parts of the world. A high incidence of enteric fever correlates with poor sanitation and lack of access to clean drinking water. In endemic regions, enteric fever is more common in urban than rural areas and among young children and adolescents. Risk factors include contaminated water or ice, flooding, food and drinks purchased from street vendors, raw fruits and vegetables grown in fields fertilized with sewage, ill household contacts, lack of hand washing and toilet access, and evidence of prior *Helicobacter pylori* infection (an association probably related to chronically reduced gastric acidity). It is estimated that there is one case of paratyphoid fever for every four cases of typhoid fever, but the incidence of infection associated with *S. paratyphi* A appears to be increasing, especially in India; this increase may be a result of vaccination for *S. typhi*. Multidrug-resistant (MDR) strains of *S. typhi* emerged in 1989 in China and Southeast Asia and have since disseminated widely. These strains contain plasmids encoding resistance to chloramphenicol, ampicillin, and trimethoprim—antibiotics long used to treat enteric fever. With the increased use of fluoroquinolones to treat MDR enteric fever in the 1990s, strains of *S. typhi* and *S. paratyphi* with reduced susceptibility to ciprofloxacin [minimal inhibitory concentration (MIC), 0.125–1 g/mL] have emerged in the Indian subcontinent,

southern Asia, and (most recently) sub-Saharan Africa and have been associated with clinical treatment failure. Testing of isolates for resistance to the first-generation quinolone nalidixic acid detects most but not all strains with reduced susceptibility to ciprofloxacin.

The incidence of enteric fever among U.S. travelers is estimated at 3–30 cases per 100,000. Of 1902 cases of *S. typhi*–associated enteric fever reported to the Centers for Disease Control and Prevention (CDC) in 1999–2006, 79% were associated with recent international travel, most commonly to India (47%), Pakistan (10%), Bangladesh (10%), Mexico (7%), and the Philippines (4%). Only 5% of travelers diagnosed with enteric fever had received *S. typhi*vaccine. Overall, 13% of *S. typhi* isolates in the United States were resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP-SMX), and the proportion of isolates resistant to nalidixic acid increased from 19% in 1999 to 58% in 2006. Infection with nalidixic acid-resistant (NAR) *S. typhi* was associated with travel to the Indian subcontinent. Of the 25–30% of reported cases of enteric fever in the United States that are domestically acquired, the majority are sporadic, but outbreaks linked to contaminated food products and previously unrecognized chronic carriers continue to occur.[39 H3]

CLINICAL FEATURE:

Enteric fever, the hallmark features of this disease -fever and abdominal pain.The incubation period for *S. typhi* averages 10–14 days but ranges from 3–21 days, depending on the inoculum size and the host's health and immune status The most prominent symptom is prolonged fever (38.8°–40.5°C; 101.8°–104.9°F), which can continue for up to 4 weeks if untreated. *S.* paratyphi A is thought to cause milder disease than *S.* typhi, with predominantly gastrointestinal symptoms. However, a

prospective study of 669 consecutive cases of enteric fever in Kathmandu, Nepal, found that the infections were clinically indistinguishable. In this series, symptoms reported on initial medical evaluation included headache (80%), chills (35–45%), cough (30%), sweating (20–25%), myalgias (20%), malaise (10%), and arthralgia (2–4%). Gastrointestinal symptoms included anorexia (55%), abdominal pain (30–40%), nausea (18–24%), vomiting (18%), and diarrhea (22–28%) more commonly than constipation (13–16%). Physical findings included coated tongue (51–56%), splenomegaly (5–6%), and abdominal tenderness (4–5%).Early physical findings of enteric fever include rash ("rose spots"; 30%), hepatosplenomegaly (3–6%), epistaxis, and relative bradycardia at the peak of high fever (<50%). Rose spots make up a faint, salmon-colored, blanching, maculopapular rash located primarily on the trunk and chest. The rash is evident in 30% of patients at the end of the first week and resolves without a trace after 2–5 days. Patients can have two or three crops of lesions, and *Salmonella* can be cultured from punch biopsies of these lesions. The faintness of the rash makes it difficult to detect in highly pigmented patients. The development of severe disease (which occurs in 10–15% of patients) depends on host factors (immunosuppression, antacid therapy, previous exposure, and vaccination), strain virulence and inoculum, and choice of antibiotic therapy. Gastrointestinal bleeding (10–20%) and intestinal perforation (1–3%) most commonly occur in the third and fourth weeks of illness and result from hyperplasia, ulceration, and necrosis of the ileocecal Peyer's patches at the initial site of *Salmonella* infiltration. Both complications are life-threatening and require immediate fluid resuscitation and surgical intervention, with broadened antibiotic coverage for polymicrobial peritonitis and treatment of gastrointestinal hemorrhages, including bowel resection. Neurologic manifestations occur in 2–40% of patients and include meningitis, Guillain-Barré

syndrome, neuritis, and neuropsychiatric symptoms (described as "muttering delirium" or "coma vigil"), with picking at bedclothes or imaginary objects.[40 H4]

COMPLICATIONS:

Intestinal perforation and intestinal hemorrhages are two most feared complications of typhoid fever .[41] Overall, each occurs in approximately 5% of adult patients with typhoid fever, slightly less in children [42.] A previous report from Durban, South Africa noted intestinal perforation and intestinal hemorrhage occurring in 13.1% and 4.7% of typhoid patients respectively [43.] Overall, 2-3% of typhoid patients will relapse days or weeks after apparent cure of their diseases [44,45] .Approximately 2-3 % of typhoid fever patients become chronic carriers [46] in that these individuals will excrete S.typhi usually in the stools ,sometimes in the urine over a period of many years without having the systemic manifestations of typhoid fever [47] .Chronic typhoid carriers are not uncommonly seen in typhoid endemic areas where gallbladder disease or urinary schistosomiasis is also common [48] .As has been observed for nontyphoidal Salmonella, relapse and chronic carriership for S.typhi are expected to be more frequent in AIDS patients with typhoid fever [49]. The biological plausibility of such a contention is understandable, considering the facts that the hepatic Kupffer cells play a very important role in clearing of circulating bacteria [50] and that this clearing function is impaired even during the asymptomatic phase of HIV infection [51] However, apart from a study reported from Peru [52] there appears to be no published report in the English language literature that showed an increased frequency of either relapse of typhoid fever or chronic carrier ship for S.typhi in AIDS patients with typhoid fever. Chronic carriers clearly pose a hazard to the community [53,54] Radiologically proven penumonia, mostly bronchopneumonia occurs in 1% of

typhoid patients [55] Electrocardiographic evidence of myocarditis with prolonged P-R and Q-Tc intervals and T-wave changes may be found in 12% of patients with typhoid fever [56] Typhoid hepatitis with clinical jaundice and a palpable liver has been observed in 0.4 –8.3 % of patients [57,58,59,60] In some cases [61,62] the clinical course of typhoid fever is complicated by glomerulonephritis (associated with or without acute renal failure or acute tubular necrosis). However, the true incidence of these in typhoid patients remains unknown as renal biopsy is seldom performed in this patient population [63] Neurologic complications [64,65] include myelitis (6%),cerebellitis (1.1%) meningitis (0.5%),and encephalitis (0.3%). Typhoid fever increases the risk of abortion, especially during the first trimester [66,67] Intrauterine transmission of S.typhi has been suspected by several investigators [68] Typhoid fever in the ethnic African population is not infrequently complicated by hemolytic anemia [69] In some reports [70] from Asia, cases of typhoid fever are documented in which clinical courses had been complicated by circulatory failure. In the pre-chloramphenicol era [71] occasionally clinical courses of typhoid fever were complicated by cholecystitis, arthritis, osteitis, and myositis. These complications are very infrequently seen now-a-days .[72]

DIAGNOSIS:

Since the clinical presentation of enteric fever is relatively nonspecific, the diagnosis needs to be considered in any febrile traveler returning from a developing region, especially the Indian subcontinent, the Philippines, or Latin America. Other diagnoses that should be considered in these travelers include malaria, hepatitis, bacterial enteritis, dengue fever, rickettsial infections, leptospirosis, amebic liver abscesses, and acute HIV infection .Other than a positive culture, no specific laboratory test is diagnostic for enteric fever. In 15–25% of cases, leukopenia and neutropenia are

detectable. Leukocytosis is more common among children, during the first 10 days of illness, and in cases complicated by intestinal perforation or secondary infection. Other nonspecific laboratory findings include moderately elevated liver function tests and muscle enzyme levels. The definitive diagnosis of enteric fever requires the isolation of *S.* typhi or *S.* paratyphi from blood, bone marrow, other sterile sites, rose spots, stool, or intestinal secretions. The sensitivity of blood culture is only 40–80%, probably because of high rates of antibiotic use in endemic areas and the small quantities of *S. typhi* (i.e., <15 organisms/mL) typically present in the blood. Since almost all *S.* typhi organisms in blood are associated with the mononuclear-cell/platelet fraction, centrifugation of blood and culture of the buffy coat can substantially reduce the time to isolation of the organism but do not increase sensitivity. Bone marrow culture is 55–90% sensitive, and, unlike that of blood culture, its yield is not reduced by up to 5 days of prior antibiotic therapy. Culture of intestinal secretions (best obtained by a noninvasive duodenal string test) can be positive despite a negative bone marrow culture. If blood, bone marrow, and intestinal secretions are all cultured, the yield is >90%. Stool cultures, while negative in 60–70% of cases during the first week, can become positive during the third week of infection in untreated patients.Several serologic tests, including the classic Widal test for "febrile agglutinins," are available. None of these tests is sufficiently sensitive or specific to replace culture-based methods for the diagnosis of enteric fever in developed countries. PCR and DNA probe assays to detect *S. typhi* in blood have been identified but have not yet been developed for clinical use.[73]

TREATMENT:

Enteric (Typhoid) Fever

Prompt administration of appropriate antibiotic therapy prevents severe complications of enteric fever and results in a case-fatality rate of <1%. The initial choice of antibiotics depends on the susceptibility of the *S. typhi* and *S. paratyphi* strains in the area of residence or travel. For treatment of drug-susceptible typhoid fever, fluoroquinolones are the most effective class of agents, with cure rates of 98% and relapse and fecal carriage rates of <2%. Experience is most extensive with ciprofloxacin. Short-course ofloxacin therapy is similarly successful against infection caused by nalidixic acid–susceptible strains. However, the increased incidence of NAR *S.* typhi in Asia, which is probably related to the widespread availability of fluoroquinolones over the counter, is now limiting the use of this drug class for empirical therapy. Patients infected with NAR *S.* typhi strains should be treated with ceftriaxone, azithromycin, or high-dose ciprofloxacin. High-dose fluoroquinolone therapy for 7 days for NAR enteric fever has been associated with delayed resolution of fever and high rates of fecal carriage during convalescence. For NAR strains, 10–14 days of high-dose ciprofloxacin is preferred. Ceftriaxone, cefotaxime, and (oral) cefixime are effective for treatment of MDR enteric fever, including NAR and fluoroquinolone-resistant strains. These agents clear fever in 1 week, with failure rates of 5–10%, fecal carriage rates of <3%, and relapse rates of 3–6%. Oral azithromycin results in defervescence in 4–6 days, with rates of relapse and convalescent stool carriage of <3%. Against NAR strains, azithromycin is associated with lower rates of treatment failure and shorter durations of hospitalization than are fluoroquinolones. Despite efficient in vitro killing of *Salmonella*, first- and second-generation

cephalosporins as well as aminoglycosides are ineffective in the treatment of clinical infections.Most patients with uncomplicated enteric fever can be managed at home with oral antibiotics and antipyretics. Patients with persistent vomiting, diarrhea, and/or abdominal distension should be hospitalized and given supportive therapy as well as a parenteral third-generation cephalosporin or fluoroquinolone, depending on the susceptibility profile. Therapy should be administered for at least 10 days or for 5 days after fever resolution.In a randomized, prospective, double-blind study of critically ill patients with enteric fever (i.e., those with shock and obtundation) in Indonesia in the early 1980s, the administration of dexamethasone (an initial dose of 3 mg/kg followed by eight doses of 1 mg/kg every 6 h) with chloramphenicol was associated with a substantially lower mortality rate than was treatment with chloramphenicol alone (10% vs 55%). Although this study has not been repeated in the "post-chloramphenicol era," severe enteric fever remains one of the few indications for glucocorticoid treatment of an acute bacterial infection.The 1–5% of patients who develop chronic carriage of *Salmonella* can be treated for 4–6 weeks with an appropriate oral antibiotic. Treatment with oral amoxicillin, TMP-SMX, ciprofloxacin, or norfloxacin is 80% effective in eradicating chronic carriage of susceptible organisms. However, in cases of anatomic abnormality (e.g., biliary or kidney stones), eradication often requires both antibiotic therapy and surgical correction.

Indication	Agent	Dosage (Route)	Duration, Days
Empirical Treatment			
	Ceftriaxone[a]	1–2 g/d (IV)	7–14
	Azithromycin	1 g/d (PO)	5
Fully Susceptible			
	Ciprofloxacin[b] (first line)	500 mg bid (PO) or 400 mg q12h (IV)	5–7
	Amoxicillin (second line)	1 g tid (PO) or 2 g q6h (IV)	14
	Chloramphenicol	25 mg/kg tid (PO or IV)	14–21
	Trimethoprim-sulfamethoxazole	160/800 mg bid (PO)	7–14
Multidrug-Resistant			
	Ciprofloxacin	500 mg bid (PO) or 400 mg q12h (IV)	5–7
	Ceftriaxone	2–3 g/d (IV)	7–14
	Azithromycin	1 g/d (PO)[c]	5
Nalidixic Acid–Resistant			
	Ceftriaxone	2–3 g/d (IV)	7–14
	Azithromycin	1 g/d (PO)	5
	High-dose ciprofloxacin	750 mg bid (PO) or 400 mg q8h (IV)	10–14

Table 1 Antibiotic Therapy for Enteric Fever in Adults

[a]Or another third-generation cephalosporin [e.g., cefotaxime, 2 g q8h (IV); or cefixime, 400 mg bid (PO)].

[b]Or ofloxacin, 400 mg bid (PO) for 2–5 days.

[c]Or 1 g on day 1 followed by 500 mg/d PO for 6 days[73]

PREVENTION AND CONTROL:

Theoretically, it is possible to eliminate the salmonellae that cause enteric fever since they survive only in human hosts and are spread by contaminated food and water. However, given the high prevalence of the disease in developing countries that lack adequate sewage disposal and water treatment, this goal is currently unrealistic. Thus, travelers to developing countries should be advised to monitor their food and water intake carefully and to consider vaccination. Two typhoid vaccines are commercially available: (1) Ty21a, an oral live attenuated *S. typhi*vaccine (given on days 1, 3, 5, and 7, with a booster every 5 years); and (2) Vi CPS, a parenteral vaccine consisting of purified Vi polysaccharide from the bacterial capsule (given in 1 dose, with a booster every 2 years). The old parenteral whole-cell typhoid/paratyphoid A and B vaccine is no longer licensed, largely because of significant side effects (see below). An acetone-killed whole-cell vaccine is available only for use by the U.S. military. The minimal age for vaccination is 6 years for Ty21a and 2 years for Vi CPS. Currently, there is no licensed vaccine for paratyphoid fever.A large-scale meta-analysis of vaccine trials comparing whole-cell vaccine, Ty21a, and Vi CPS in populations in endemic areas indicates that, while all three vaccines are similarly effective for the first year, the 3-year cumulative efficacy of the whole-cell vaccine (73%) exceeds that of both Ty21a (51%) and Vi CPS (55%). In addition, the heat-killed whole-cell vaccine maintains its efficacy for 5 years, whereas Ty21a and Vi CPS maintain their efficacy for 4 and 2

years, respectively. However, the whole-cell vaccine is associated with a much higher incidence of side effects (especially fever: 16% vs 1–2%) than the other two vaccines.Vi CPS typhoid vaccine is poorly immunogenic in children <5 years of age because of T cell–independent properties. In the recently developed Vi-rEPA vaccine, Vi is bound to a nontoxic recombinant protein that is identical to *Pseudomonas aeruginosa* exotoxin A. In 2- to 4-year-olds, two injections of Vi-rEPA induced higher T cell responses and higher levels of serum IgG antibody to Vi than did Vi CPS in 5- to 14-year-olds. In a two-dose trial in 2- to 5-year-old children in Vietnam, Vi-rEPA provided 91% efficacy at 27 months and 88% efficacy at 43 months and was very well tolerated. This vaccine is not yet commercially available in the United States. At least three new live vaccines are in clinical development and may prove more efficacious and longer-lasting than previous live vaccines.Typhoid vaccine is not required for international travel, but it is recommended for travelers to areas where there is a moderate to high risk of exposure to *S. typhi*, especially those who are traveling to southern Asia and other developing regions of Asia, Africa, the Caribbean, and Central and South America and who will be exposed to potentially contaminated food and drink. Typhoid vaccine should be considered even for persons planning <2 weeks of travel to high-risk areas. In addition, laboratory workers who deal with *S. typhi* and household contacts of known *S. typhi* carriers should be vaccinated. Because the protective efficacy of vaccine can be overcome by the high inoculate that are commonly encountered in food-borne exposures, immunization is an adjunct and not a substitute for avoiding high-risk foods and beverages. Immunization is not recommended for adults residing in typhoid-endemic areas or for the management of persons who may have been exposed in a common-source outbreak. Enteric fever is a noticeable disease in the United States. Individual health

departments have their own guidelines for allowing ill or colonized food handlers or health care workers to return to their jobs. The reporting system enables public health departments to identify potential source patients and to treat chronic carriers in order to prevent further outbreaks. In addition, since 1–4% of patients with *S. typhi* infection become chronic carriers, it is important to monitor patients (especially child-care providers and food handlers) for chronic carriage and to treat this condition if indicated.[73]

REVIEW OF PREVIOUS STUDIES:

Ashish Kakarial et al had studies clinical profile of enteric fever patients in western India[74].

In the study incidence of fever 100%, chills 26%, vomiting 44%, diarrhea 28%, abdominal pain 64%, headache 26%, and signs as splenomegaly 36%, hepatomegaly 42%, rose spots 6%, relative bradycardia 34% were reported. Anemia, leukocytosis and leukopenia and elevated liver enzymes were found in 42.9%, 10%, 21% and 45% respectively. Incidence of Salmonella Typhi, Salmonella Paratyphi was 80% and 20% respectively. There was no mortality in the study. They Concluded that Clinical presentation, signs and symptoms of Typhoid fever patients are varying. For the confirmatory diagnosis in addition to a high index of suspicion, Widal test and blood culture are required. For the proper treatment of Typhoid fever in view of emergence of resistant strains of S. Typhi antibiotic sensitivity and resistance test should be done whenever facilities available[74].

R Leon Ochiai [a], Camilo J Acosta [a] et al studied typhoid fever burden in five Asian countries.

A total of 441 435 persons were under surveillance, 159 856 of whom were aged 5–15 years. Findings A total of 21 874 episodes of fever were detected. Salmonella typhi was isolated from 475 (2%) blood cultures, 57% (273/475) of which were from 5–15 year-olds. The annual typhoid incidence (per 100 000 person years) among this age group varied from 24.2 and 29.3 in sites in Viet Nam and China, respectively, to 180.3 in the site in Indonesia; and to 412.9 and 493.5 in sites in Pakistan and India, respectively. Altogether, 23% (96/413) of isolates were multidrug resistant (chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole). They Concluded that the incidence of typhoid varied substantially between sites, being high in India and Pakistan, intermediate in Indonesia, and low in China and Viet Nam. These findings highlight the considerable, but geographically heterogeneous, burden of typhoid fever in endemic areas of Asia, and underscore the importance of evidence on disease burden in making policy decisions about interventions to control this disease[75].

Tohme A[1], Zein E, Nasnas R. et al done clinical and therapeutic study of patients with typhoid fever.

They found that among the 70 patients, 25 pediatric cases were noted. The patients were aged a mean of 28+/-22 years. Average duration of symptoms before the diagnosis was 10+/-7 days. Fever were observed in 97% of cases and the other predominant symptoms were abdominal pain (41%), diarrhoea (36%), chills (31%) and headache (29%). Febrile gastroenteritis was a frequent manifestation in children (52%). Complications were noted in 31% of cases and were predominantly digestive. Leucopenia was not a helpful diagnostic marker. S. typhi was the most frequent (87%) serotype identified. Resistance to ampicilline was 10%, to cotrimoxazole and

chloramphenicol 7% for each and to ofloxacine 2%. One death was reported (1%) of an immunosuppressed patient76.

Study done in sourthern India by Vinay Pandit, Ashwini Kumar et al had reported increasing resistance.

Increasing resistance to fluoroquinolones and sensitivity to chloramphenicol. Considering the changing trend in the sensitivity pattern, the recommendations of treatment for enteric fever need to be rationalized and re-considered[77].

MATERIALS AND METHOD

This is the hospital based Cross sectional study was performed in the parent institute from December 2015 to September 2017. All the subjects were interviewed, examined and investigated as per the predesigned proforma.

The study was proved by the institutional Ethics committee in December 2015.

Study Site: Medicine department , Dhiraj Hospital, SBKS & MIRC

Study Design: Cross sectional study

Sample size: Minimum 50 patient

All enteric fever patients come to medicine dept (IPD and OPD) will be enrolled in the study after taking informed written consent.

DIAGNOSTIC CRITERIA OF ENTERIC FEVER:

- Suggestive clinical picture **and**
- Blood culture positive for salmonella typhi and/or salmonella paratyphi organisms **and /or**
- Widal test +ve as per following criteria -
- titer of O 1:100 or more and /or H 1:200
- a rise in titre which is at least four fold. [29]

- **INCLUSION CRITERIA :**

All adult patients having clinical picture of enteric fever with widal positive and / or blood culture positive for enteric fever .

- **EXCLUSION CRITERIA :**

All those patients who are not willing to participate in my study.

- The socio- demographic, epidemiological data will be collected. Detailed history and clinical examination will be done and recorded in predesigned profoma.
- All patients will be subjected to S. Widal test and blood culture for s. typhi.
- Patients will be also subjected to other biochemical investigations like CBC, RFT, LFT, S. electrolytes, urine routine micro, USG abdo-pelvis, X-ray chest.
- Patients will be followed up till they get discharged or till good outcome during hospital stay.
- Data regarding hospital stay , complications and outcome will also be recorded.

RESULT AND ANALYSIS

50 adult patients diagnosed as having enteric fever were enrolled in the study. Analysis of demographic profile, the mean age of the study group was 34.86±15.6,

patient range from 19 year to 65 year. 33(66%) patients were young adult, while 12(24%) were middle aged and 5(10%) were elderly. Almost two third patients 35(70%) were male. Male to female ratio was 2:1.

Table 2- Age and Sex distribution among patients.

Sex and Age	n (%)
<35	33(66.0)
35-60	12(24.0)
>60	5(10.0)
Male	35(70.0)
Female	15(30.0)

Table 3-Frequency distribution of various clinical features.

Symptoms	Frequency(%)
Fever	50(100.0%)
Vomiting	21(42.0%)
Abdominal pain	28(56.0%)
Diarrhoea	28(56.0%)
Constipation	6(12.0%)
Headache	14(28.0%)
Cough	8(16.0%)
Altered sensorium	1(2.0%)

Graph 1 : Frequency distribution of various clinical feature.

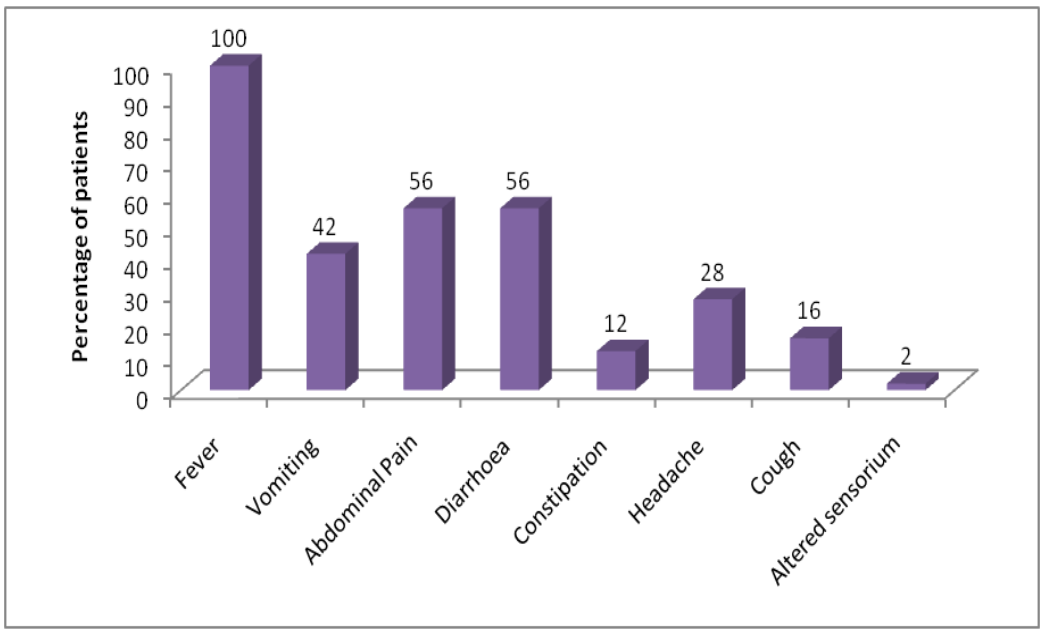
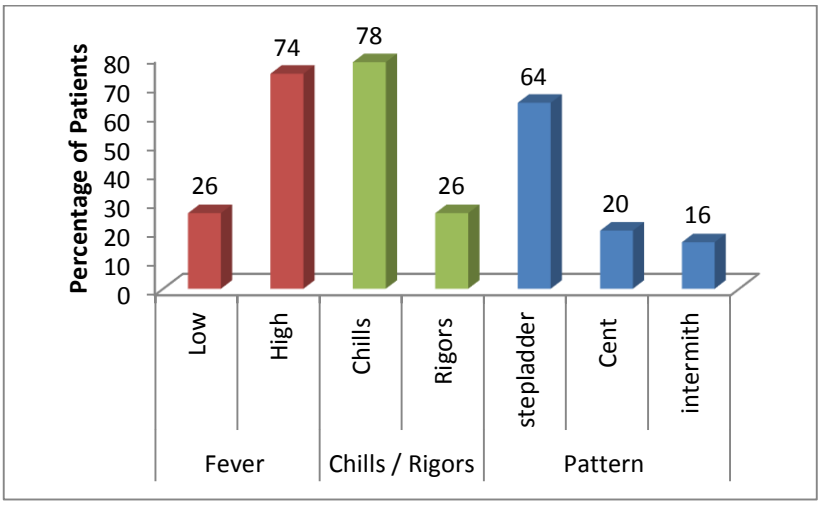


Table 4: pattern/characteristics of fever

		Frequency(%)
Severity	Low	13(26.0)
	High	37(74.0)
Chills / Rigors	Chills	39(78.0)
	Rigors	13(26.0)
Pattern	stepladder	32(64.0)
	Continuous	10(20.0)
	Intermitted	8(16.0)

Graph : 2 Pattern/characteristics of fever

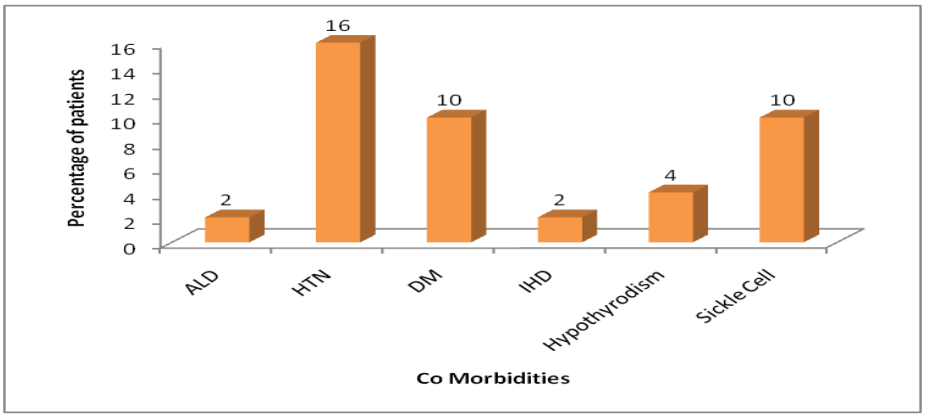


Being classical symptom of enteric fever, Fever is the presenting symptom in all patients. High grade fever is present in only 74% of patients, while considerable no of patients (26%) had low grade fever. 78% patients had chills and only 26% had rigors with fever. Classical pattern of enteric fever is stepladder type which was seen in 64% of study population. Other patterns observed are intermittent and continuous type. G.I. Tract is the most common involved system symptoms are vomiting, abdominal pain , diarrhoea ,and constipation.Almost half of patients had abdominal pain and diarrhea.

Table 5 Frequency distribution of comorbidities :

Comorbidities		IPD (n=24)	OPD (n=26)	Chi-Square Value	p-value
ALD	Yes	0(0%)	1(100.0%)	NA	NA
	No	24(48.9%)	25(51.1%)		
HTN	Yes	5(62.5%)	3(37.5%)	0.802	0.370
	No	19(45.2%)	23(54.8%)		
DM	Yes	3(60.0%)	2(40.0%)	0.321	0.571
	No	21(46.7%)	24(53.3%)		
IHD	Yes	1(100.0%)	0(0%)	NA	NA
	No	23(46.9%)	26(53.1%)		
Hypothyrodism	Yes	1(50.0%)	1(50.0%)	NA	NA
	No	23(47.9%)	25(52.1%)		
Sickle Cell	Yes	2(40.0%)	3(60.0%)	0.142	0.706
	No	22(48.9%)	23(51.1%)		

Graph 3: Frequency distribution of comorbidities :

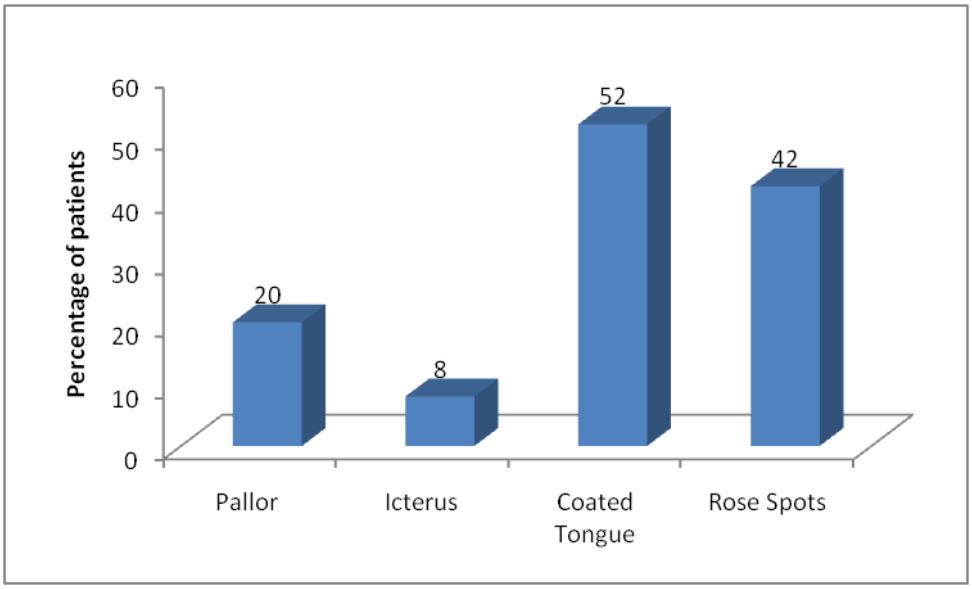


Total 22 (44%) patients out of 50 presented had co morbidities,most common is HTN (16%) and DM(10%),followed by sickle cell, hypothyroidism ,ALD and IHD. There was no association between presence of co morbidities and rate of hospitalization.(table-4)

Table 6: frequency distribution of common sign presentation

Sign	Frequency
Pallor	10(20%)
Icterus	4(8.0%)
Coated Tongue	26(52.0%)
Rose Spots	10(20%)

Graph 4: Frequency distribution of common sign presentation



Most common clinical sign at the time of presentation is coated tongue(52%) and rose spots(42%) , followed by pallor and icterus.

Table 7: Vital parameters at the time of presentation

	Minimum	Maximum	Mean±SD
PULSE	44	118	74.44±188.80
SBP	70	182	115.72±23.38
DBP	50	98	77.76±11.97

Table 8 : Vital parameters at the time of presentation

		Total (%)	IPD	OPD	Chi-Square Value	p-value
Heart rate	Bradycardia	15(30%)	11	4	5.529	0.063
	Normal	32(64%)	12	20		
	Tachycardia	3(6%)	1	2		
Blood pressure	Hypotension	23(46%)	10	13	0.653	0.721
	Normal	16(32%)	9	7		
	Hypertension	11(22%)	5	6		

Temperature- Out of 50 patients, 41(82.0%) patients were febrile and 9(18.0%)patients were afebrile at the time of presentation,but all had a history of fever.

Pulse- Mean pulse rate was 74.44(SD- 18.804) with range from 44/min to 118/min. Out of 50 patients, 3(6.0%) patients had tachycardia , 32(64.0%) patients normal pulse rate and 15(30.0%) had bradycardia at time of presentation.

Blood pressure- Mean systolic BP was 115.72(SD- 23.383)mm of hg with range from 70 mm of hg to 180 mm of hg and mean diastolic BP was 77.7with range from 50 mmhg to 98 mmhg. Out of 50 patients, 23(46.0%) patients had hypotension and 11(22.0%) patients had hypertension and 16(32.0%) patients had normal blood pressure at time of presentation.

Table 9 : Haematological parameters

	RANGE	Mean±SD	Std. Deviation
Hb	8-16	12.18±1.79	1.787
TC	3000-18000	9004.20±3781.80	3781.802
N	40-84	62.12±11.28	11.286
L	8-50	28.72±10.73	10.732
M	2-8	3.90±0.953	.953
E	2-5	4.36±0.964	.964
PLATELATS	1-4	2.58±0.729	.729
UREA	11-65	23.60±10.32	10.325
S.CREATININE	0-2	.93±0.348	.348
SGPT	10-342	43.80±66.53	66.532
SGOT	10-567	43.10±85.29	85.297
BILLIRUBIN	1-12	1.80±2.204	2.204
DIRECT	0-9	1.07±1.450	1.450
INDIRECT	0-4	.73±0.818	.818

Table 10: frequency distribution and abnormal biochemical parameter

		Total (%)	Admission	p-value
Hb	<=10	5(10%)	3(60%)	0.571
	>10	45(90%)	21(46%)	
S. Creat	Abnormal	12(24%)	6	0.874
	Normal	38(76%)	18	
S. Billi	Abnormal	16(32%)	9	0.423
	Normal	34(68%)	15	
SGOT	Abnormal	9(18%)	7	0.048
	Normal	41(82%)	17	
SGPT	Abnormal	4(8%)	3	0.260
	Normal	46(92%)	21	
Platelate	>1.5	30(60%)	12	0.456
	1-1.5	8(16%)	4	
	0.5-1	7(14%)	5	
	<0.5	5(10%)	3	

On analysis of biochemical parameter of study participants, mean value of almost all parameters was with in normal range except serum bilirubin (table 7). Most common biochemical abnormalities found were thrombocytopenia (40%) and hyperbillirubinemia (32%) followed by abnormal serum creatinine value (24%), only 10% patients had anemia(≤10). Liver enzyme were abnormal in minority of patients but the rise in SGOT and SGPT is clinical insignificant (<5 times of normal value). These abnormal biochemical parameters did not lead to increase rate of hospital admission in our study and P value is more than(0.05) (table 8). On ultrasonography 5(10%) patients having hepatomegaly and 2 patients having splenomegaly (table-9).

Table 11 : USG abdo pelvis result

USG ABDO PELVIS	Frequency
CIRROSHIS LIVER, PHTN	1(2.0%)
HEPATOMEGALY	5(10.0%)
SPLENOMEGALY	2(4.0%)

Table 12: widal test analysis

		S. TYPHI		p-value
		1:180 O	1:320 O	
Age Group	<35	7(21.2%)	26(78.8%)	0.132
	35-60	2(16.7%)	10(83.3%)	
	>60	3(60.0%)	2(40.0%)	
Fever	Low	3(23.1%)	10(76.9%)	0.928
	High	9(24.3%)	28(75.7%)	
HTN	Yes	1(12.5%)	7(87.5%)	0.406
	No	11(26.2%)	31(73.8%)	
DM	Yes	2(40.0%)	3(60.0%)	0.377
	No	10(22.2%)	35(77.8%)	
Sickle Cell	Yes	1(20.0%)	4(80.0%)	0.825
	No	11(24.4%)	34(75.6%)	
ALD	Yes	0(0%)	1(100.0%)	NA
	No	12(24.5%)	37(75.5%)	
IHD	Yes	0(0%)	1(100.0%)	NA
	No	12(24.5%)	37(75.5%)	
Hypothyrodism	Yes	0(0%)	2(100.0%)	NA
	No	12(25.0%))	36(75.0%)	

Table 13: Blood culture results:

Blood Culture	Frequency(%)
Positive	2(4.0)
Negative	10(20.0)
Not Done	38(76.0)

Blood culture for s.typhi was sent for 12 patients out of which only 2 were positive for s.typhi organism growth. The reason for not sent allpatientsfor bllod culture were already given treatment and non complicated patients were treatment have been taken.

Table 14:Association of serum widal titre with hospital admission

		Total	IPD	Chi-Square Value	p-value
S. Typhi	1:180	12	7 (58%)	0.675	0.411
	1:320	38	17(45%)		

On subanalysis, 38 patients with 1:320 ratio of widal titre 17(45%) patients was admitted to hospital, 1:180 ratio of widal titre in total 12 patients and out of them 7(58%) admitted and treatment given, p value of admitted study population with widal titre ratio is 0.411,which is not significant so study population of admission is not correlated. Out of 50 patients, 38 patients 1:320 and 12 patients 1:180,In this study group, 38 patients had s.widal titre of 1:320 and 12 patients had 1:180. 17

patients(45%)of higher titre(1:320) required hospital admission, while 7 patients (58%) of 1:180 titre were aditted to hospital,suggesting no relation between higher s.widal titre with rate of hospital admission.Increasing age as well as presence of co morbidity were also as well as presence of co morbidity were also not associated with higher titre of s.widal test. No severe complication or mortality was noted in this study.

DISCUSSION

Typhoid fever caused by Salmonella typhi remains an important public health problem in many tropical and sub-tropical countries where clean water supply and sanitation are poor. It is a multi-system septicemic febrile illness where the portal of entry of the causative organism is the gastrointestinal tract

Enteric fever, being transmissible by faeco-oral route, is primarily a disease of regions where overcrowding, poor sanitation and untreated water. A high incidence of enteric fever correlates with poor sanitation and lack of access to clean drinking water. In endemic regions, enteric fever is more common in urban than rural areas and among young children and adolescents.

Enteric fever patients were detected through out the year in my study, suggesting endemicity of the disease in this geographical area. Maximam number of patients were admitted during May-September, in summer and monsoon seasons.This suggest poor sanitation and poor hygiene is still prevalent and one of the important preventable causative factor for high prevalence of this tropical infectious disease in this area.

Infectious diseases are more common in younger age group as they are more exposed to various precipiting and causative factors. In my study 66% of the study partipants were younger than 35 years of age. Only 10% were elderly Ashish Kakarial et al also reported the same results. Almost two third patients 35(70%) were male. Male to female ratio was 2:1. Incidentally this preponderance of infection in males probably could be due to the fact that male goes outside more, takes outside food more frequently than females. The population affected most was of low socioeconomic

group which possibly as a result of poor sanitation and overcrowding. Ashish Kakarial et al reported almost similar rate of occurrence in both sexes.

Table 12 Comparison of mean age

no	Study	Mean age
1.	Tohme A[1] et al	28±22
2.	My study	34.86±15.6

Table 13 Comparison of gender distribution with other studies.

no	Study	Male(%)	Female(%)
1.	Ashish Kakarial et al	28(56%)	22(44%)
2.	Vinay pandit, et al	71(64.5%)	39(45.5%)
3.	My study	35(70%)	15(30%)

Classically described pattern of fever in enteric fever is high grade, continuous, step-ladder tpe of fever. such classical pattern is seen in more than half of patients. The stepladder fever pattern that was once the hallmark of typhoid fever occurred in 32(64%) which was 12% in study by Gupta SP[74]. This suggests classical pattern of fever is not common. Other symptoms like abdominal pain, diarrhea, vomiting, and constipation suggestive of that GI system is more common involved in all patients. Coated tongue is more common presentation in enteric fever,in my study 26(52%) presented with coated tongue. Rose sports are pink, blinching erthematous maculopapular lesions approximately 2-4 mm in diameter that appers in crops on the chest and abdomen, they appears during the second week and resolve in 2 to 5 days

reported in 5-30% of cases. Rose spots were present only in 10% which could have been missed due to dark complexion of population in our study.

Table 14 Comparison of frequency of clinical symptoms with various studies.

No	Symptoms	Ashish Kakarial et al	Vinay pandit, et al	My study
1	Fever	50(100%)	110(100%)	50(100.0%)
2	Vomiting	22(44%)	35(31.1%)	21(42.0%)
3	Abdominal pain	32(64%)	15(13.6%)	28(56.0%)
4	Diarrhoea	14(28%)	23.6%	28(56.0%)
5	Constipation	5(10%)	_	6(12.0%)
6	Headache	13(26%)	_	14(28.0%)
7	Cough	5(10%)	_	8(16.0%)

Though clinical symptoms like fever, diarrhea, vomitimg, abdominal pain, headache, were consistently present in enteric fever, they are not diagnostic of enteric fever, so has to be supported by laboratory results. Almost 3/4th of patients had high titre (1:320) of serum widal test. Age, sex and presence of co morbidities does not affected the titre of serum widal nor hospital admission. Ever The increase in titre does not correlate with more frequency of hospital treatment. On subanalysis out of 38 patients with 1:320 ratio of widal titre 17(45%) patients was admitted to hospital while 1:180 ratio of widal titre was found in total 12 patients and out of them 7(58%) admitted and treatment given, p value of admitted study population with widal titre ratio is 0.411,which is not significant.Increasing age as well as presence of co morbidity were

also as well as presence of co morbidity were also not associated with higher titre of s.widal test.

In this study, Anemia (hemoglobin <10gm/dl) was found in 10% of cases, thrombocytopenia <1.0 lac was found in 40% of cases. Leucopenia, thrombocytopenia and anemia in typhoid can be attributed to the myeloid maturation arrest, decrease in the number of erythroblasts and megakaryocytes and increased phagocytic activity of histiocytes in the bone marrow. Leucopenia and lmphoctosis, common hematological finding of enteric fever is not found in m study. Hyperbilirubinrmia was most common biochemical abnormality observed in m study(32%). Most of the patients had mild hyperbilirubinemia with normal or slightly raised levels of liver enzmes(SGOT,SGPT).It is well appreciated that the liver is very often involved in typhoid fever with most patients having only minor elevation of serum aminotransferase levels without clinical jaundice. However, in a small minority of patients with typhoid fever, hepatic dysfunction may manifest itself with clinical jaundice and other signs and symptoms that are clinically and biochemically indistinguishable from those of viral hepatitis. The development of clinical jaundice in typhoid fever may be very significant, considering the premise that the development of clinical jaundice in bacterial sepsis is a serious development and usually part of multi-organ failure. Fortunatel, none of our patients developed clinically significant jaundice, sepsis or multiorgan failure. Other know serious complication like glomerulonephritis, intestinal perforation, encephalopathy etc are not observed in m study no mortalities was observed.

SUMMARY

1. High endemecity with more cases in summer and monsoon season is noted.
2. Disease affect young adults specially males more frequently.
3. Classical pattern of fever observed in around 60% of cases. The most commonly involved system is Gastro Intestinal System.
4. Widal titre has only diagnostic value, not prognostic value as it is not the deciding factor for hospital admission and do not have impact on complication and mortality.
5. Anemia and thrombocytopenia are common hematological abnormalities found in enteric fever.
6. Almost one third patients had mild hyperybilirubinemia but did not developed hepatitis or clinically significant jaundice.
7. No serious complication or mortality is observed in m study.

CONCLUSION

- Typhoid fever is still an endemic disease in this region of India. For the prevention of disease in developing countries like India public education measures should be to encouraged regarding sanitation and hygiene. In the diagnosis of typhoid fever, none of the clinical symptoms and sign have very high accuracy.so high index of clinicalsuspicion and relevant supporting laboratory investigations are required to diagnose and treat enteric fever.

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74. Clinical profile of enteric fever: a prospective study of fifty enteric fever patients Ashish Kakaria1,*, Dilip Asgaonkar2, Meenakshi Narkhede3

75. A study of typhoid fever in five Asian countries: disease burden and implications for controls R Leon Ochiai [a], Camilo J Acosta [a], M Carolina Danovaro-Holliday [a], Dong Baiqing [b], Sujit K Bhattacharya [c], Magdarina D Agtini [d], Zulfiqar A Bhutta [e], Do Gia Canh [f], Mohammad Ali [a], Seonghye Shin [a], John Wain [g], Anne-Laure Page [a], M John Albert [h], Jeremy Farrar [i], Remon Abu-Elyazeed [j], Tikki Pang [k], Claudia M Galindo [a], Lorenz von Seidlein [a], John D Clemens [a], the Domi Typhoid Study Group.

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77. Study of Clinical Profile and Antibiotic Sensitivity in Paratyphoid Fever Cases Admitted at Teaching Hospital in South India

78 Vinay Pandit, Ashwini Kumar,1 Muralidhar Madhav Kulkarni,1 Sanjay M. Pattanshetty,1 Charmine Samarasinghe,2 and Sneha Kamath

ANNEXURE-A

ABREVIATIONS

NTS	:	nontyphoidal salmonella
LPS	:	lipopolysaccharide
CDC	:	Centers for disease control and prevention
PCR	:	polymerase chain reaction
MDR	:	multidrug resistance
MIC	:	minimal inhibitory concentration
TMP	:	trimethoprim
SMX	:	sulfamethoxazole
NAR	:	nalidixic acid resistant
AIDS	:	acquired immunodeficiency syndrome
HIV	:	human immunodeficiency virus
DNA	:	Deoxyribonucleic acid
IV	:	intravenous
PO	:	per os,by mouth
PPV	:	positive predicative value
NPV	:	negative predicative value
IPD	:	Indoor patients department
OPD	:	outdoor patients department
CBC	:	Complete blood count
ESR	:	Erythrocyte sedimentation rate
RFT	:	Renal function test
PT	:	Prothrombin time
APTT	:	Activated partial thromboplastin time

LFT	:	Liver function test
RBS	:	Random blood sugar
ECG	:	Electrocardiography
USG	:	ultrasonography

ANNEXURE-B

Sumandeep Vidyapeeth University

Piparia, Ta. Waghodia, Dist. Vadodara Pin: 391760

PARTICIPANT INFORMATION SHEET

Title of the study: A CROSS SECTIONAL STUD OF CLINICAL AND BIOCHEMICAL PROFILE OF ENTERIC FEVER.

Study No. **Date:**

INVITATION TO PARTICIPANT:

1. **Purpose & Nature of the study:** To study various clinical manifestations of hepatic encephalopathy and to determine correlation of serum ammonia level & severity of hepatic encephalopathy.
2. **Voluntary Nature of the Participation:** It is an absolutely voluntary participation in the study program.
3. **Participants Responsibilities:** After agreeing to participate in the study, the participant should extend full support. He/ She should provide real facts when inquired into and make his/ her self available whenever requires.
4. **Expected Adverse Events, Risk and Solution:** As such in this study no experiment will be done on patients, so there is no issue of adverse effect or risk.
5. **The benefits of participation:** The study is beneficial to the participant as it will give them their illness status and help in optimal management. The study is also likely to benefit the community by helping in early recognition of Hepatic encephalopathy.

6. **Confidentiality of the Record:** Information regarding patient's health and other personal facts if any, will be kept confidential.

7. **If any Problem Develops, you can contact:**

Name : Dr. PRIYAL PATEL

Address : Department of medicine, S.B.K.S & MI & RC, Piparia.

Tal: Waghodia Dist: Vadodara

Mobile No. : 9909910542

8. **Financial consideration**: No extra financial burden will be levied on the participant.

9. **Protection for patient and security:** If any type of threat or untoward event, consequent to present study, is met with, the patient will be provided every type of protection. Nature of this protection can be decided when such an event actually is faced with.

10. **Obtaining Additional information:** If need arises, the patient may be contacted to inquire about past, personal and family history. Also religious background, social customs, benefits etc can be inquired into.

ANNEXURE-C

Sumandeep Vidyapeeth University

Piparia, Ta. Waghodia, Dist. Vadodara Pin: 391760

Informed Consent Form (ICF) for Participants in Research Programmes involving studies on human beings

Study Title: "A CROSS SECTIONAL STUD OF CLINICAL AND BIOCHEMICAL PROFILE OF ENTERIC FEVER"

Subject's number: SVU/SBKS/ 2015-

Subject's Initials:

Subject's name:

Age:

Date of birth:

Details of Nominee (s):

Name of Nominee:

Address of Nominee:

Relation to Subject:

(i) I confirm that I have read and understood the information sheet dated ……....….for the above study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any

time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any furtherresearch that may be conducted in relation to it,even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. ☐

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) ☐

(v) I agree to take part in the above study ☐

Signature/Thumb impression of the participant_____

Legally acceptable representative_____

Signatory's Name_____ Date_____

Signature of the investigator_____ Date_____

Study Investigator's Name_____ Date_____

Signature of the impartial witness_____ Date_____

Name of the witness_____

ANNEXURE-D

સુમનદીપ વિદ્યાપીઠ યુનિવર્સિટી

પીપારિયા, તા. વાઘોડિયા, જિ. વડોદરા પિન: 391760

પક્ષકાર માહિતી શીટ

અભ્યાસનું શીર્ષક: .

અભ્યાસ નં. તારીખ: શામેલ થવા માટે આમંત્રણ:

1. અભ્યાસનો હેતુ અને સ્વભાવ: યકૃતમાં આવેલી એન્સેફાલોપથીના વિવિધ તબીબી અભિવ્યક્તિઓનો અભ્યાસ કરવા અને સીરમ એમોનિયા સ્તર અને હીપેટિક એન્સેફાલોપથીની તીવ્રતાનો સહમતી નક્કી કરવા.
2. ભાગીદારીના સ્વૈચ્છિક પ્રકૃતિ: અભ્યાસ કાર્યક્રમમાં તે સંપૂર્ણપણે સ્વૈચ્છિક ભાગીદારી છે.
3. સહભાગીઓ જવાબદારીઓ: અભ્યાસમાં ભાગ લેવા માટે સંમત થયા પછી, સહભાગીએ સંપૂર્ણ સમર્થન આપવું જોઈએ. જ્યારે જરૂર હોય ત્યારે તેની / તેણીને સ્વયં ઉપલબ્ધ થતી વખતે વાસ્તવિક હકીકતો આપવી જોઈએ.
4. અપેક્ષિત પ્રતિકૂળ ઘટનાઓ, જોખમ અને ઉકેલ: જેમ કે આ અભ્યાસમાં દર્દીઓ પર કોઈ પ્રયોગ કરવામાં આવશે નહીં, તેથી પ્રતિકૂળ અસર અથવા જોખમનો કોઈ મુદ્દો નથી.
5. સહભાગિતાના ફાયદા: આ અભ્યાસ સહભાગીને લાભદાયક છે કારણ કે તે તેમની બીમારીની સ્થિતિ અને શ્રેષ્ઠ સંચાલનમાં મદદ કરશે. હેપેટિક એન્સેફાલોપથીના પ્રારંભિક માન્યતામાં મદદ કરીને આ સમુદાયના સમુદાયને પણ લાભ થવાની શક્યતા છે.
6. રેકોર્ડની ગુપ્તતા: દર્દીના સ્વાસ્થ્ય અને અન્ય અંગત હકીકતો જો કોઈ હોય તો તે અંગેની માહિતી ગુપ્ત રાખવામાં આવશે.
7. જો કોઈ સમસ્યા ઊભી થાય, તો તમે સંપર્ક કરી શકો છો:
   નામ: ડૉ.
   સરનામું: દવા વિભાગ, એસ.બી.કે.એસ. અને એમઆઇ અને આરસી, પીપારિયા.
   તાલ: વાઘોડિયા જી: વડોદરા
   મોબાઇલ નંબર: 9909910542
8. નાણાકીય વિચારણા: સહભાગી પર કોઈ વધારાની નાણાકીય બોજ વસૂલ કરવામાં આવશે નહીં.

9. દર્દી અને સુરક્ષા માટે રક્ષણ: જો કોઈ પ્રકારનું ધમકી અથવા અયોગ્ય ઘટના, અભ્યાસ રજૂ કરવાના પરિણામે, તેની સાથે મળેલું હોય, દર્દીને દરેક પ્રકારના રક્ષણ પૂરું પાડવામાં આવશે. જ્યારે આવી ઘટના ખરેખર સામનો કરવો પડે છે ત્યારે આ રક્ષણનો સ્વભાવ નક્કી કરી શકાય છે.
10. વધારાની માહિતી મેળવી: જો જરૂર ઊભી થાય તો દર્દીને ભૂતકાળ, અંગત અને પારિવારિક ઇતિહાસ વિશે પૂછપરછ કરવા માટે સંપર્ક કરી શકાય છે. પણ ધાર્મિક પૃષ્ઠભૂમિ, સામાજિક રિવાજો, લાભ વગેરે માં તપાસ કરી શકાય છે.

ANNEXURE-E

સુમનદીપ વિદ્યાપીઠ યુનિવર્સિટી
પીપારિયા, તા. વાઘોડિયા, જિ. વડોદરા પિન: 391760

મનુષ્યો પરના અભ્યાસોને સંલગ્ન રિસર્ચ પ્રોગ્રામ્સના સહભાગીઓ માટે જાણકાર સંમતિ પત્ર (આઈસીએફ)

અભ્યાસનું શીર્ષક: ""

વિષયનો નંબર: એસવીયુ / એસબીકેએસ / 2015-
વિષયના આદ્યાક્ષણો:
વિષયનું નામ:
ઉંમર:
જન્મ તારીખ:

નોમિની (ઓ) ની વિગતો:

નોમિની નામ:
નોમીનીનું સરનામું:
વિષય સાથે સંબંધ:

(i) હું પુષ્ટિ કરું છું કે મેં માહિતી શીટ વાંચી અને સમજી લીધી .... ઉપરના અભ્યાસ માટે અને પ્રશ્નો પૂછવાની તક મળી છે.

(ii) હું સમજી શકું છું કે અભ્યાસમાં મારો સહભાગિંહ સ્વૈચ્છિક છે અને તે કોઈપણ તબીબી કાળજી અથવા કાયદાકીય અધિકારોને પ્રભાવિત કર્યા વિના, કોઈપણ કારણ વગર, કોઈપણ સમયે હું પાછી ખેંચી શકું છું.

(iii) હું સમજું છું કે ક્લિનિકલ ટ્રાયલના પ્રાયોજક, અન્યો

પ્રાયોજકની વતી કાર્યરત, એથિક્સ કમિટી અને નિયમનકારી સત્તાવાળાઓને વર્તમાન અભ્યાસ અને તેના સંબંધમાં હાથ ધરવામાં આવેલા કોઈપણ વધુ સંશોધન બંને માટે મારા સ્વાસ્થ્યના વિકમની તપાસ કરવાની મારી પરવાનગીની જરૂર નથી.
જો હું અજમાયશમાંથી પાછો ખેંચી લો હું આ ઍક્સેસથી સંમત છું જો કે, હું સમજું છું કે તૃતીય પક્ષો માટે પ્રકાશિત કરેલી કોઈપણ માહિતીમાં અથવા પ્રકાશિત કરેલી મારી ઓળખ જાહેર કરવામાં આવશે નહીં.

(iv) હું આ અભ્યાસમાંથી જન્મેલા કોઈપણ ડેટા અથવા પરિણામોના ઉપયોગ પર પ્રતિબંધિત થવામાં સંમત છું, પરંતુ આવા ઉપયોગ વૈજ્ઞાનિક હેતુ માટે જ છે.

(v) હું ઉપરના અભ્યાસમાં ભાગ લેવા માટે સંમત છું

સહભાગી_____ ના હસ્તાક્ષર / અંગૂઠાની છાપ
કાયદેસર રીતે સ્વીકાર્ય પ્રતિનિધિ_____
હસ્તાક્ષરનું નામ _____ તારીખ_____
તપાસકર્તાના હસ્તાક્ષર_____ તારીખ_____
અભ્યાસ તપાસ કરનારનું નામ_____ તારીખ_____
નિષ્પક્ષ સાક્ષીના હસ્તાક્ષર_____ તારીખ_____
સાક્ષીનું નામ_____

ANNEXURE-F

सुमनदीप विद्यापीठ विश्वविद्यालय
पापीरिया, ता। वाघोडिया, जि। वडोदरा पिन: 391760

भाग लेने वाली सूचना पत्र
अध्ययन का शीर्षक:

अध्ययन सं। दिनांक:

सहभागी को आमंत्रण:

1. अध्ययन का उद्देश्य और प्रकृति: हिपैटिक एन्सेफलोपैथी के विभिन्न नैदानिक अभिव्यक्तियों का अध्ययन करना और सीरम अमोनिया स्तर और यकृत इन्सफालोपैथी की गंभीरता का संबंध निर्धारित करना।
2. भागीदारी की स्वैच्छिक प्रकृति: यह अध्ययन कार्यक्रम में एक पूरी तरह से स्वैच्छिक भागीदारी है।
3. प्रतिभागियों की जिम्मेदारियों: अध्ययन में भाग लेने के लिए सहमत होने के बाद, प्रतिभागी को पूर्ण समर्थन देना चाहिए। जब भी आवश्यकता हो तो उसे वास्तविक तथ्यों को प्रदान करना चाहिए और जब भी आवश्यकता होगी तब स्वयं उपलब्ध कराएं।
4. अपेक्षित प्रतिकूल घटनाओं, जोखिम और समाधान: जैसे कि इस अध्ययन में रोगियों पर कोई प्रयोग नहीं किया जाएगा, इसलिए प्रतिकूल प्रभाव या जोखिम का कोई मुद्दा नहीं है।
5. भागीदारी का लाभ: यह अध्ययन भागीदार के लिए फायदेमंद है क्योंकि यह उनकी बीमारी की स्थिति और इष्टतम प्रबंधन में मदद करेगा। हेपेटिक एन्सेफेलोपैथी की शुरुआती मान्यता में मदद करने से भी इस अध्ययन में समुदाय के लाभ होने की संभावना है।
6. रिकॉर्ड की गोपनीयता: रोगी के स्वास्थ्य और अन्य व्यक्तिगत तथ्यों, यदि कोई हो, के बारे में जानकारी गोपनीय रखी जाएगी।

7. यदि कोई समस्या विकसित होती है, तो आप संपर्क कर सकते हैं:

   नाम: डॉ।

   पता: चिकित्सा विभाग, एसबीकेएस और एमआई एंड आर सी, पिपारिया

   तल: वाघोडिया जिला: वडोदरा

   मोबाइल नंबर: 9909910542

8. वित्तीय विचार: भागीदार पर अतिरिक्त वित्तीय बोझ नहीं लगाया जाएगा।
9. रोगी और सुरक्षा के लिए संरक्षण: यदि किसी भी प्रकार का खतरा या अप्रिय घटना, जिसके परिणामस्वरूप अध्ययन को प्रस्तुत किया जाता है, तो रोगी को हर प्रकार की सुरक्षा प्रदान की जाएगी। जब इस तरह के एक घटना को वास्तव में सामना करना पड़ता है तो इस सुरक्षा की प्रकृति का निर्णय लिया जा सकता है।
10. अतिरिक्त जानकारी प्राप्त करना: यदि ज़रूरत होती है, तो मरीज को पिछले, व्यक्तिगत और पारिवारिक इतिहास के बारे में पूछताछ करने के लिए संपर्क किया जा सकता है। इसके अलावा धार्मिक पृष्ठभूमि, सामाजिक रीति-रिवाज, लाभ आदि की जांच हो सकती है।

ANNEXURE-G

सुमनदीप विद्यापीठ विश्वविद्यालय

पापीरिया, ता। वाघोडिया, जि। वडोदरा पिन: 391760

इंसानों पर अध्ययन से जुड़े अनुसंधान कार्यक्रमों में प्रतिभागियों के लिए ज्ञात सहमति पत्र (आईसीएफ)

अध्ययन शीर्षक: "यकृत इंसेफैलोपैथी और सीरम अमोनिया के सह-संबंध की गंभीरता के चिकित्सीय प्रोफाइल का अध्ययन"

विषय संख्या: एसवीयू / एसबीकेएस / 2015-
विषय के प्रारंभिक:
विषय का नाम:
उम्र:
जन्म की तारीख:

नामांकित व्यक्ति का विवरण:

नामांकित व्यक्ति का नाम:
नामांकित व्यक्ति का पता:
विषय के संबंध:

(i) मैं पुष्टि करता हूं कि मैंने सूचना पत्र की पढ़ाई और समझ ली है .... उपरोक्त अध्ययन के लिए और सवाल पूछने का अवसर मिला है।

(ii) मैं समझता हूं कि अध्ययन में मेरी भागीदारी स्वैच्छिक है और मैं किसी भी समय बिना किसी कारण के बिना किसी भी समय वापस लेने के लिए स्वतंत्र हूं या बिना मेरी चिकित्सा देखभाल या कानूनी अधिकार प्रभावित हो सकता है

(iii) मैं समझता हूं कि नैदानिक परीक्षण के प्रायोजक, अन्य प्रायोजक की ओर से काम करते हुए, एथिक्स कमेटी और नियामक प्राधिकरणों को मौजूदा अध्ययन के संबंध में अपने स्वास्थ्य अभिलेखों को देखने के लिए मेरी अनुमति की आवश्यकता नहीं होगी और इसके

संबंध में किसी अन्य शोध को आयोजित किया जा सकता है, भले ही मैं परीक्षण से वापस ले जाया मैं इस पहुंच से सहमत हूं। हालांकि, मैं समझता हूं कि मेरी पहचान तीसरी पार्टी के लिए जारी किसी भी जानकारी या प्रकाशित में प्रकट नहीं होगी।

(iv) मैं इस अध्ययन से उत्पन्न होने वाले किसी भी डेटा या परिणामों के उपयोग को तिबंधित करने के लिए सहमत हूं, लेकिन ऐसे प्रयोग केवल वैज्ञानिक उद्देश्य (प्रयोजनों) के लिए हैं

(v) मैं उपरोक्त अध्ययन में भाग लेने के लिए सहमत हूं

सहभागिता के हस्ताक्षर / अंगूठे का भाव _____

कानूनी रूप से स्वीकार्य प्रतिनिधि_____

हस्ताक्षरकर्ता का नाम_____ दिनांक_____

जांचकर्ता के हस्ताक्षर_____ तिथि_____

अध्ययन अन्वेषक का नाम_____ दिनांक_____

निष्पक्ष गवाह के हस्ताक्षर_____ दिनांक_____

साक्षी का नाम_____

ANNEXURE-H

PERFORMA

Name: DOA:

Age &Sex: Weight/Height:

Ward/unit: Regd no.:

DOD:

Address:

Present complains:

SYMPTOMS	NO. PT
Fever	
Abdominal pain	
Vomiting	
Headache	
Diarrhea	
Constipation	
Nausea	
Malaise	
SIGNS	
Hepatomegaly	
Splenomegaly	
Rose spot	
Relative bradycardia	

Past history:

Personal history:

General Physical Examination:

Built and nutrition	Pallor
General condition	Icterus
Level of consciousness	Cyanosis

Temperature : Clubbing

Pulse : /min

Lymphadenopathy

RR : /min Edema

BP : mmHg Spine&Back

Airway assessment: Jaw and Neck movement:

Mouth opening:

Oral Hygiene: Teeth:

Nose:

SYSTEMIC EXAMINATION

R/ S: P/A:

CVS : CNS:

Relevant laboratory investigations :

Hb : RBS :

BT : Blood Urea :

CT : Serum creatinine :

Urine : CXR :

ECG : Sugar :

1. WIDAL:
2. BLOOD CULTURE:

ADVICE