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TYPHOID INFECTION MANAGEMENT & ERADICATION SUPPLEMENT

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TIMES Magazine contains background information on the epidemiology, pathology, diagnosis, treatment and prevention of typhoid. It is scientifically designed for clinicians and other healthcare professionals to give an updated review on recent advancements as well as clinical experiences of experts from field. This magazine is an initiative of Getz Pharma in collaboration with Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP) and Advance Educational Institute and Research Centre (AEIRC).

Awareness Promoted By

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Message From MMIDSP

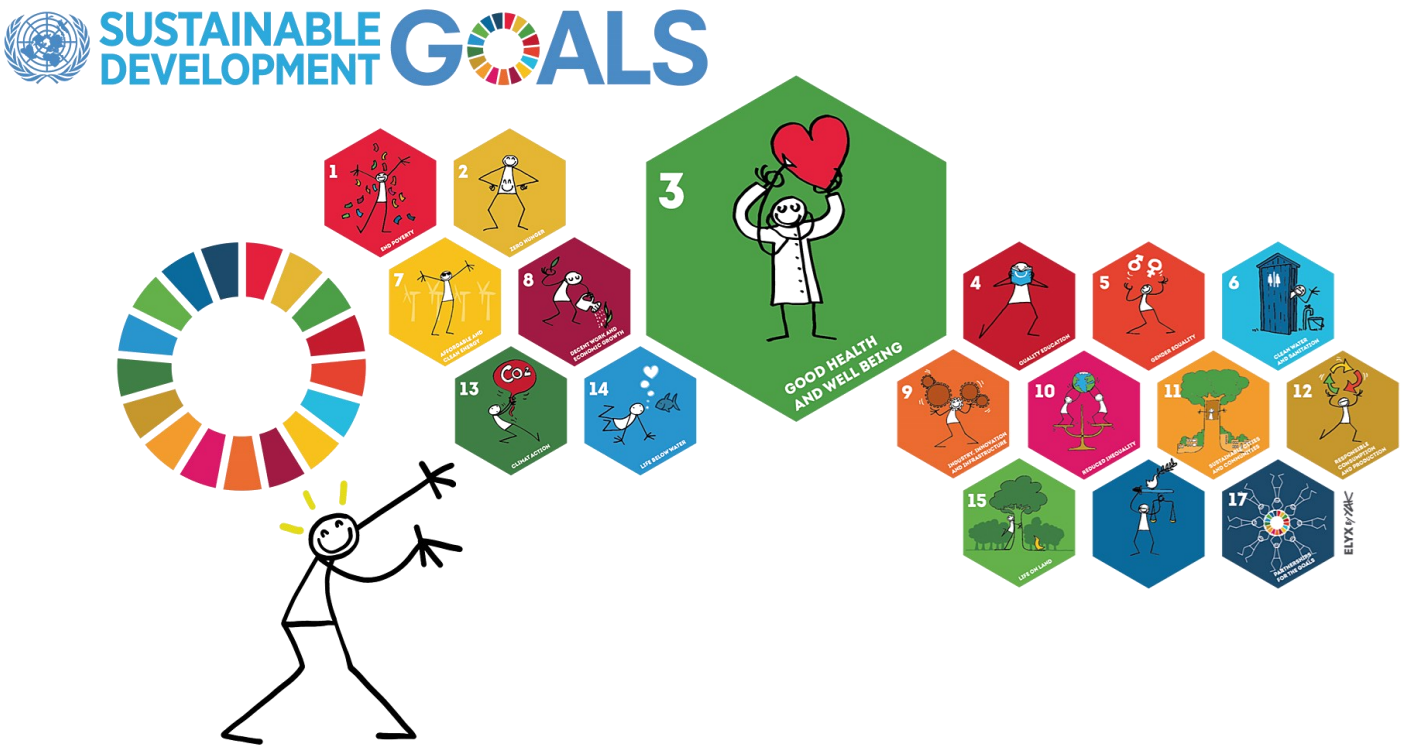
The morbidity of typhoid fever is highly prevalent in Asia with third highest incidence rate in the southeast region. Pakistan is one of the most affected states in this region. The occurrence of the disease has been linked with the considerable variations associated to the seasonal changes and population. The supply and quality of resources is considered the principal factor impacting the spread of typhoid. The causative agents mainly spread due to the poor hygiene, lack of sanitation and insufficient sewerage systems.

Pakistan is considered underprivileged due to its increasing population and depriving availability of resources that further acts as a key contributor and adds up to the burden of healthcare. The initiative of publishing a structured magazine dedicated to the typhoid and its related factors is a remarkable step. We believe that TIMES will prove to be a key facilitator in spreading the awareness and essential knowledge to all the recipients. MMIDSP recognizes the participation of Getz Pharma in the generation of this magazine as a fruitful approach that will certainly benefit both the professionals and the population of Pakistan.

Prof. Brig. Dr. Aamer Ikram, SI(M)
President MMIDSP

Fighting Typhoid: A Key to Achieving the Sustainable Development Goals (SDGs)

By Dr. Sajjad Siddiqui
PNFWH, Karachi Pakistan



Typhoid fever from a bacterial infection with *Salmonella typhi* is a significant cause of morbidity and mortality in developing countries where access to clean water and basic sanitation is not universal. Annual incidence is estimated to be 13-27 million cases, with greater than 260,000 deaths annually. Typhoid fever has been a challenging disease to address due to poor diagnostics and the emergence of resistance to antibiotics used to treat the disease. Prevention of typhoid fever through vaccination was recommended by the World Health Organization 15 years ago and two vaccines have been licensed for years. These vaccines have key limitations that limit their use, including a short duration of protection (3-5 years) and effective only in those over two years old. Several typhoid conjugated vaccine (TCV) candidates now in development have demonstrated that they can overcome the disadvantages of the current vaccines[1].

One year ago, tasked with the mission of uplifting societies around the world, the United Nations Development Program created a call to action known as the Sustainable Development Goals (SDGs) to fight poverty and promote sustainable peace and prosperity for all. These Global Goals, as they're also known, identify targets for a variety of focus areas to be met by 2030. Like many important global issues, typhoid, a bacterial infection impacting over 20 million people a year, is crucially intertwined with inequality and the environment. At its heart, typhoid is a disease of poverty, existing where communities do not have access to basic infrastructure and vaccines[2].

When considering the achievement of healthy lives and well-being for all, one finds that each target is hitched to every other SDG. Achieving SDG 3 requires a suite of measures, including ending the epidemics of communicable diseases, reducing maternal and infant mortality, providing access to reproductive healthcare and universal health coverage, reducing harm associated with drug abuse, tobacco pollution, traffic and non-communicable diseases. These targets clearly support each other. Real progress on achieving health targets also requires looking towards other SDGs e.g. SDG 6 as unsafe water and poor sanitation are linked to transmission of diseases such as cholera, diarrhea illnesses, dysentery, hepatitis A, typhoid and polio. Water, sanitation, and hygiene were responsible for 842,000 deaths from diarrheal disease alone worldwide in 2012 . Taking action on water is fundamental to ending the communicable disease epidemics[3&4].

Similarly, progress towards target 11.1 – access to adequate, safe and affordable housing – reinforces targets around ending preventable deaths of children and premature mortality from non-communicable diseases[5]. Typhoid, similar to other infectious diseases, is one of many factors that can keep families and communities in poverty. Its pervasiveness is inextricably tied to hunger, poor health, low quality education and lack of access to clean water and sanitations.[6&7] Some of the factors that SDGs target is given below:

Goal Two — No More Hunger:
Malnutrition can increase vulnerability to diseases like typhoid, which can also be transmitted through contaminated food. Safe and plentiful food can help reduce the risk of typhoid in vulnerable populations.

Goal Three — Good Health:
By preventing typhoid, we can ensure that all members of society grow up without suffering the side effects of this disease including fever, fatigue, intestinal hemorrhage, delirium, coma and death.

Goal Four — Quality Education:
Typhoid overwhelmingly targets school-age children, keeping them out of school for days or weeks at a time. By targeting school-age children for typhoid vaccines, we can keep them in school and eliminate one of the causes of school absenteeism. In other words, fully vaccinated kids are smarter kids.

Goal Six — Clean Water and Sanitation:
Clean water and improved sanitation infrastructure can reduce a large number of typhoid infections and deaths, taking the fear of disease out of drinking water. While cleaner water and sanitation is a key strategy for preventing typhoid, these will also prevent the ill effects of other waterborne infectious diseases such as shigella, E.coli and amoebic dysentery. But to successfully fight typhoid, communities must be strong economically, as well.

Goal Ten — Reduced Inequalities:
Varying access to clean water and other social determinants of health such as quality of working infrastructure and access to vaccines and treatment are directly responsible for the spread of typhoid.

Although typhoid's impact on poverty, sustainable peace and prosperity may seem limited as a single disease, it is closely connected with many of the SDGs, from health and education to jobs and infrastructure and more. Supporting typhoid prevention and control efforts is a straightforward, practical and cost-effective way to make progress on many of the Global Goals in a way that will benefit the entire world. This cycle of poverty, climate change and disease can be mitigate in future through strong vaccination program, as well as improvements in water access and sanitation. A 1995 typhoid vaccination program in Guangxi, China, for example, was effective in both significantly reducing the level of endemic typhoid and in controlling outbreaks. The case in China may provide hope for future outbreaks. By providing a base level of protection, vaccination can stop an outbreak before it begins may help in third world countries to achieve the SDGs. The public health reasons require investing in the conditions in which the poor live to prevent the spread of poverty related diseases such as cholera, typhoid and others; and international reasons to ensure sustainable societies both within and across borders (where investing in crises affected countries)[8].

Tales of Pathological changes in typhoid fever narrated by organs

Heart

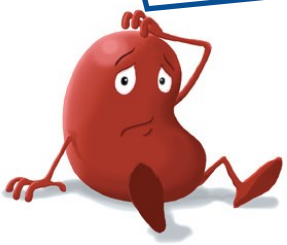
I may get enlarge and also feel affected by fatty degeneration. I also develop near-fatal myocarditis but that is rarely though. Myocardial injury or attack almost kills me and sadly it occurs commonly. My endarteritic and periarteritic change in to smaller coronary arterioles and capillaries, with occasional red thrombus formation, and patchy focal degeneration of the myocardial cells. so, it messes up with my A-V conduction, prolonged QT interval and delays it which leads to relative bradycardia. I think it happens possibly due to the action of bacterial toxins themselves upon the myocardium, or due to the increase of vagal tone. These endotoxins can collapse my cardiovascular system[9-11].

Liver

I get enlarged with fatty changes. This will raise my blood urea, creatinine, liver enzymes and bilirubin; and you know what? elevated serum enzyme level directly damages me. So, The usual histologic output becomes "nonspecific reactive hepatitis." My involvement can be seen in the form of hepatomegaly alone, or with jaundice. Isolated hepatomegaly usually is of no clinical significance but its occurrence with jaundice though rare, includes me in generalized toxaemia or liver abscess.

Kidney

I may appear cloudy, I get swelling which may results in albuminuria, Typhoid glomerulonephritis,. I face number of complications including cystitis, pyelitis, pyelonephritis, mild proteinuria. In chronic carrier states I happen to involve urinary system that leads to localized urinary tract infection (UTI) & burning micturition. I get attacked by toxins in three different mechanisms; first, toxins cause nephropathy; second, it causes immune complex glomerulonephritis; lastly, direct invasion of *S.* typhi. in the glomerular basement membrane.

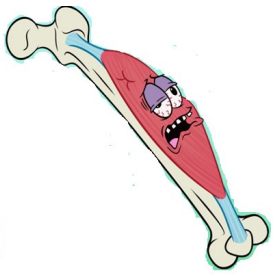


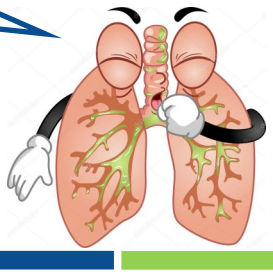
Muscle

I suffer from myositis, elevated CK levels, mild myalgias to severe pain with weakness. Actually, *Salmonella* causes a decline in my capacity to perform short time high intensity exercise as well as long time endurance efforts. S. typhi. -induced rhabdomyolysis is common in me. It goes like; direct bacterial invasion of muscle, hypoxia in my tissue is caused by sepsis, toxins release and altered muscle metabolic capacity[18-20].

Lungs

Bronchitis & pulmonary congestion are my common complaints during typhoid. While severe exposure can cause gangrene, pleuritis, salmonella abscess and pneumonitis with either serous or purulent exudation in me. Salmonella get settled in my tissues, and possibly they initiate the development of empyema. I think it is due to poor immune status, so the organism which are already settled in my pleural cavity get the chance to multiply and start damaging me[21&24].



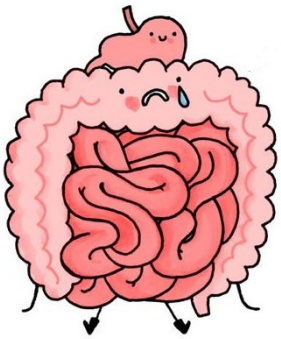


Gall Bladder

Cholecystitis leads to the formation of infected gall stones in me and it may be a potent source of infection in the carrier of typhoid. S. Typhi colonization in me, then they induce a localized inflammatory response and I loss my epithelial integrity, thickening of my mucosa and my tissue gets damaged[25-27].

Stomach

Salmonella causes perforation, salpingitis, and peritonitis in me. My condition which is called mesenteric lymphadenitis associated with *Salmonella typhi* looks exactly like acute appendicitis and can make it difficult to establish proper diagnosis. Hemorrhage and perforation that occur in my terminal ileum secondary to necrosis of Peyer's patches at 2 -3 weeks after the onset of the disease. Trans epithelial migration of neutrophils (PMN) inflames mesenteric lymph nodes that caused appendicitis like symptoms, and leads to my acute blockage and then I happen to go in emergency surgery. The most severe manifestations of typhoid in me leads to sepsis and death[28-31].



Skin

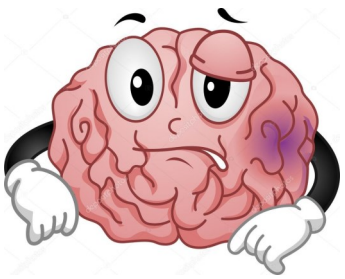
I get rose spots as rash that occurs in up to 30% other fellow skin of people infected with S.typhi, I start getting affected between the second and fourth week of illness. Then I will develop more groups of 5-15 pink blanching papules (little bumps). Apart from rose spots, other rashes may also effect me in salmonella infections like erythema typhosum; a generalized rash, haemorrhagic bullae (blood-filled blisters), pustular dermatitis and erythema multiforme. Typhoid fever may also cause visceral leishmaniasis[32-34].

Spleen

I become large and soft. S. typhi reach inside me through dendritic cells, before colonizing resident marginal zone and red pulp macrophages. Clear majority of bacteria are found within my tissue macrophages, pass on to the reticuloendothelial cells. S. typhi organisms are able to survive and multiply within these mononuclear phagocytic cells of the lymphoid follicles and dendritic cells in me[35-37].

Brain

Bacteremia, sepsis, and meningitis are my common complains in children with Salmonella infection but I do get intracranial abscesses rarely. Other complications of S. typhi, I face include, edema, cerebral infarction, pus collection in cerebral cavities, and brain inflammation.. Neuropsychiatric complications also develops in us around 45–76 % of patients during every stage of typhoid fever as a part of the "Typhoid toxaemia", where I develop delirium and confusion during the initial stages of the disease. However, I do show extrapyramidal signs, like peripheral neuropathy, mononeuritis multiplex and late development of post typhoidal schizophreniform psychosis. while gait and limb ataxia are my universal conditions. All my neurological manifestations reversed completely within 6 weeks[38-41].

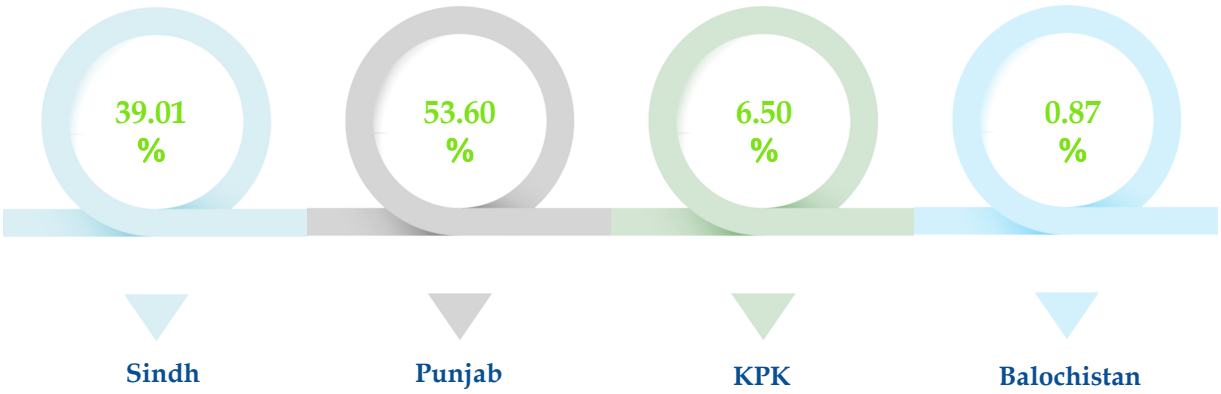


Follow-up Pattern of Typhoid Fever Patients

A Cross-sectional survey was distributed through TIMES Magazine Volume - 2 during Sep - Nov 2017 among Health Care Providers in all four provinces of Pakistan i.e Sindh, Punjab, Balochistan & KPK. The main focus of the survey was to collect information related to follow-up pattern of typhoid fever patients.

The survey consisted of seven questions and it was conducted to get better understanding of relapse & resistance cases of typhoid fever patient, followed by quality of life during treatment. All the questions were closed ended and responses were recorded on pre designed questionnaire. The survey was distributed to 1800 participants and responses were received from (n=1138) for which results are shown below, most of the respondents were general practitioners who see typhoid patients in their routine clinical practice.

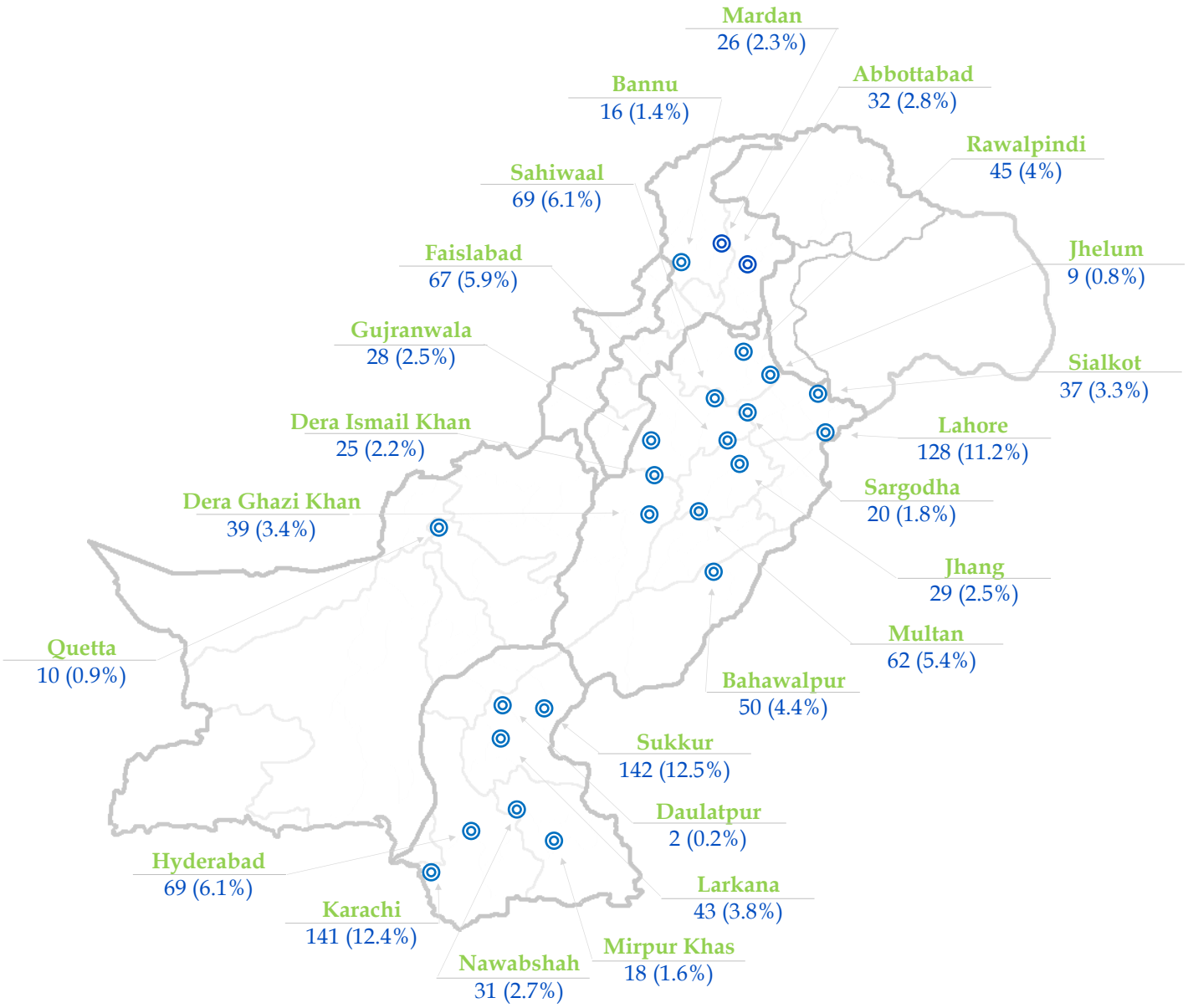
Table 1: Number of responses from four provinces of Pakistan



The survey was disseminated in all major cities throughout Pakistan. The city wise distribution shows that from Sindh the maximum number of responses were received from Sukkur (n=142) located on the western bank of the Indus River. It is the 12th most populous city of Pakistan and the third largest city in Sindh province. Only (n=10) physicians were recruited from Quetta, provincial capital of Balochistan.

It was observed that relapse cases were reported more as compared to resistance that is approximately 69% of the patients were observed having relapse while resistance cases were only 31%. Our results also indicated that 90.4% of the clinicians recommended follow up after treatment. 65.4% clinicians advised that follow-up must be taken at least 1 month after completion of treatment while 19% suggested it to should be taken after 3 months. 25% of patient have a great effect of typhoid on quality of life.

City Wise Distribution of Responses From Each Province of Pakistan



Typhoid fever patients are strongly recommended for follow up after treatment

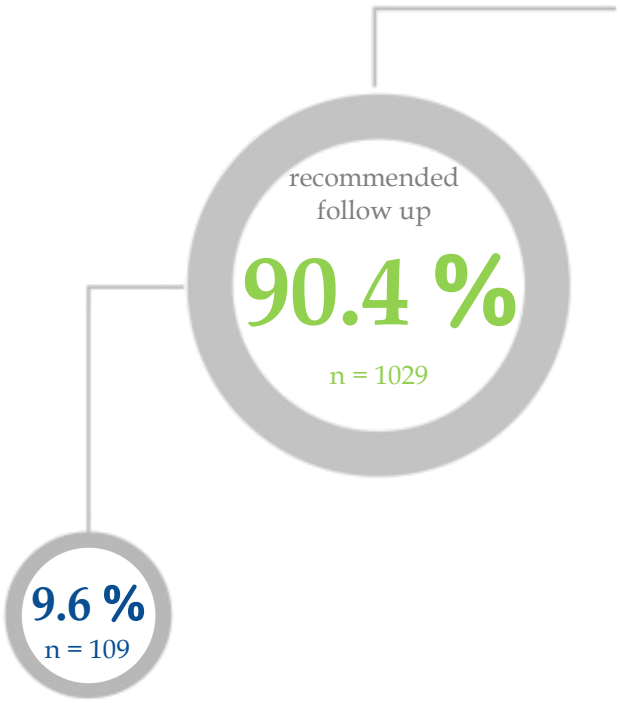


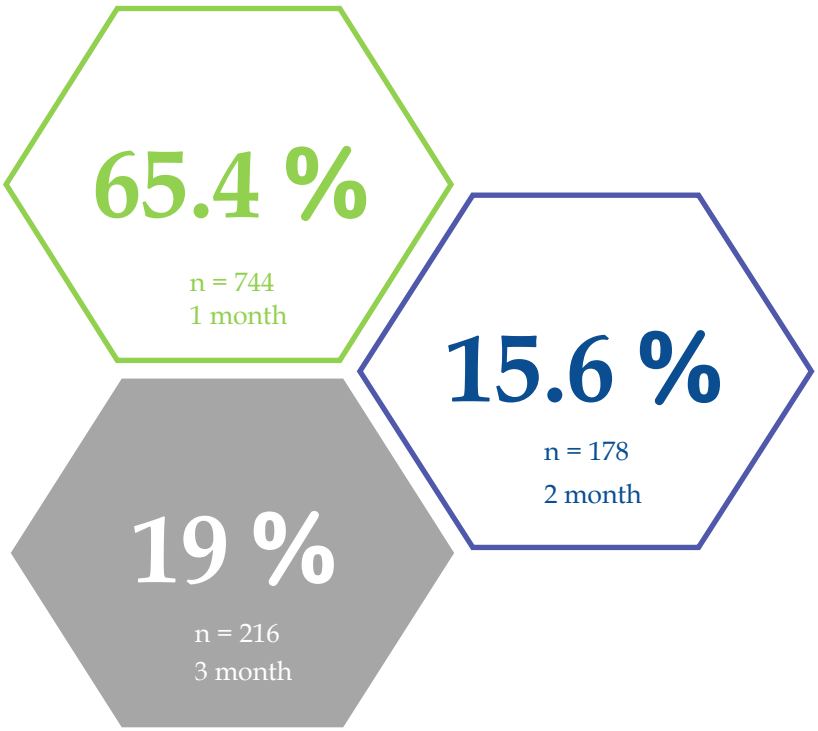
Figure 1: Showing Follow up recommendation after treatment of typhoid

Graph indicates that 90.4% of the clinicians recommended follow up after treatment while only 9.6% disagreed that follow up is not necessarily required after treatment. Regular follow-up and monitoring are recommended to avoid complications and clinical relapse (this may include confirmation of stool clearance in non-endemic areas or in high risk groups such as food handlers).[42]

Follow-up duration advised to typhoid patients after completion of treatment

Figure 2: Showing Follow-up duration advised to typhoid patients after completion of treatment

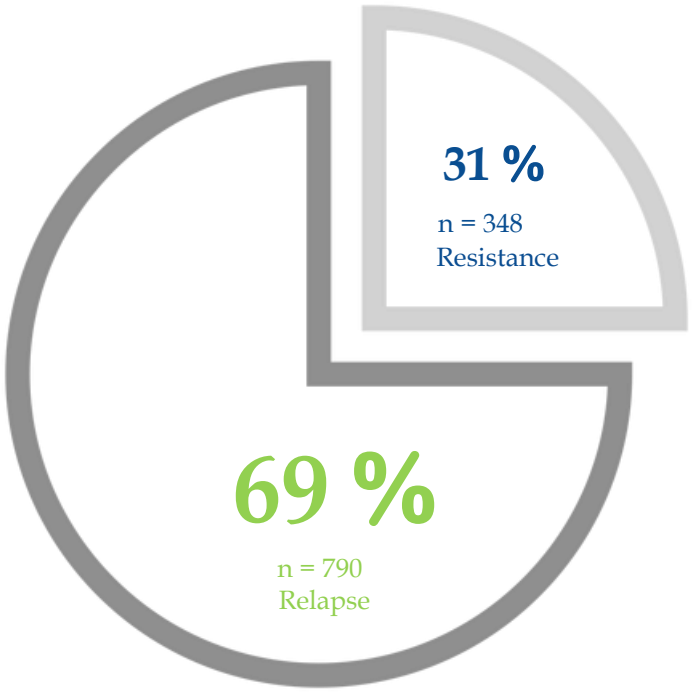
Graph 2 shows that 65.4% clinicians advised that follow-up must be taken at least 1 month after completion of treatment, 15.6% agreed on 2 months duration between the treatment completion and follow-up while 19% suggested it to be taken after 3 months. John L. Brusch and his colleagues in a study revealed that patients should be monitored for relapse or complications for 3 months after treatment has commenced[43]. Shortly one week after the treatment, follow-up must be taken and the stool culture must be taken to check that whether the infectious agents have cleared or not. If the results are positive, retreatment is necessary[44].



Relapse cases are more common In comparison with resistance cases

Figure 3: Showing the Type of typhoid cases reported in their clinical practice

Relapse cases were reported more as compared to resistance that is approximately 69% of the patients were observed having relapse while only 31% of the patients were observed with disease resistance. Typhoid has an estimated global burden of greater than 27 million cases per annum with a clinical relapse rate of 5% to 20%. Despite the large relapse burden, the factors associated with relapse are largely unknown.[45,46]



Relationship of relapse & medication compliance

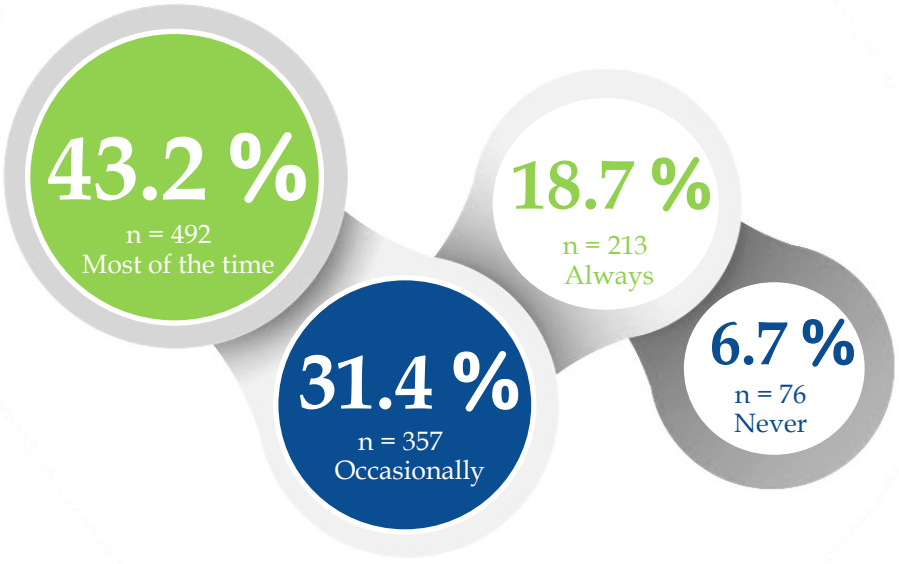


Figure 4: Showing the observed Relation between Relapse of the Disease and Medication compliance

Results indicate approximately 18.7% of the typhoid relapse patients follow the therapeutic advice of their consultant while 43.2% agreed that they remain adhered with the medication for most of the time, 31.4% were found following the advised therapy occasionally while 6.7% were those who never followed the treatment advised by the consultant. According to the guidelines for the diagnosis, management and prevention of typhoid fever, 2010 typhoid relapse usually occur due failure to complete the entire course of antibiotics.[47] 1 in 10 patients face typhoid recurrence, this usually occurs a week after stopping the medication. However, It is reported that 1 in every 5 people die from typhoid mostly due to medication non- adherence.[44]

Duration of relapse visit after discontinuation of therapy

Most of the patient's usually visited the doctor after discontinuing the therapy for 3 week duration (35.6%), 34.6% visited the doctor after 2 weeks, while 29.8% returned for doctor's help due to adverse effects caused by discontinuity of the therapy within a week. As stated in a study published in Annals of Saudi medicine, before antibiotics administration, mortality rate was almost 20%. However, relapse usually occurs in 5-10% of the patients within two to three weeks after the resolution of fever and this may be associated with medication non- adherence.[48]

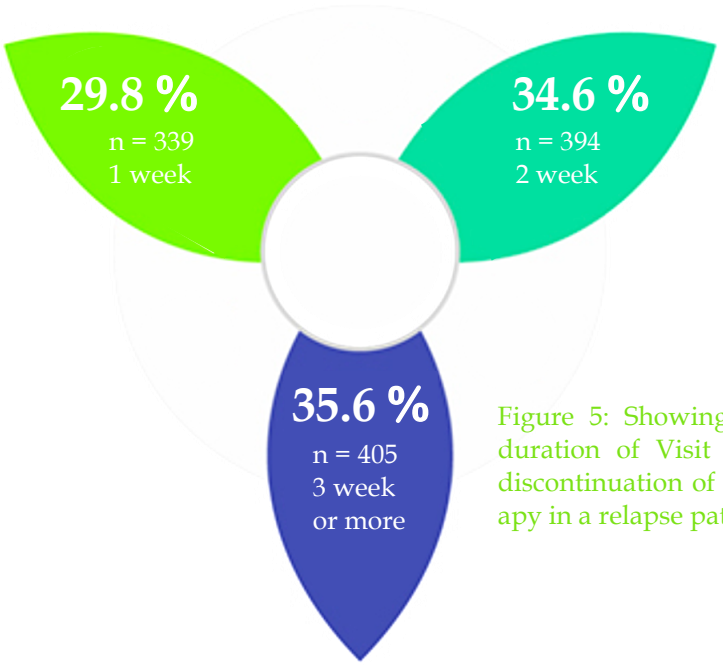


Figure 5: Showing the duration of Visit after discontinuation of therapy in a relapse patient

Patient's quality of life during treatment

Figure 6: 51% patients reported moderate effect of typhoid infection on the quality of life of patient's while 20% patients had a little effect, 25% reported a great effect of typhoid on life of the patient while only 4% said that typhoid had no effect on patient's life. There are convincing data to show that the consequences of a severe infection extend well beyond the immediate affects. Studies define that there are factors influence long-term outcomes, and especially management of the acute infection. The investigation of long-term outcomes of treatment modalities should focus on recovery of patient to return on the same well-being and quality of life route as earlier.[49]

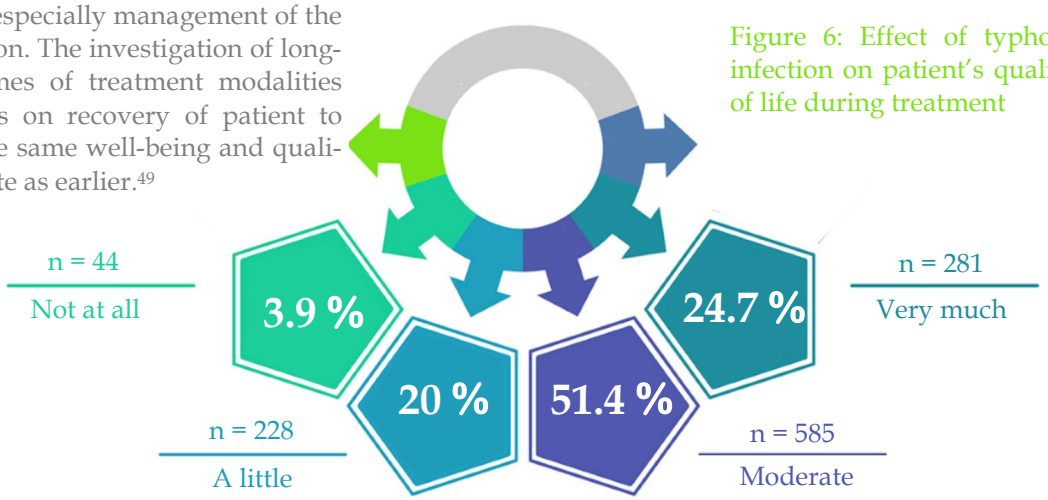
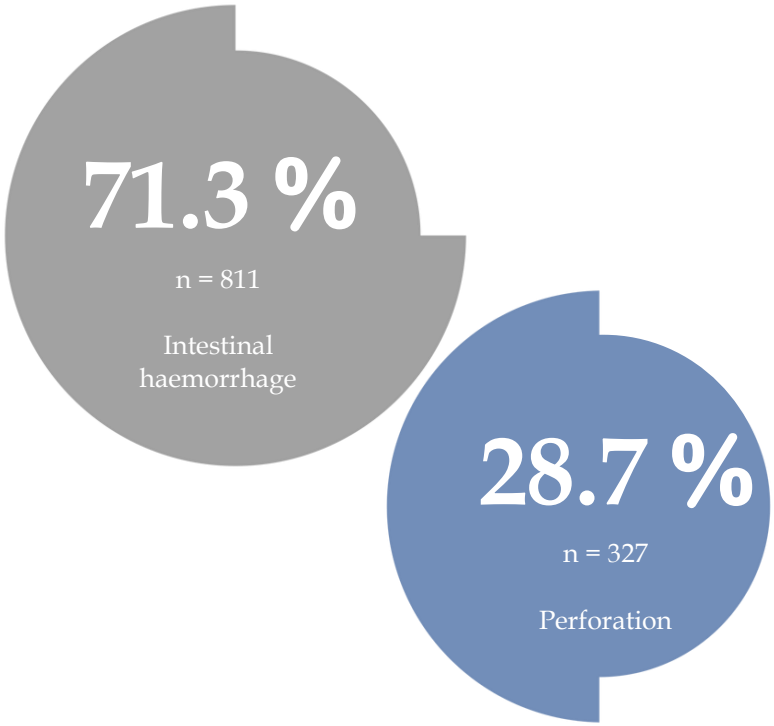


Figure 6: Effect of typhoid infection on patient's quality of life during treatment

Complications reported by patients in long-term treatment

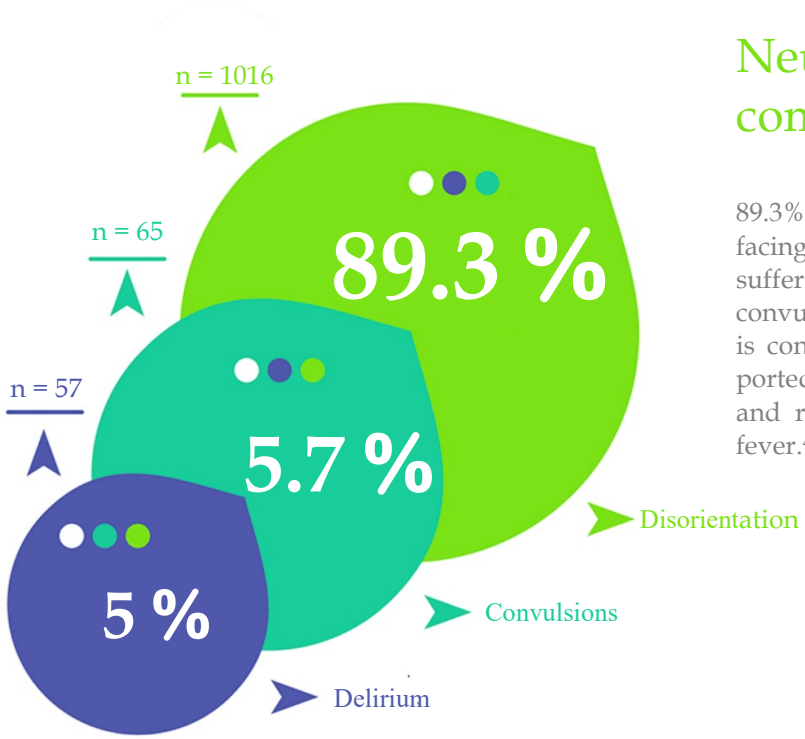


Gastrointestinal complications

Figure 7: Showing Complications reported in long term by patients treated for typhoid

Most common complications observed in typhoid patients during treatment are related to gastrointestinal, neuropsychiatric, respiratory and cardiovascular system.

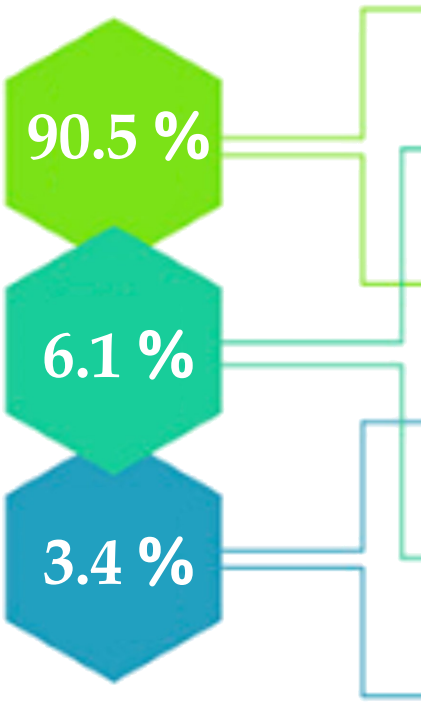
Among gastrointestinal damage 71.3% patients had intestinal hemorrhage while only 28.7% were having gastrointestinal perforation. John L. Brusch in his study on "Typhoid Fever Follow-up" mentioned common gastrointestinal complications like intestinal hemorrhage in 12% of the patients and perforation (3%-4.6%). Previously the mortality rate in patients with intestinal perforation due to typhoid fever was 66%-90% but is now it is significantly lower. Diagnosis is particularly difficult in asymptomatic patients with perforation and peritonitis. In many cases, the discovery of free intra-abdominal fluid is the only sign of perforation.[43]



Neuropsychiatric complications

89.3% of the patients treated for typhoid were facing problem in orientation while 5% were suffering from delirium and 5.7% were having convulsions. As far as neuropsychiatric system is concerned the most common symptoms reported globally are disorientation, delirium, and restlessness, mostly in late-stage typhoid fever.[43]

Relapse cases are more common
In Comparison with resistance cases

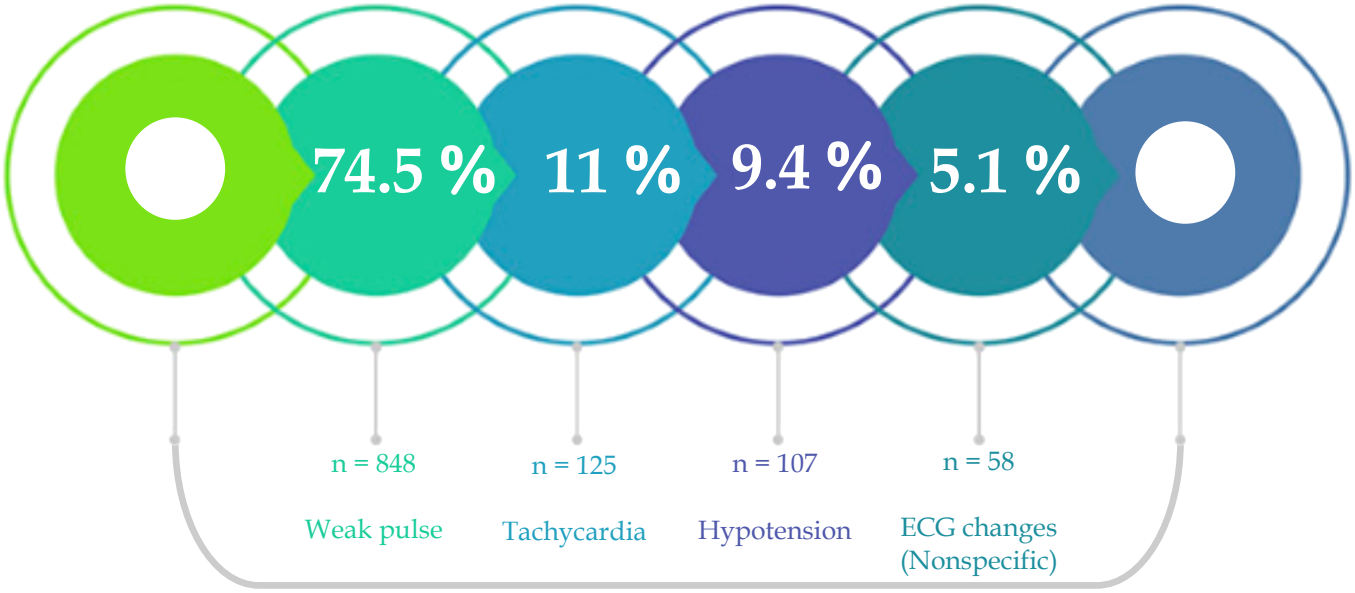


Respiratory complications

Cough, Ulceration of posterior pharynx, and Occasional presentation as acute lobar pneumonia (pneumotyphoid) are the most common respiratory complications reported worldwide.[43] According to results cough was observed in 90.5%, pneumotyphoid in 6.1% and ulceration of posterior pharynx in 3.4%.

Cardiovascular complications

Among cardiovascular changes related to typhoid were ECG changes (5.1%), tachycardia (11%), weak pulse was observed in large group of people in response to typhoid (74.5%) and only 9. 4% were reported having hypotension. In an article published in Medscape in 2017 cardiovascular complications like Nonspecific ECG changes usually occurs in 10-15% of patients with typhoid fever. Toxic myocarditis is also observed in typhoid patients with cardiovascular complications and is a significant cause of death in endemic countries. Toxic myocarditis is characterized by tachycardia, weak pulse and heart sounds, hypotension, and electrocardiographic abnormalities. Pericarditis is rare, but peripheral vascular collapse without other cardiac findings is increasingly observed in typhoid patients.[43]



Clinical Experience

Effective Therapeutic Management of Poorly Managed Typhoid Fever

By Professor Dr. Mujeeb-ur-Rehman Abid Butt

Professor Dr. Mujeeb-ur-Rehman Abid Butt is a consultant at the Shalamar Hospital/ Shalamar Institute of Health Sciences. His Research and therapeutic interests include enteric fever and infectious disease

Introduction

Safe water provision is highly inadequate in many parts of the world, therefore Typhoid is a very common Public Health issue in those areas. Salmonella Typhi is main reason of most typhoid cases. In 2000, estimated illness due to typhoid were 21.7 million and deaths around 217,000 worldwide. South central and Southeastern Asia experience the greatest burden of illness.[50]

Many evidence proposes that the fine measures taken for improving the quality of drinking water will lead to prevent and reduce in enteric fever.[51] S. Enetrica multi drug resistance is with the traditional first line treatment drugs for example; ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole.[52]

Case History

A 28 years old man laborer by occupation reports to the emergency department of a teaching hospital with 2 weeks history of cough, fever, generalized lassitude, abdominal pain and black colored stools. He had developed altered sensorium one day before reporting to the hospital. He was in a healthy state 2 weeks ago when he started having rising fever progressively, episodes were more occurring in the evenings with chills and dry cough. He consulted a local doctor and was prescribed with tablet Augmentin 625 mg thrice daily for 5 days.

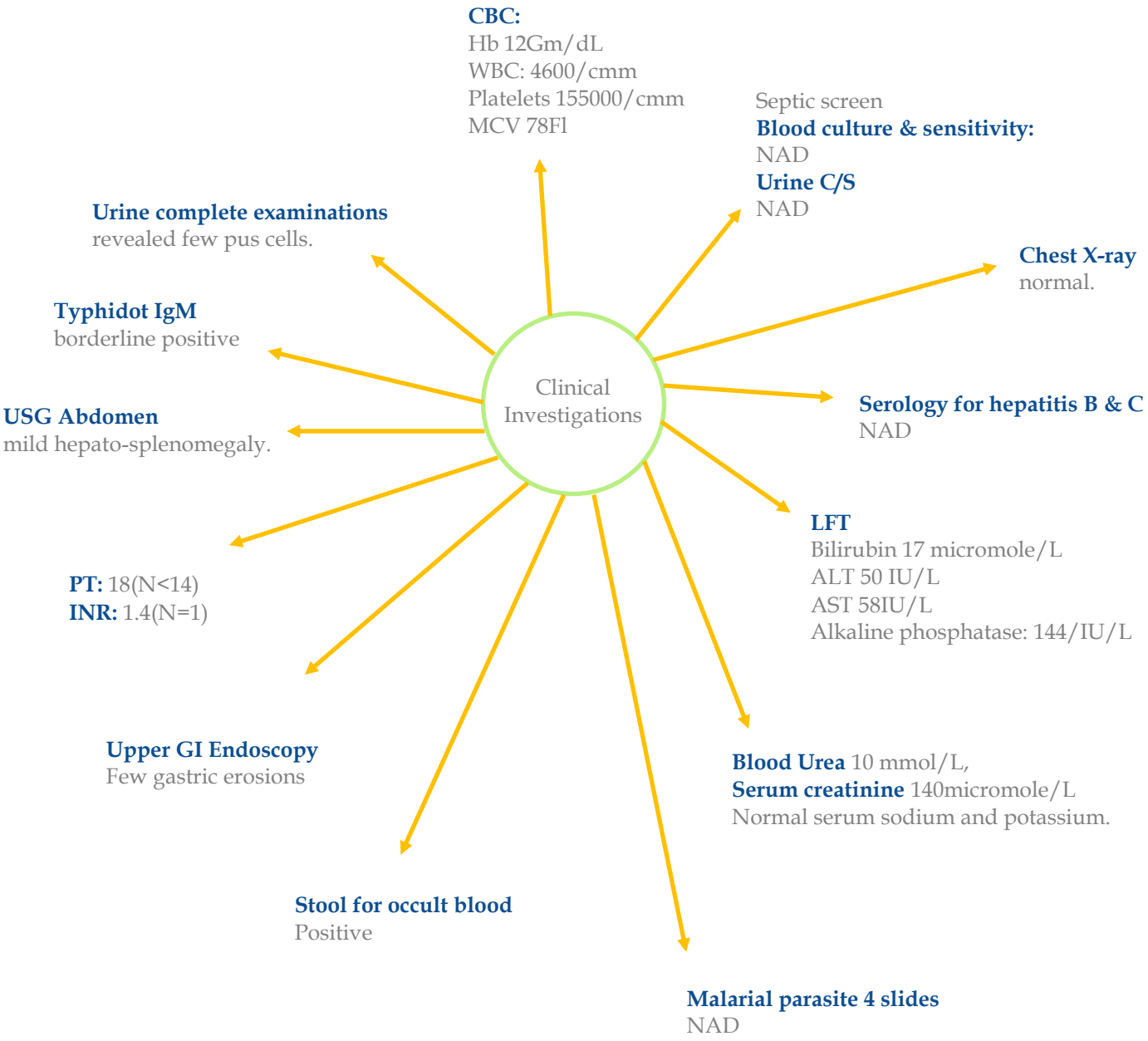
His fever didn't subside and patient meanwhile developed severe headache which was generalized and accompanied by vomiting. He started having anorexia meanwhile and felt generalized lassitude. Few days later he developed per umbilical pain followed by malena which subsided after 3 episodes. This patient was subsequently given cefixime and ciprofloxacin which he took only for 5 days but his fever didn't subside.

One day before reporting to our hospital he developed altered conscious state though was not fully unconscious. There was no history of seizures during current ailment. His past history was insignificant. He belonged to a lower socioeconomic status, lives in a two-room house with his wife, one child and his parents.

On arrival to the emergency department following were the clinical findings:

- Pulse: 119/min,
- Temp: 101 ^{0}F,
- BP: 100/60mm Hg
- Respiratory rate: 20/min.

He was conscious though lethargic and had toxic look. His look was sallow and had coated tongue with thick white secretions. Examination of trunk revealed few purpuric spots over front of chest and they were blanchable. No rose spot over the skin in this case. Abdomen was soft to touch with lower abdominal tenderness and mild splenomegaly. Examination of chest revealed bilateral harsh vesicular breath sounds while there were no signs of meningeal irritation. Rest of the systemic examination was unremarkable. He underwent investigations and the reports as follows:



Discussion

Patient was started with general supportive treatment including IV fluids comprising Ringers Lactate and antipyretics. Meanwhile considering the history and clinical findings and the socioeconomic status of the individual patient was started with anti typhoidal treatment empirically. For this IV Ceftriaxone 1 gm BD and IV Ciprofloxacin 400 mg twice daily. In addition to above IV PPI: Omeprazole started at the dose of 40 mg twice daily.

Patient's fever started regressing on 6th day of antibiotics. Ceftriaxone was continued for 10 days while ciprofloxacin was given for total of 2 weeks. Initially 6 days of injectable ciprofloxacin was given while remaining course was given with oral preparation. Patient was discharged on 11th day of admission. He had a follow up after 2 weeks of stopping the antibiotics and he was fine then.

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