Changing Profile of Enteric Fever in Tertiary care hospitals of Kathmandu

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ABSTRACT

Enteric fever is associated with poor sanitation and unsafe food and water, it continues to be important causes of morbidity and mortality in south-central and Southeast Asia. Nepal has been one of the countries having high incidence of typhoid fever. In this study we examined the cases of fever, which weremanagedas enteric fever by the treating physician. We compared symptoms and signs between culture positive and culture negative cases. We also looked into the antibiotics sensitivity pattern. Among the 122 cases of fever enrolled in the study, 46 of them were culture positive typhoid. Rest of the patients were culture negative. Headache and myalgia were significantly correlated with culture positivity (Yates 7.36 p=0.007Pearson 8.61, p=0.0042 and Yates 3.93, p=0.047432, Pearson 4.51,p=0.033697 respectively). Malaise, cough and arthralgia were not significantly correlated with culture positive enteric fever. Anorexia was the most common GI symptom, which was present in 87% of the culture positive population and 57% of the culture negative population. Anorexia was associated with culture positivity (Yates 20.86, p= <.0001 Pearson 22.32, p= <.0001). Nausea and vomiting were almost equally in culture positive and negative cases at about 39 and 38 percentage. Other GI symptoms like abdominal pain, constipation and diarrhea were less frequent in both the groups. Nausea, vomiting, abdominal pain, constipation and diarrhea were not significantly associated with culture positive typhoid fever. Therewas no case with hepatospleenomegly. Significant numbers of culture isolates were resistant to floruoquinolone, while all of them were sensitive to cefixime, ceftriaxone and azithromycin.

Keywords: Enteric Fever, Typhoid, Culture positive/Culture Negative.

INTRODUCTION

Typhoid Fever is caused by a gram-negative organism Salmonella enterica either serovarTyphoid (*S.typhi*) or SerovarParatyphi (*S.paratyphi*).[1] Globally, Enteric fever affects 21.6 million people and causes 216500 deaths annually. World Health Organization (WHO) conservatively estimates the annual global incidence of typhoid fever at 0.3%.The incidence of typhoid fever is estimated to be 100/100,000 cases. Between 1-5% of patients with acute typhoid infection have been reported to become chronic carriers of infection depending on age, sex and treatment regimen.[2]

In a study done in Nepal, out of 876 febrile patients, 323 (37%) patients were identified by blood culture to have enteric fever, the most common being Salmonella enteric Serotype *typhi* and serotype *paratyphi A*.[3] This shows that typhoid fever is one of the most common febrile illness encountered by practitioners in Nepal.[4] But its real impact is difficult to estimate because the clinical picture is confused with those of many other febrile infections, however, definite diagnosis needs blood culture. There are no bacteriology laboratories in most areas of developing countries.[5] These are the main factors believed to result in many cases going undiagnosed. Although various clinical trials are done for easy, early and cost effective diagnosis of Enteric fever but no such trials have quoted to reliably distinguish between different epidemic infections causing fever mimicking typhoid.Emergence of Multi Drug Resistant strains of *salmonella typhi*, over the counter use of antibiotics due to easy availability which superimposes the typical clinical features.[6] This study is designed to characterize the emerging clinical features of enteric fever their difference in culture positive and clinician suspected enteric fever and see antibiotic sensitivity in case of culture positivity and its sensitivity to the antibiotics.

MATERIAL AND METHODS

Thiscross-sectional, descriptive study conducted in Nepal Medical College Teaching Hospital, Kathmandu, Nepal. Nepal Medical College is a multi-speciality tertiary care hospital in Kathmandu. Data was collected through interview of study group using pre-designed questionnaire. Age group of 14-80years were included after taking informed consent, which comprised of 122 cases over a period of one year from July 2014 to June 2015. All the patients were evaluated by history and general clinical evaluation with the features of enteric fever. Haematological evaluation involved blood examination for complete count differential count, renal function test, liver biochemistries

and blood culture for salmonella. They also underwent radiological evaluation for the evaluation of organomeglay. Data were analysed by using SPSS and MSExcel.

Inclusion criteria:Patients with an elevation of body temperature to a level >38.3°C (101°F) for 3 or more days and no clinical localisation.

Exclusion Criteria: Fever for less than 3 days. Fever with obvious clinical like, sore throat, coughs with muco-purulent sputum, haemoptysis, and chest pain suggesting pneumonia or dysuria and frequency suggesting a urinary tract infection. Overt jaundice and underlying disease suggesting particular localisation (like spontaneous bacterial peritonitis in cirrhotic patients with ascites) were also excluded. Already investigated and diagnosed fevers on their way to recovery.

RESULTS

Among the 122 cases of fever enrolled in the study, 46 of them were culture positive typhoid and the rest of the patients were culture negative. Mean duration of fever that the patients presented with was 6 days, minimum 3 days and maximum 8 days. Symptoms were divided into Gastrointestinal (GI) and non-GIsymptoms (Table 1). Headache, myalgia, malaise, cough and arthralgia were non GI symptoms. Headache and myalgia are present in 67%, 60% and 44%, 47% in culture positive and culture negative patient (Figure 1). Both of the symptoms are significantly correlated with culture positivity (Yates 7.36 p=0.007,Pearson 8.61,p=0.0042 and Yates 3.93,p=0.047432, Pearson 4.51,p=0.033697 respectively) Malaise, cough and arthralgia were present in 50%,28%,13% of culture positive and 50%, 30%,16% of culture negative patients respectively. These symptoms were not statistically significant.

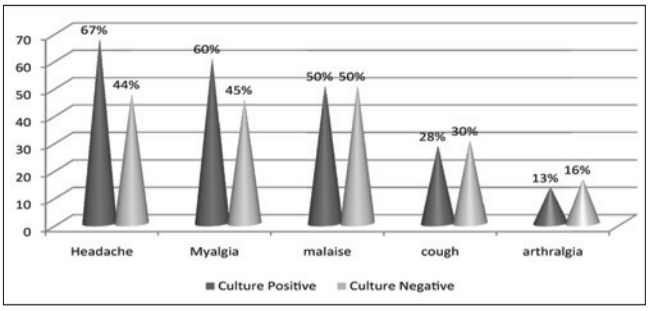

Fig. 1: Non GI Symptoms of Patitent with Fever

In the study population, there area significant number of patients who had GI symptoms (Figure2). Anorexia was the most common, present in 87% of the culture positive and57% of the culture negative population. Anorexia was associated with culture positivity (Yates 20.86,p= <.0001 Pearson 22.32,p= <.0001). Nausea and vomiting were present in 39%, 39% of culture positive enteric fever and 38%, 38% of culture negative population respectively. Abdominal pain, constipation and diarrhea were less frequently amounting to 37%, 22%, 13% of culture positive and 25%, 18%, 11% culture negative patient respectively. Nausea, vomiting, abdominalpain, constipation and diarrhea were not significantly associated with culture positive typhoid fever.

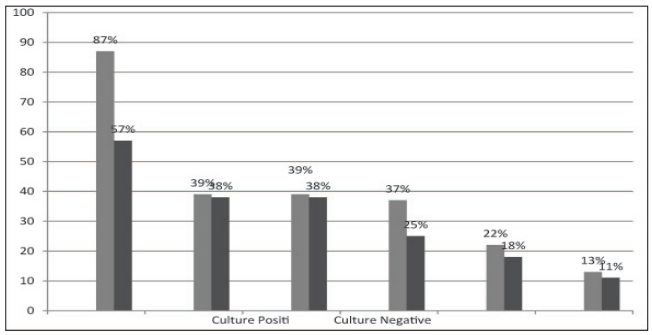

Fig. 2: GI Symptoms with Patients with Fever

During general physical examination, coated tongue was present in 56%of culture positive cases while it is present in 26% of the patients who are culturenegative (Table1). Coated tongue is correlated with culture positive enteric feverYates Correlation 7.55, p-value=0.005, Pearson's Correlation 8.78, p=0.003). During general physical examination and Ultrasonographic evaluation of abdomen there were no cases of hepatomegaly and spleenomegaly in both the groups. This shows that more than organomegaly coated tongue is significantly associated with culture positive typhoid.

Table 1: Symptoms and signs of culture positive and negative cases.

	Culture Positive (46)	Culture Negative (76)	Yates Correlation	Pearson's Correlation
Non GI symptoms				
Headache	31	34	7.36 p=0.007	8.61,p=0.0042
Myalgia	27	33	3.93,p=0.047	4.51,p=0.033
Malaise	23	38	0.02,p=0.88	0,p=1
Cough	13	23	0.02,p=0.88	0.1,p=0.75
Arthralgia	6	11	0.16,p=0.68	0.36,p=0.54
GI symptoms				
Anorexia	40	42	20.86,p= <.0001	22.32,p=<.0001
Nausea	18	28	0,p=1	0.02,p=0.887
Vomiting	18	28	0,p=1	0.02,p=0.887
Abdominal Pain	9	18	2.83,p=0.09	3.37,p=0.06
Constipation	10	13	0.28,p=0.59	0.5,p=0.47
Diarrhoea	6	8	0.05,p=0.82	0.19,p=0.66
Examination Findings				
Coated Tongue	26	19	7.55,p=0.005	8.78,p=0.003
Hepatomegaly	0	0	NA	NA
Spleenomegaly	0	0	NA	NA

Culture isolates of 46 patients shows 70 % were *Salmonella tyhpi* and 30% were *salmonella paratyphi*. All the culture isolates were sensitive to Azithromycin, Ceftriaxone and Cefixime, whereas, flouroquinolone sensitivity was seen onlyin 15.6 % (Figure 3).

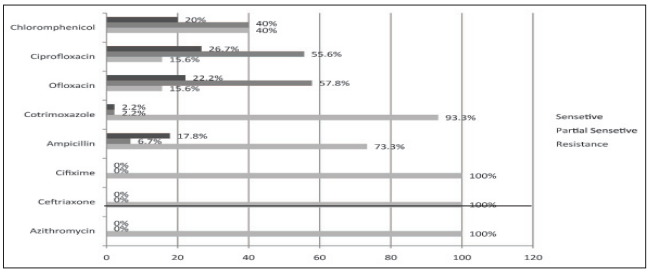

Fig. 2: GI Symptoms with Patients with Fever

DISCUSSION

Typhoid fever is a systemic infection caused by *Salmonella enterica* serotype Typhi (*S. typhi*). The disease remains an important public health problem in developing countries. In 2000, it was estimated that over 2.16 million episodes of typhoid occurred worldwide, resulting in 216 000 deaths, and that more than 90% of this morbidity and mortality occurred in Asia.[7] In Nepal typhoid fever is prevalent in mountains; valleys andsouthern belts of the country as an endemic disease with its peak incidence in May to August and is one of the leading diagnoses of fever in most of the hospitals in Nepal.[8] Typhoid fever was considered responsible for deaths of many patients admitted in the hospitals in Kathmandu, the capital of Nepal, in late 1960s when the National Public Health Laboratory came into being.[9]

A study done by Butler and Islam[10] shows that Patients typically present to the hospital toward the end of the first week after the onset of symptoms with fever, influenza-like symptoms with chills (although rigors are rare), a dull frontal headache, malaise, anorexia, nausea, poorly localized abdominal discomfort, a dry cough, and myalgia, but with few physical signs. In our study apart from fever headache, myalgia, malaise cough and arthralgia were presenting symptoms. Among them headache and myalgia were significantly associated with culture positive typhoid. A coated tongue, tender abdomen, hepatomegaly, and splenomegaly are common in other studies. Adults often have constipation, but in young children diarrhoea is more common.[11] In our study there were no cases of hepatospleenomeglay however coated tongue was significantly associated with culture positive enteric fever. A few rose spots, blanching erythematous maculopapular lesions approximately 2 to 4 mm in diameter, are reported in 5 to 30 percent of cases. They usually occur on the abdomen and chest and more rarely on the back, arms, and legs. These lesions are easily missed in dark-skinned patient.[12]. Anorexia was significantly associated with culture positive enteric fever. A prospective study done in Kathmandu by Maskey et al in 669 patients showed headache in 80%, myalgia in 30%, malaise in 10%, cough in 2-4% of the study population,whereas, gastrointestinal symptoms like anorexia was present in 55%, abdominal pain in 30-40%,diarrhoea in 22-28%, nausea in 18-24%, vomiting in 18% and constipation in 13-16%.[13] The definitive diagnosis of enteric fever is blood cultures.[14]. The sensitivity of blood culture is higher in the first week of the illness, is reduced by prior use of antibiotics, and increases with the volume of blood cultured and the ratio of blood to broth. The sensitivity of stool culture depends on the amount of faeces cultured, and the positivity rate increases with the duration of the illness. Stool cultures are positive in 30 per cent of patients with acute typhoid fever. For the detection of carriers, several samples should be examined because of the irregular nature of shedding.[15]In this study, among the patients enrolled, we had only 27% of culture positivity. Various studies quote culture positivity to be 40-80%[16]. This still shows we are missing a significant number of culture positive cases.

Many signs and symptoms of enteric fever are common with other epidemic infectious diseases with high prevalence, which may lead to unnecessary exposure to antibiotic agents and spread of increasingly common multidrug resistant strains. Also isolation of bacterium is not awaited to initiate the treatment of enteric fever because of long duration, their frequency of complication, accompanying death rate and prolonged hospital stay.[17] Other diagnostic test like Widal test, which is still used as a supportive diagnostic tool, has limited its clinical use because of high number of false positive and false negative results. Rapid serological diagnostic tests for typhoid fever are available. In an evaluation of three commercial kits, the sensitivity and specificity for identifying blood-culture-positive cases of typhoid fever was 89% and 53% for multi-testdip –sticks (PANBIO INDX, Baltimore, MD, USA), 79% and 89% for typhidot (Malaysian Bio-diagnostic Research SDN BHD,Malaysia),78% and 89% for tubex test (IDL Bidesh,Soletuna,Sweden) as compared with 64% and 76% for Widal.[18]

In this study more than 50 per cent of the isolates were resistant to ciprofloxacin and ofloxacin. Resistance to Chlormmphenicol, AmpicillinandCotrimoxazolewere 20%, 17.8%, 2.2%, respectively. All the isolates were sensitive to cefixime, ceftrixone and azithromycin. A population based study done in 5 Asian countries showed that 23% (96/413) of isolates were multidrug resistant (chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole) [19]

Clinical presentation of typhoid is changing. It is indistinguishable from various other fevers prevalent in tropical region. Despite of advances in diagnostics there is still need for an easy and sensitive test. Antibiotics available over the counter are making organisms resistant to many antibiotics. This is causing more problem in diagnosis and as well as increasing the cost of treatment.

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