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Audit

Management of Typhoid fever in the Department of Medicine at Kathmandu Medical College.

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Aim

1. To assess the ongoing management strategy of typhoid fever in department of medicine at Kathmandu Medical College, Sinamangal, Kathmandu.

1. To suggest changes, if required for the benefit of patients and doctors

Method

Prospective study of clinically suspected enteric fever from 2060/01/29 to 2060/04/25. Assessment and analysis of the rationality of the diagnostic parameters that are being used in the ward for clinically suspected enteric fever in unit one of department of medicine. Treatment outcome of the patients with the commonly used antibiotics. Analysis of the sensitivity pattern of the salmonellae isolated among the study group.

Result

1. Only 11 cases (37%) were actually culture proven among the 30 cases suspected to be enteric fever on clinical basis.
2. 19 cases (63 %) of the clinically suspected enteric fever were diagnosed only on the basis of single widal test (titre more than 1:320), blood culture being negative.
3. Bone marrow was subjected to culture for salmonella only in 4 Cases (13%) despite blood culture being sterile.
4. The laboratory could provide sensitivity pattern of salmonellae only in 5 cases out of 11 culture positive cases (45%).
5. Eighteen cases (60%) had to be given 3rd generation cephalosporin after not responding to 5 days course of fluoroquinolones (ciprofloxacin or ofloxacin). On the other hand all the cases in the study group subjected to 3rd generation cephalosporin (injection ceftriaxone or cefixime orally) responded well to the treatment.

Conclusion

1. We shouldn't be relying too heavily on a single titre of widal test for the diagnosis of enteric fever and should be sending blood for culture for salmonella and even bone marrow culture, if necessary. This can be concluded on the basis of lots of literature against single widal test in the diagnosis of enteric fever.
2. Widal test should be positive with clearly significant rising titre (with paired sample) or modified widal test has to be performed if one wants to give gravity to the test for the diagnosis of enteric fever.
3. Laboratory personnel's need to be more serious in their works so as to try to see sensitivity pattern in all positive cultures, if rational use of antibiotics is really desired in view of increasing antibiotic resistance.
4. Fluoroquinolones, once thought to be super powerful antibiotic & still taken as the drug of choice almost everywhere, has been found to be resistant in most of the cases in this study. Though the sample size is too small and there are lots of limitations in this study to come to a firm conclusion, it has borne one serious question in the minds of our unit doctors:

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whether we are over-using fluoroquinolones for trivial infections and leading to the emergence of resistant strains of salmonellae?

Discussion

Typhoid fever is an acute generalized infection of the reticulo-endothelial system, intestinal lymphoid tissue, and the gall bladder. It is a communicable disease, found only in man and occurs due to systemic infection mainly by Salmonella typhi organisms. Until the early 19th century, it was not taken as a separate clinical entity and was often confused with other prolonged febrile syndromes such as rickettsial typhus fever. Typhos in Greek means smoke and typhus fever got its name from smoke that was believed to cause it. Typhoid means typhus-like and thus the name given to this disease. Finally in late 19th century the disease was finally established as a distinct clinical entity. The term enteric fever includes both typhoid and paratyphoid fevers. Typhoid is usually acquired through ingestion of water or food contaminated by the urine or faeces of infected carriers and, as such, is a common illness in poor-sanitation areas. One of the most famous carriers was Typhoid Mary, a cook who infected at least 51 people[1]. In some areas the annual incidence is as high as 198 cases per 100 000, and, contrary to a previously held view, the disease causes considerable morbidity in children Worldwide, at least 17 million new cases and up to 600000 deaths are reported annually[2]. It is a disease of poor environmental sanitation and hence occurs in parts of the world where water supply is unsafe and sanitation is substandard. Outbreaks of typhoid fever occur most often in developing countries, in refugee camps and in overwhelmed areas with a high population density. It is a disease of poverty & still remains an important public health problem in many developing countries of the world although it is difficult to estimate its real global impact due to problems related to clinical and laboratory diagnosis. Thus, the mean incidence of typhoid fever in developing countries is estimated between 150 cases/million population/year in Latin America to 1000 cases/million population/year in some Asian countries. Developed countries, on the other hand, have brought down the incidence of typhoid fever to very low levels. The disease is less common in North America: an estimated 400 cases are reported each year in the United States, 70% occurring in travellers returning from endemic areas. Similarly, in UK, the incidence of this disease is reported to be just one case per 100000 population. However, the disease is still rampant in Asia, Africa, and Latin America. The incidence of typhoid fever in US citizens travelling to the Indian subcontinent was at least 18 times higher than for any other geographic region. American travellers to less industrialized countries, especially those travelling to the Indian subcontinent, continue to be at risk for typhoid fever[3-6].

Paratyphoid fever is also a systemic disease, caused by *Salmonella paratyphi*. Its presenting symptoms are similar to those of typhoid fever, but they are milder and the case-fatality rate is much lower. Incubation period of typhoid fever is usually 10-14 days but it may be as short as 3 days or as long as 21 days depending upon the dose of the inoculum. The peak incidence of typhoid fever is reported during July – September though the cases are observed through out the year. This peak incidence coincides with the rainy season and a substantial increase in fly population. Mode of transmission is usually faeco -oral or urine - oral routes - either directly through hands or indirectly by ingestion of contaminated water, milk, food, or through flies. Contaminated ice, ice creams, and milk products are a rich source of infection[7-10].

Typhoid fever may occur at any age but it is considered to be a disease mainly of children and young adults. In endemic areas, the highest attack rate occurs in children aged 8-13 years. In a recent study carried out in slum areas of Delhi, it was found that contrary to popular belief, the disease affects even children aged 1-5 years. Certain categories of persons handling the infective material and live cultures of S. typhi are at increased risk of acquiring infection. Cooks, who are carriers, obviously pose a great threat of causing outbreaks. However, cooks are not at any increased risk to become carriers. Malnutrition may enhance the susceptibility to typhoid fever by altering the intestinal flora or other host defences. But there is no concrete evidence to indicate that malnutrition increases or decreases susceptibility to typhoid fever[11-15].

Typhoid bacilli are commonly found in water, ice, food, milk, and soil. The Bacterium S. enterica serotype typhi is a member of the family Enterobacteriaciae. The bacterium is serologically positive for lipopolysaccharide antigens O9 and O12, protein flagellar antigen Hd, and polysaccharide capsular antigen Vi. The Vi capsular antigen is largely restricted to S. enterica serotype typhi. Phage typing, pulse-field gel electrophoresis, and ribotyping have shown that areas of endemic disease usually have many strains in circulation but that outbreaks are usually due to a restricted number of strains. These organisms do not multiply in water. Many of them perish within 48 hours but some may survive for about 7 days. Survival can be up to a month in ice and ice creams and upto 70 days in the soil irrigated with sewage. Typhoid bacilli grow in milk without altering its taste or appearance. Vegetables grown in sewage farms or washed in contaminated water are a health hazard. These factors are compounded by social factors such as pollution of drinking water supplies, open-air defecation, and urination, low standards of food and personal hygiene, and health ignorance[14,15].

Man is the only known reservoir of infection - cases or carriers. A case is infectious as long as the bacilli appear in stool or urine. Carriers may be temporary or chronic. Temporary carriers, which may be convalescent or incubatory, usually excrete bacilli up to 6-8 weeks. By the end of one year, 3-4% of cases continue to excrete typhoid bacilli. A chronic carrier state (excreting the bacilli for more than a year after a clinical attack) can be expected to develop in about 3% of cases & may excrete bacilli for several years either continuously or intermittently. Faecal carriers are more frequent than urinary carriers. It is a disease that is amenable to control through modern public health measures[15].

Clinical features: Most cases are asymptomatic during an incubation period of 7–14 days although in many cases a transient and mild episode of diarrhoea develops shortly after ingesting *S.* typhi bacteria. The disease manifests most often a week or so after ingestion and begins with an intermittent fever that becomes high and sustained, severe headache, poorly localized abdominal discomfort, malaise and anorexia. There may also be a nonproductive cough. Although the focus of the infection is the intestine, constipation is more common than diarrhoea in adults. The reverse is true in AIDS patients and children. Physical signs are few. Bradycardia in the presence of high fever, once considered a hallmark of typhoid fever, is not common. The abdomen may be tender to palpation, with poorly localized discomfort. Rose-coloured spots (small maculopapular blanching lesions) appear on the trunk of about 25% of patients with light skin. The spots are less frequent and more difficult to locate in people with darker skin. Laboratory screening may reveal a normal haemoglobin level, normal leukocyte and platelet counts, and elevated liver enzyme levels. Complications occur in 10–15% of cases; gastrointestinal bleeding, perforation and typhoid encephalopathy are the most serious. Gastrointestinal bleeding can occur in up to 10% of cases, most likely from intestinal erosion, but it is clinically significant in only 2% of cases [4,5,9,10,15].

Differential diagnosis: Typhoid must be distinguished from other endemic acute and subacute febrile illnesses.. For patients in countries where typhoid is not endemic, a travel history is crucial. When all the classic clinical manifestations are present, including rose spots, prolonged fever, relative bradycardia, and leukopenia, the diagnosis of typhoid will be strongly suggested. However, most cases do not fit this "typical" profile. Differential diagnosis includes infections associated with prolonged fever, such as Malaria, deep abscesses, tuberculosis, amoebic liver abscess, encephalitis, influenza, dengue, leptospirosis, infectious mononucleosis, endocarditis, brucellosis, typhus, visceral leishmaniasis, toxoplasmosis, lymphoproliferative disease, and connective-tissue diseases should be considered. In the United States, typhoid should be considered in any patient with prolonged, unexplained fever, especially after recent travel to places with endemic typhoid fever. Typhoid should figure high on the list of possible diagnoses of unexplained fever in travellers and patients in whom suspected malaria has not been confirmed or has not responded to antimalarial therapy[15-17].

Diagnosis: The definitive diagnosis of typhoid rests on demonstrating, by means of culture, that a patient with symptoms of the disease is infected

with S. typhi. The absence of specific symptoms or signs makes the clinical diagnosis of typhoid difficult. In areas of endemic disease, a fever without evident cause that lasts more than one week should be considered typhoid until proved otherwise[18-20].

Blood cultures are the standard diagnostic method; provided a large volume of blood is cultured (15 ml in adults), they are positive in 60 to 80 percent of patients with typhoid. Blood culture is usually done and is most sensitive in the first week of illness. Cultures have also been made from the buffy coat of blood, streptokinase-treated blood clots, intestinal secretions (with the use of a duodenal string capsule), and skin snips of rose spots. Though technically more difficult to perform bone marrow culture is more sensitive (The result is positive in 80 to 95 percent of patients with typhoid) than blood culture, regardless of the duration of illness or treatment with antibiotics. Faecal culture yields positive results in only one-third of cases. For the detection of carriers, several samples should be examined because of the irregular nature of shedding[18-22].

Serologic testing for *Salmonella* antibodies (Widal's test) is possible but has sensitivity of only 70% & shows cross-reactivity with some other *Salmonella* species. The role of Widal's test is controversial, because the sensitivity, specificity, and predictive values of this widely used test vary considerably among geographic areas. The test detects agglutinating antibodies to the O and H antigens of *S. enterica* serotype typhi. Unfortunately, *S. enterica* serotype typhi shares these antigens with other salmonella serotypes and shares cross-reacting epitopes with other Enterobacteriaceae. Furthermore, patients with typhoid may mount no detectable antibody response or have no demonstrable rise in antibody titre. Despite this, some centres have found Widal's test helpful when it is used with locally determined cut-off points. A Vi agglutination reaction has been used to screen for *S. enterica* serotype typhi carriers. Its reported sensitivity is 70 to 80 %, with a specificity of 80 to 95 %. Newer serologic tests are being developed but do not yet perform well enough to ensure their widespread adoption. DNA probes and polymerase-chain-reaction protocols have been developed to detect *S. enterica* serotype typhi directly in the blood. The methods are not yet widely used and are impractical in many areas where typhoid is common[18-25].

Management: The aims of management are to eliminate the infection with antibiotics swiftly, to restore fluid and nutritional deficits, and to monitor the patient for dangerous complications. In areas of endemic disease, more than 60 to 90 percent of cases of typhoid fever are managed at home with antibiotics and bed rest. For hospitalized patients, effective antibiotics, good nursing care, adequate nutrition, careful attention to fluid and electrolyte balance, and prompt recognition and treatment of complications are necessary to avert death[26-28].

Though there is strong evidence that the fluoroquinolones are the most effective drugs for the treatment of typhoid fever, the emergence of quinolone resistance in areas where these drugs are inexpensive and readily available is likely to be the greatest limitation on their use.
The prevalence of resistance to multiple first-line oral drugs has been rising among strains of *S. typhi* in developing countries, especially in the Indian subcontinent and Southeast Asia. Where multidrug resistance is a problem, ceftriaxone should be administered initially to adults over 17 years of age, also is the best choice for children because of concerns about quinolone-induced arthropathy and cartilage damage in this age group[29-33].

Since its introduction, chloramphenicol has been the antimicrobial "gold standard" for treatment. No drug has been better in promoting a favourable clinical response, which usually becomes apparent within 24 to 48 h of the start of treatment in the appropriate dosages (3 to 4 g/d in adults or 50 to 75 mg/kg of body weight per day in young children). Chloramphenicol is given orally for 2 weeks; the dose may be reduced to 2 g/d or 30 mg/kg per day when the patient becomes afebrile usually by day 5 of treatment. However, chloramphenicol is little used in the United States & developing countries because of the specter of aplastic anaemia associated with it. The extent to which irreversible marrow aplasia follows chloramphenicol treatment for typhoid in endemic countries is unknown but many physicians believe it may be substantially lower than in Caucasian populations. Chloramphenicol

can induce haemolytic crises in patients with more severe forms of glucose 6-phosphate dehydrogenase deficiency. The chief rivals to chloramphenicol among the cheaper antibiotics are co-trimoxazole, amoxycillin (4 to 6 g/d in four divided doses in adults or 100 mg/kg per day in children) (not ampicillin), and furazolidone. The clinical efficacy of each is roughly comparable and to choose between them is largely a matter of taking into account local data on antibiotic susceptibility and weighing up the various adverse reactions associated with each. Both chloramphenicol and trimethoprim-sulfamethoxazole can be given intravenously to patients who cannot take oral medications. Other effective parenteral antimicrobials include high-dose ampicillin, cefotaxime, cefoperazone, and the 4-fluoroquinolones. However, none has been as rapidly acting or as effective as ceftriaxone, which rivals or betters chloramphenicol in rapidity of defervescence. Initial recommendations for a 7-day course of ceftriaxone have been pared down (to 3 days of 2 to 4 g once daily in adults or 5 days of 50 to 80 mg/kg once daily in children) without apparent loss of efficacy. In addition, compared with that for other drugs, the relapse rate for ceftriaxone appears lower. Alternative oral agents that reportedly are effective for this indication include furazolidone (7.5 mg/kg per day) and cefixime (5 mg/kg every 12 h). The high cost of ceftriaxone is somewhat offset by the efficacy of a short course and the economy of once-daily dosing[29-39].

Eradication of the chronic carrier state, especially in the presence of gallstones, is notoriously difficult. Traditional regimens have used ampicillin or amoxicillin (100 mg/kg per day) plus probenecid (30 mg/kg per day) or trimethoprim-sulfamethoxazole (160/800 mg twice daily) plus rifampin (600 mg once daily) for at least 6 weeks[41].

Preliminary data on the use of fluorinated quinolones (ciprofloxacin, fleroxacin, norfloxacin, pefloxacin, and ofloxacin) and cephalosporins (cefoperazone, cefixime, and ceftriaxone) suggest that these drugs, when compared with chloramphenicol or co-trimoxazole, produce lower mortality in mouse models, and, in man, higher cure rates, faster defervescence and resolution of symptoms, lower relapse rates, and lower rates of asymptomatic carriage after recovery. These are good grounds to recommend these drugs where resources permit and particularly for patients from regions with significant amounts of multiresistant S. typhi. Fluorinated quinolones remain relatively contraindicated for pregnant women and children although favourable results have been reported from the use of ciprofloxacin in children with severe typhoid. Optimum dosage schedules remain to be established. Some investigators are examining courses as short as 3 days with these drugs but while success rates are encouraging the advantages are likely to be offset by increases in relapse and carriage rates and by the emergence of resistant organisms. Chloramphenicol, amoxicillin, and trimethoprim–sulfamethoxazole remain appropriate for the treatment of typhoid fever in areas of the world where the bacterium is still fully susceptible to these drugs and where the fluoroquinolones are not available or affordable[42-48].

In areas where quinolone-resistant strains are uncommon, the fluoroquinolones are the current treatment of choice for all age groups. Short courses of treatment (three to five days) are particularly useful to contain epidemics. Fluoroquinolones should be used at the maximal possible dose for a minimum of 10 to 14 days, and the patients should be carefully followed to determine whether they are excreting *S. enterica* serotype typhi in their faeces. Unfortunately, quinolone-resistant strains are often also multidrug-resistant, and therefore the choice of drugs is limited to azithromycin or the cephalosporins, which are expensive[35,37,42,48-50].

The third-generation cephalosporins (ceftriaxone, cefixime, cefotaxime, and cefoperazone) and azithromycin are also effective drugs for typhoid. In randomized, controlled trials of third-generation cephalosporins, principally ceftriaxone and cefixime, the fever-clearance times averaged one week and the rates of treatment failure were 5 to 10 percent. The relapse rates were 3 to 6 percent, and the faecal-carriage rates were less than 3 percent. Cure rates of 95 percent were achieved with five to seven days of treatment with azithromycin. Fever resolved in four to six days, and the rates of relapse and convalescent faecal carriage were less than 3 percent. Aztreonam and imipenem are potential third-line drugs[51-58].

Most of the data from randomized, controlled trials come from patients treated in regions where disease is endemic. There are few data from such trials of treatment in patients living in regions where the disease is not endemic or in returning travellers. Knowledge of the antibiotic susceptibility of the infecting strain is crucial in determining which drug to use. If no culture is available, knowledge of the likely susceptibility from the available global data may be useful[58-59].

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