MANAGEMENT OF ENTERIC FEVER IN 2012

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Enteric fever is a severe systemic illness characterized by fever and abdominal pain that is caused by dissemination of S. typhi and S. paratyphi. Patients with immunosuppression, biliary and urinary tract abnormalities, hemoglobinopathies, malaria, schistosomiasis, bartonellosis, histoplasmosis and Helicobacter co infections are at increased risk of severe disease. Typhoid and paratyphoid fever continue to be important causes of illness and death particularly among children and adolescents in south-central and south-east Asia due to poor sanitation and unsafe food and water supply. The incidence is 102-2219 cases per 1,00,000 population. The growing importance of S. paratyphi A in Asia is concerning.

Classic presentation is rising fever in first week of illness accompanied by relative bradycardia. In second week, abdominal pain develops and ‘rose spots’ may be seen. Diarrhoea or constipation may occur. During the third week, hepatosplenomegaly, intestinal bleeding and perforation with secondary bacteremia and peritonitis may develop. Less commonly neurologic symptoms may be observed. Focal extraintestinal manifestations have been described as a result of bacteremic seeding. Chronic salmonella carriage is defined as excretion of the organism in stool or urine more than 12 months after acute infection. Chronic carriers frequently have high serum antibody titres against Vi antigen which is clinically useful test for rapid identification of such patients.

In post antibiotic era the average case fatality rate is estimated to be less than 1% but this may be 10-20 fold higher in most resource limited settings.

A center for disease control (CDC) compilation of 10 hospital based typhoid fever series reported a mean case fatality rate of 2% (range 0 – 14.8%) which included very severe hospitalized cases with access to care.

DIAGNOSIS

Blood culture is the gold standard for diagnosis of typhoid fever. Cultures are positive in 40 – 80% of patients. Stool, urine, rose spots or duodenal contents may also be cultured. Bone marrow culture may remain positive up to 5 days after starting antibiotics. The cost, non availability of laboratory facilities, failure to do culture and prior antibiotic use often cause underutilization of valuable diagnostic method. Advantage of doing cultures is availability of antibiotic susceptibility of the isolate which is of paramount therapeutic importance.

Widal test is commonly used. A fourfold or greater increase in titer (when paired acute and convalescent samples are compared) is considered positive. However, seropositivity amongst healthy blood donors in a study performed in Central India was 8 – 14%. Hence clinical utility is doubtful in endemic areas as positive results may represent previous infection.

Newer serologic assays using Elisa and dipstick methods have still not been approved for routine diagnostic use in view of variable sensitivity and specificity.

Other laboratory findings may include anemia, leucopenia, absolute eosinopenia and abnormal liver function tests. Often salmonella hepatitis and acute viral hepatitis may coexist posing a diagnostic challenge.
TREATMENT OF TYPHOID FEVER

Antimicrobial resistance is a major public health problem in both S. typhi and S. paratyphi and timely treatment with appropriate antimicrobial agents is important for reducing the mortality of enteric fever. Chloramphenicol was the drug of choice for several decades after its introduction in 1948 but was set aside due to emergence of plasmid mediated resistance and rare but fatal occurrence of bone marrow aplasia. Trimethoprim sulfmethoxazole and ampicillin used in 1970s met a similar fate. In 1980s, ceftriaxone and ciprofloxacin were shown to be effective against the multidrug resistant strains and became drugs of choice. In the past decade strains of bacteria with decreased ciprofloxacin susceptibility have emerged and rendered older fluoroquinolones ineffective. Azithromycin was tested in 1990s and can now be regarded promising alternative.

AZITHROMYCIN

Nine prospective clinical trials have been done. Drug was received by a total 453 patients including children. Azithromycin was used in dose of 500mg – 1 gm /day for 5-7 days.

No relapses were recorded in 267 patients treated with azithromycin followed up for 1 month after therapy where as relapses were recorded in 16 of 276 patients (5.8%) treated with ceftriaxone, ofloxacin or gatifloxacin.

Bacteriological responses were very good with only 1.5% patients whose blood was recultured after treatment showed salmonella.

Azithromycin is capable of achieving very high intracellular concentrations and its ability to achieve intracellular concentrations 50-100 times greater than serum levels explains its efficacy against salmonella species. It has half life of 2-3 days. Raised MICS of azithromycin have been reported in S. and paratyphi A. Recently azithromycin resistance and treatment failure in patient with S. paratyphi A infection has been reported.

FLUOROQUINOLONES

Quinolones including ciprofloxacin and ofloxacin were drugs of choice for most cases of enteric fever. However reports of resistance to fluoroquinolones in the form of nalidixic acid resistance which correlates with decreased ciprofloxacin susceptibility (DCS) was reported in 1990s. In Asian countries this gave rise to them being rendered ineffective therapy. Gatifloxacin gave good results in 2 trials that used 7 day courses, had low MIC (minimum inhibitory concentration) for bacterial strains with DCS and is suggested to be more effective than older fluoroquinolones owing to better results of time-kill experiments but its use was associated with more relapses than with azithromycin. In a recent paper in the Lancet infectious disease from Nepal Gatifloxacin was compared to chloramphenicol where it showed similar efficacy. However, on basis of its shorter treatment duration, fewer adverse events and lower cost, authors recommend it as preferred treatment of enteric fever.

CEPHALOSPORINS

Trials of ceftriaxone show that fever defervescence takes longer and relapses occur in patients treated for shorter duration. It is recommended for 14 days. This antibiotic is safe and achieves good clinical cure.

CHLORAMPHENICOL

The reduced use of chloramphenicol has increased sensitivity to chloramphenicol. Reversal may be due to loss of plasmids encoding resistance to chloramphenicol. It is making a comeback in developing countries.

PREVENTION

The availability of full genome sequences for S. typhi and S. A confirms their place as monomorphic human adapted pathogens vulnerable to control measures if efforts for the same can be intensified.

Interventions to improve availability of safe water, food and basic sanitation measures are underway in most countries. The identification and management of S. carriers particularly those involved with food handling has proved to be important strategy for control.

VACCINES

While Ty 21a and Vi polysaccharide vaccines are effective, development of cheap, safe vaccines with efficacy among infants which can provide protective immunity after single does is required. The growing importance of S. A as a cause of enteric fever is of great concern particularly due to lack of effective vaccine available. CDC has issued special guidelines for typhoid vaccination in travelers to endemic countries.

CONCLUSIONS

Enteric fever continues to be an important cause of illness with estimated global burden of greater than 27 million cases per annum with a clinical relapse rate of 5% to 20%. In India there have been increasing reports of Salmonella enterica serotype A causing enteric fever in addition to serotype Typhoid vaccine does not offer protection against paratyphi.

Antimicrobial resistance has rendered many drugs particularly older fluoroquinolones useless as therapy for typhoid. There is greater use of third generation cephalosporins. Azithromycin and newer fluoroquinolone Gatifloxacin have showed promise in the treatment of multidrug resistant typhoid. Safe water supply and improvement in sanitation facility will go a long way in the control of typhoid especially in developing countries.
REFERENCES


