Management of Enteric fever

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Introduction:

Enteric fever is a systemic infection caused by Salmonella enterica subspecies enterica serovars Typhi (S. Typhi, causing typhoid fever) or Paratyphi A, B or C (S. Paratyphi A, B or C, causing paratyphoid fever). This infective condition is common in resource-constrained regions of the world. These regions harbour poor sanitary conditions and inadequate clean water provision which facilitates the spread of infection via faeco-oral transmission. Global estimates in 2000 suggested 21 million illnesses and >210 000 deaths due to typhoid fever, plus 5.4 million cases of paratyphoid fever, with similar estimates for 2010. S. typhi is the commonest cause of disease globally, but S. paratyphi A infections are common in some parts of the world, especially Asia. Provision of clean water and good sewage systems in Europe and the USA since the early 20th century has led to decline in the incidence of typhoid fever, but the disease remains a serious public-health problem in developing countries. The incidence of typhoid fever in some parts of South Asia is as high 1600 per 100 000 population. Studies from India and Nepal suggest that in some settings and times, paratyphoid fever caused by S paratyphi A can contribute up to half of all cases of enteric fever. About 10% of people recovering from untreated typhoid fever patients excrete S typhi for at least 3 months in the stools. Chronic carrier state develops in 1% and 5% of typhoid patients (defined as excretion of S typhi in urine or stools for more than one year), and the rate is higher for women, those older than 50 years, and patients with schistosomiasis, cholelithiasis, carcinoma of the gall bladder, and other gastrointestinal malignancies. Most chronic carriers are asymptomatic and almost a quarter may have had no history of typhoid fever.

Pathogenesis:

Natural host and reservoir for S typhi is human beings. It can survive for days in groundwater, pondwater, or seawater, and for months in contaminated eggs. Food and water contaminated with faeces lead to transmission of infection. Typhoid organism rapidly penetrates the mucosal epithelium via either microfold cells or enterocytes and arrives in the lamina propria on reaching small intestine, where they rapidly elicit an influx of macrophages that ingest the bacilli but do not kill them. Typhoid bacilli reach the bloodstream principally by lymph drainage from mesenteric nodes, after which they enter the thoracic duct and then the general circulation. This silent primary bacteraemia leads to dissemination of pathogen throughout the organs of the reticuloendothelial system (liver, spleen, bone marrow, etc.) where it resides during the incubation period, usually of 8 to 14 days. The quantity of inoculum is one of the factors which decides the incubation period in an individual patient besides various host factors.

Clinical presentation:

Clinical features of typhoid fever are similar to those of paratyphoid fever. Variable spectrum of clinical presentation is seen in typhoid fever patients, ranging from fever to marked toxaemia and associated complications involving many systems. Non-specific features like diarrhoea and vomiting, or predominant respiratory symptoms may lead to a state of missed diagnosis. Overall clinical outcome and severity of the infection is influenced by many factors. They include the age, the bacterial strain virulence, the quantity of inoculum ingested, host factors including HLA type and any immunosuppressive state, duration of illness before the initiation of appropriate treatment, the choice of antimicrobial agents, and whether the patient was taking medications which may diminish gastric acidity.

Typhoid fever is characterized by prolonged fever, disturbances of bowel function (constipation in adults, diarrhoea in children), malaise, anorexia and headache. During early stage of the illness bronchitic cough is common. Exanthems (rose spots) are seen on the chest, abdomen and back especially in fair skinned individuals in up to 25% of patients. Overall, about 10–15% of patients develop severe disease.

Complications:

Among various complications, relatively common ones are gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy. During the later period of the illness, a rapid drop in temperature suggests intestinal bleeding or perforation. Gastrointestinal bleeding occurs in 10–20% of cases due to erosion of the peyer's patch into an intestinal vessel and is usually restricted to either occult blood in stool or malaena. The most common site involved is terminal ileum followed by the ileocaecal valve, the ascending then the transverse colon on colonoscopy. Multiple punched out ulcers with slightly elevated margins are seen. Intestinal perforation occurs in 1–3% of cases in hospital.

The average case fatality rates for typhoid are less than 1% as majority receive early and appropriate antibiotic therapy. Relapses are seen in 5–10% of cases, but these episodes carry much lower clinical severity. These relapse can occur without therapeutic intervention but more often it follows antibiotic treatment. The incidence of relapse after treatment with fluoroquinolones (1·5%) or broad-spectrum cephalosporins (5%) is lower than that after treatment with chloramphenicol, trimethoprim-sulfamethoxazole, and ampicillin. Same S typhi strain having the similar antibiotic susceptibility patterns as the initial episode causes most relapses. Reinfection with distinct and possibly newly acquired isolates does occur in some patients. S paratyphi A or paratyphi B can present with jaundice, thrombosis and systemic infections. S paratyphi B sometimes can have a presentation similar to non-specific salmonella gastroenteritis. S paratyphi C usually does not present with gastrointestinal symptoms but there have been cases with systemic complications such as septicaemia and arthritis. A relapse rate of 8% has been reported with S paratyphi A.

Laboratory diagnosis:

Confirmation of typhoid or paratyphoid fever requires isolation of S typhi or S paratyphi, respectively, from blood, bone marrow, stool, or duodenal fluid. The sensitivity of bone marrow aspirate culture is around 80–95%. Salmonella is isolated in 30–90% of patients with clinical typhoid using standard blood cultures. Increasing duration of illness leads to decrease in sensitivity. Bood culture yield is determined by the volume of blood and the ratio of blood to broth: 10–15 mL of blood is necessary to maintain an optimum ratio of 1 to 12. Some simple inexpensive rapid serological diagnostic tests for typhoid fever are available as well. 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-test dip-sticks (PANBIO INDX, Baltimore, MD, USA), 79% and 89% for typhidot (Malaysian Biodiagnostic Research SDN BHD, Malaysia), 78% and 89% for tubex test (IDL Bideh, Solletuna, Sweden) as compared with 64% and 76% for Widal.

Treatment:

The most important aspects of treatment of enteric fever are: administration of effective antimicrobials, management of fluid and electrolyte balance, and prompt recognition/ management of complications. It is also essential to eradicate the microorganism promptly to prevent relapses and faecal carriage. Substantial percentage (around 90%) of patients are managed at home with oral antibiotics, rest, and close follow up. Admission to hospital and parenteral antibiotic therapy are required in patients with persistent vomiting, severe diarrhoea, or abdominal distension.

The important criteria for the selection of first-line antibiotics to be used in developing countries are: sensitivity pattern, availability and cost. Enteric fever should be a serious consideration in an endemic area when a fever lasts longer than a week. Among the three criteria for selection of initial antibiotic as stated earlier, sensitivity patterns of S typhi and paratyphi isolates in the area the paramount criteria in deciding the initial choice of antibiotics. S typhi isolates can be broadly classified as sensitive to first-line antimicrobials, multidrug resistant (MDR) but nalidixic-acid sensitive, and nalidixic-acid resistant (often also multidrug resistant). Chloramphenicol was the drug of choice for several decades after its introduction in 1948 but later emergence of resistance and rare but fatal occurrence of bone marrow aplasia, its use decreased markedly.

The fluoroquinolones were the effective and preferred antimicrobial for treatment of typhoid fever in adults in 1980s. They are relatively cheap, well tolerated and more effective than the former first-line drugs, viz. chloramphenicol, ampicillin, amoxicillin and trimethoprim-sulfamethoxazole. The majority of isolates are still sensitive to fluoroquinolones. This antibiotic achieves excellent tissue penetration, kills S. typhi in its intracellular stage in monocytes/ macrophages and achieves higher active drug concentration in the gall bladder than other antibiotics. Therapeutic response is rapid as fever and other symptoms respond in three to five days. Clinical cure rate of about 98%, relapse and faecal carriage rates of less than 2% are seen

with treatment with fluoroquinolones. However, the emergence of MDR strains has reduced the efficacy of fluoroquinolones in many areas.

There are two categories of drug resistance as noted previously: resistance to antibiotics such as chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole (MDR strains) and resistance to the fluoroquinolone drugs. Resistance to the fluoroquinolones may be total or partial. The so-called nalidixic-acid-resistant S. typhi (NARST) is a marker of reduced susceptibility to fluoroquinolones compared with nalidixic-acid-sensitive strains. These isolates are susceptible to fluoroquinolones in disc sensitivity testing according to current guidelines. However, clinical response to infection with nalidixic-acid-resistant strains is significantly worse than with nalidixic-acid-senstive strains to treatment with fluoroquinolones. The available fluoroquinolones (ofloxacin, ciprofloxacin, fleroxacin, perfloxacin) are highly active and equivalent in efficacy in susceptible isolates. Azithromycin, and cefixime, an oral third-generation cepahalosporin, have a clinical cure rate of over 90% with a fever clearance time of 5–7 days and relapse and faecal carriage rates of less than 4% in typhoid fever.

Quinolone-resistant typhoid and paratyphoid fever patients respond to these antimicrobials and therefore these antimicrobials are regarded as acceptable therapy for them. High cost and low availability are their major limitations in developing world. Azithromycin achieves 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. In a systematic review of seven trials involving 773 uncomplicated enteric fever patients which included participants with drug-resistant strains, Azithromycin appeared better than fluoroquinolone. It was also concluded that Azithromycin may perform better than ceftriaxone in these patients. Combinations of antimicrobials are being assessed to provide more affordable options for treatment of quinolone-resistant typhoid fever. Ciprofloxacin proved to be more effective in combination with amoxicillin than ciprofloxacin alone against S typhi strains.

Supportive therapy:

Patients requiring admission with persistent vomiting, severe diarrhoea or abdominal distension, and those with complications should be treated for severe typhoid fever. Areas with low prevalence of quinolone-resistant isolates, Fluoroquinolones remain the antibiotic of choice. Third-generation cephalosporins (ceftriaxone or cefotaxime) are choice of antibiotics where quinolone resistant isolates are prevalent. Antibiotics should be given parenterally for at least 10 days, or for at least for 5 days after defervescence. Death was reduced from 50% to 10% for those given dexamethasone as an initial dose of 3 mg/kg by slow intravenous infusion over 30 min followed by 1 mg/kg at the same rate every 6 h for eight additional doses in Indonesian adults and children with delirium, obtundation, stupor, coma, or shock.

Intensive care unit management and blood transfusion are required in patients with intestinal haemorrhage. Surgical consultation for suspected intestinal perforation is indicated. If perforation is confirmed, surgical repair should not be delayed. Metronidazole and gentamicin

or ceftriazone should be administered before and after surgery if a fluoroquinolone is not being used due to resistance issues. Mortality rates increase as the delay between perforation and surgery lengthens, therefore early intervention is important. Mortality rates vary between 10% and 32%. 1-5% of typhoid fever patients become chronic carriers.

Chronic carriers:

The rate of carriage is slightly higher among female patients, patients older than 50 years, and patients with cholelithiasis or schistosomiasis. If cholelithiasis or schistosomiasis is present the patient probably requires cholecystectomy or antiparasitic medication in addition to antibiotics in order to achieve bacteriological cure. In order to eradicate S. typhi carriage, amoxicillin or ampicillin plus probenecid or TMP-SMZ is administered for six weeks; about 60% of persons treated with either regimen can be expected to have negative cultures on follow-up. Clearance of up to 80% of chronic carriers can be achieved with the administration of 750 mg of ciprofloxacin twice daily for 28 days or 400 mg of norfloxacin.

Vaccines:

Two typhoid vaccines are available, both with proved efficacy of 60-80%. Oral Ty21a vaccine, live oral vaccine is available in enteric-coated capsules. Three doses are recommended each given 2 days apart. A booster may be required every three to five years. Vi polysaccharide vaccine is given as a single intramuscular dose for persons older than 2 years. A booster may be required every two years.

Conclusions:

S. typhi/paratyphi infection is an important public health problem in developing world. Emergence and worldwide spread of strains resistant to many antibiotics has resulted in increase in morbidity and mortality attributable to enteric fever. There is greater use of third generation cephalosporins. Azithromycin has showed promise in the treatment of multidrug resistant typhoid.

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