Multi - Drug Resistant Typhoid

P. Ramachandran *

Enteric fever (Typhoid or paratyphoid fever) is a potentially serious systemic infection. Typhoid fever is caused by Salmonella enterica serovar Typhi (S typhi) and paratyphoid fever is caused by Salmonella enterica serovar Paratyphi (S paratyphi) A, B or C. These organisms cause disease specifically in humans. Paratyphoid fever is usually a less serious infection. An estimated 21.6 million new cases of typhoid fever with about 2,16,150 deaths and about 5.4 million cases of paratyphoid fever occurred globally in 2000 (1). Endemic enteric fever is common in the Indian subcontinent, South-East Asia, Africa, Central and South America and the Mediterranean region. Reported incidence rates in the country vary. 980 per 100,000 population was the incidence reported from Delhi(2). Another study reported an annual incidence rate of 493.5 cases per 100,000 person years in the country(3). Contrary to earlier belief, typhoid fever is widely prevalent among young children under five years of age with higher morbidity and hospitalisation rates(4).

The mortality rate is 10 to 15% if untreated and is highest among children less than one year of age and the elderly(5).

Emergence of drug resistance

Multi-drug resistant (MDR) S typhi denotes those strains which are resistant to all the three first line antibiotics (Chloramphenicol, ampicillin and co-trimaxazole). For many decades, antibiotics such as chloramphenicol, ampicillin and co-trimaxazole were the drugs of choice for treating enteric fever. With effective treatment, the duration of disease was reduced and mortality rates fell from more than 10% to less than 1%. Chloramphenicol was widely used throughout the world from 1940s till mid-1970s. Major resistance to chloramphenicol with outbreaks were reported in 1972. From 1980s, multi-drug resistant (MDR) Salmonella strains have been reported from all parts of the world(1). Outbreaks of MDR typhoid have been reported from the Indian sub-continent since 1983(4) and also from South-East Asia and Africa(6).

Magnitude of the problem of MDR Enteric fever

Emergence of MDR strains of S typhi began from mid-eighties in the Indian sub-continent. These strains rapidly assumed epidemic proportions accounting for 60% to 90% of all cases of typhoid in certain reports (7). In Quetta, Pakistan, 69% of isolates of S typhi were MDR (8). The incidence of MDR S typhi in the UK was reported as over 50% in 1999, up from 34% in 1995 and 1.5% six years earlier (1) and chloramphenicol resistance was 100% in 1995. MDR typhoid has become endemic in many developing countries from 1990s and these strains were also isolated from returning travellers in developed countries. In a study from Singapore in 1990 to 1992, all the MDR typhoid cases had a recent travel history to the Indian sub-continent(9).

From 1991, use of ciprofloxacin was recommended in the UK for treating enteric fever, particularly for those returning from areas where MDR strains were endemic. Extensive use of ciprofloxacin began for the treatment of typhoid, both in developing and developed countries (10). It was initially thought that quinolones have an inherent advantage due to low risk of plasmid mediated resistance. But chromosomally encoded ciprofloxacin resistance in strains of S typhi has been observed in the UK since 1991, majority of which were also MDR (11). Patients infected with such strains had recently returned from several countries in the Indian sub-continent.

Salmonella typhi isolates from Calcutta School of Tropical Medicine from 1991 to 2001 have shown fluctuating levels of multi-drug resistance. Changing pattern of sensitivity has been reported with re-emergence of sensitivity to chloramphenicol, ampicillin and co-trimaxazole due to the withdrawal of selection pressure (4). Some other recent reports also suggest a fall in proportion of MDR typhoid (12, 13).

* Dr. P. Ramachandran , Former Director,
Institute Of Child Health & Hospital for Children,
Chennai

Factors responsible for emergence of MDR Salmonella

Numerous factors are responsible for the emergence of MDR Salmonella strains, namely the administration of antibiotics to farm animals and antibiotic treatment to animals and humans with Salmonella gastroenteritis(14). The contributing factors for drug resistance are the overuse, misuse and inappropriate prescribing practices of physicians, along with the intrinsic microbiological plasmid mediated factors. Large scale irrational use of anti-typhoid antibiotics such as chloramphenicol, co-trimaxazole and furazolidine for common diarrhoeal illnesses prepared fertile grounds for multi-drug resistance. The other contributing factor is the fact that most physicians in India are used to diagnosing infection without bacteriological proof which evolved from lack of bacteriological facilities, compounded by lack of initiative to pursue proof of infection (15). Compared to the earlier days of chloramphenicol therapy when defervescence was noted in 3-4 days, it takes several days for defervescence to occur with currently used drugs such as quinolone or third generation cephalosporins. The way is paved for various drug combinations, frequent change of antibiotics and irrationality in treatment protocols, leading onto drug resistance with newer drugs as well. Despite the sensitivity, minimum inhibitory concentration (MIC) levels of drugs has gone up considerably. Conventional doses have led to a poor response even when the strain was sensitive to the drug (15).

Clinical aspects of MDR typhoid

MDR typhoid appears to be a more severe illness with a larger duration of fever in comparison to drug susceptible typhoid fever (9). Many patients take more than 10-14 days to become afebrile even when a sensitive drug is used in adequate doses (15). The persistence of fever in most patients is maintained by the release of pyrogenic cytokines from macrophages and necrotic tissue. MDR typhoid infections have been documented to be associated with significantly higher case fatality rates, approaching 4-10%, similar to 'pre-antibiotic era'(4). Besides delay in treatment, the increased toxicity may be due to greater virulence of MDR Salmonella typhi (7). Significantly higher rates of quantitative bacteremia have been observed among patients with MDR typhoid in Vietnam (16).

Diagnosis of MDR typhoid

The definitive diagnosis of enteric fever is the isolation of organisms from the blood or bone marrow. Cultures of bone marrow aspirate are reported to be positive in 60% to 90% of the cases and the organisms can be cultured from bone marrow even after exposure to antibiotics for some days.

Infections with strains susceptible to nalidixic acid (NA) respond extremely well to other fluoroquinolones used for treatment such as ciprofloxacin. There have been several reports of fluoroquinolone resistant S typhi. Progressive rise in MIC to ciprofloxacin has been observed in the past two decades. S typhi resistant to NA may not respond to ciprofloxacin despite having MIC values within the current NCCLS (National Committee for Clinical Laboratory Standards) susceptibility break point. Laboratories will continue to report these

S typhi / paratyphi as sensitive to ciprofloxacin. But there is a high incidence of treatment failures in such situations and the in-vitro susceptibility may not always translate to in-vivo efficacy(1, 17). Resistance to NA is a surrogate marker of reduced susceptibility to ciprofloxacin with higher MICs and predicts treatment failure. If the culture shows resistance to NA, irrespective of the results of ciprofloxacin / ofloxacin sensitivity, quinolones should not be used for the treatment, or if used, high doses should be given (17). Essentially, there are three categories of susceptibility to fluoroquinolones (1) :

a) Fully susceptible (sensitive to NA and ciprofloxacin)
b) Reduced susceptibility (NA resistant but sensitive to ciprofloxacin)
c) Resistant (NA and ciprofloxacin resistant)

It is of some concern that isolates fully resistant to fluoroquinolones and extended spectrum cephalosporins are being reported (18, 19).

Treatment of MDR typhoid

A good clinical evaluation is essential in any child suspected to have typhoid fever. Complicated typhoid fever refers to the presence of complications including intestinal perforation, intestinal bleeding, shock, pancreatitis, pneumonia, myocarditis, meningitis and psychosis (1). Blood culture should be sent in any child suspected to have enteric fever before starting empirical antibiotics. Though there are some reports of the re-emergence of fully susceptible strains of

S typhi / paratyphi to first line drugs (chloramphenicol, ampicillin, co-trimaxazole), they are few and unless antibiotic sensitivity testing shows the organisms to be fully susceptible to first line drugs, they are not advocated for empirical therapy in typhoid (17). In areas with a high prevalence of MDR S typhi infection like the Indian sub-continent, all patients suspected of typhoid fever should be treated with fluoroquinolones or a third generation cephalosporin until the results of culture and sensitivity studies become available. Recently, azithromycin is being used as an alternative agent for uncomplicated MDR typhoid (17). Aztreonam and imipenem are also potential third line drugs used recently.

Quinolones

Ciprofloxacin has been found to be highly effective for infections due to MDR S typhi and S paratyphi. But resistance of these organisms to ciprofloxacin seems to be increasing, especially in the Indian sub-continent (11, 20). The minimum inhibitory concentration to ciprofloxacin was reported to steadily increase from 0.025 to 0.5 mcg/ml (21). Patients infected with relatively quinolone-resistant S typhi strains (resistant to NA and an MIC of 0.125 to 1.5 mcg/dl) may not demonstrate clinical recovery. High NA resistance, a surrogate marker of relative quinolone resistance, has been reported in more than 80% in some Indian studies (12, 13). Patients with NA-resistant strains should be treated with a higher dose of ciprofloxacin or ofloxacin.

Cephalosporins

Third generation cephalosporin is now considered the first drug of choice for MDR enteric fever, in view of increasing fluoroquinolone resistance. Of the third generation cephalosporins, oral cefixime has been widely used in children, in a dose of 15-20 mg/kg/day in two divided doses for uncomplicated MDR typhoid (17). Injectable forms of cephalosporins are the drugs of choice for complicated MDR typhoid. Ceftriaxone, cefotaxime and cefoperazone are used, of which ceftriaxone is the most convenient, administered in a dose of 50-75 mg/kg/day in one or two divided doses. It must be remembered that resolution of fever and symptoms is slow.

Azithromycin

Sporadic reports of resistance to third generation cephalosporins have followed. Azithromycin, a macrolide, has been used as an alternative drug for uncomplicated MDR typhoid fever. It is given as once daily dose and is well tolerated when used orally. There are no reports of resistance of S typhi to azithromycin (23). In a systematic review of seven trials conducted in Egypt, Vietnam and India, azithromycin was compared to ceftriaxone, ciprofloxacin, gatifloxacin and chloramphenicol (1). Azithromycin reduced the clinical failure rate and the duration of hospital stay in comparison to fluoroquinolones, and reduced the relapse rate in comparison to ceftriaxone, when used in typhoid fever in populations with MDR typhoid. Azithromycin is given in a dose of 20mg/kg/day for upto 7 days. IAP Task Force recommends azithromycin as the second line drug in uncomplicated MDR typhoid fever (17).

Treatment guidelines according to IAP Task Force (17)

MDR Typhoid – Uncomplicated :

I Line : Oral cefixime, 15-20 mg/kg/day for 14 days
II Line : Oral azithromycin, 10-20 mg/kg/day for 7 days

MDR Typhoid – Complicated :

I Line : Ceftriaxone or Cefotaxime, 50-75 mg/kg/day for 14 days
II Line : Aztreonam, 50-100 mg/kg/day for 14 days

Imipenem is a potential second line drug. Fluoroquinolones can be used in life threatening infections resistant to other recommended antibiotics.

Prevention of MDR Typhoid

Emergence and spread of MDR Salmonella typhi has made effective treatment of typhoid increasingly difficult and expensive. Emphasis must be placed on prevention with the provision of safe drinking water, proper sanitation and public health education. Rational choice of drugs to treat bacteriologically proven infections and vaccine coverage of susceptible population will help in averting such epidemics in future.

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