

### THE CHALLENGE OF MULTI-DRUG RESISTANT TYPHOID FEVER

Typhoid fever is a relatively common water-borne disease caused by *S. typhi* with outbreaks in summer months in tropical countries. Till recently, most patients could be effectively managed by oral administration of either chloramphenicol, amoxycillin, ampicillin and co-trimoxazole on an ambulatory basis. Of late there has been an emergence of multi-drug resistant *S. typhi* (MDRST) strains throughout the world especially in the Middle-East and South-East Asia. The report by Koul *et al.*(1) in this issue has focussed attention on several facets of the problem in children. It is amazing that a disease, which could be managed in the past with ease, safety and low-cost is posing a serious therapeutic challenge. We need to critically look into various issues pertaining to MDRST in order to evolve strategies and guidelines to manage the menace.

#### The Extent of Problem

Chloramphenicol-resistant *S. typhi* were first reported in 1950(2) and outbreaks of typhoid fever due to *S. typhi* resistant to chloramphenicol and/or ampicillin have been reported from throughout the world(3,4) and several parts of India(5-7). Resistance of *S. typhi* to co-trimoxazole was first reported from France in 1975 and later from other countries(8). The epi-

demic proportion of typhoid fever resistant to multiple drugs is a relatively recent phenomenon and mostly seen during the last two years. Wang *et al.*(9) reported in 1989 from Shanghai that about 80% of *S. typhi* are resistant to the conventional anti-typhoid drugs such as chloramphenicol, ampicillin and co-trimoxazole. The incidence of MDRST is rapidly increasing in India and is currently ranging between 10-50%(1,10,11).

#### Mechanism of Resistance

It is believed that resistance of *S. typhi* against chloramphenicol and other agents develops either by mutation or acquisition of plasmid-mediated R factor. It appears that the R factor has originated from non-pathogenic enterobacteria like *E. coli* or *Shigella* pathogens. It has been documented that this R factor transfers from the resistant *S. typhi* to *E. coli* K<sub>12</sub> at a frequency of about 10<sup>-4</sup> and from *E. coli* K<sub>12</sub> to Vi type A *S. typhi* at a rate of about 10<sup>-6</sup> in overnight crosses. The R factor mediated resistance has been demonstrated in *S. typhi* strains belonging to phage types A<sub>1</sub>, C<sub>1</sub>, E<sub>1</sub>, M<sub>1</sub> and 46 and 51. The relatively high incidence of typhoid fever and indiscriminate use of antibiotics in India provides an ideal milieu for emergence of strains of *S. typhi* carrying R factor coding for resistance against multiple drugs. It is heartening to know that isolated epidemics of drug-resistant *S. typhi* in the past have been transient and are usually followed by reappearance of the garden variety of *S. typhi* once the incriminated drugs are withheld.

## Clinical Features

There are no characteristic clinical features or bedside laboratory markers to identify children with typhoid fever due to MDRST. These patients however run a protracted course with moderate pyrexia and minimal toxemia(7,10). Splenomegaly occurs in about 20% of these patients as compared to its reported incidence of 60-75% in the conventional typhoid fever. As opposed to these observations, Koul *et al.*(1) have reported increased incidence of shock, encephalopathy and myocarditis in children with typhoid fever caused by MDRST. The blood culture may remain positive for several weeks unless specific antibacterial therapy is instituted.

## Therapeutic Approaches

There is a need to conduct nationwide studies to identify the prevalence of MDRST in different parts of the country. In the light of currently available information, it would appear that conventional antibiotics cannot be recommended as first line therapy in a patient suspected to have typhoid fever. It is suggested that a combination of co-trimoxazole (10 mg/kg/day of trimethoprim q 12 h) and cephalixin (50 mg/kg/day q 6 h) or furazolidine (20 mg/kg/day q 6-8 h) may be tried orally as an alternative first line drug combination in ambulatory patients. These drugs have the advantages of easy availability, safety, and low cost and can be administered orally. Most strains of MDRST are susceptible to furazolidine and cephalixin *in vitro* and in combination with a higher dose of co-trimoxazole it is likely to be beneficial. Augmentin, a combination of ampicillin and clavulanic acid is of limited utility due to variable response, high cost and frequent

occurrence of diarrhea as a side effect. Aminoglycosides have limited efficacy against *S. typhi in vivo* because they reside within phagolysosomes which have extremely low pH.

The third generation cephalosporins, cefotaxime, ceftriaxone, cefaperazone and cefamandole have been used for the treatment of typhoid fever due to MDRST with a cure rate of 90%. Their utility is limited due to the need for hospitalization of the patient and prohibitive cost. Ceftriaxone in a dose of 50-60 mg/kg per day intravenously in two divided doses for a period of 7 days is adequate for most patients(12). Ceftriaxone can be tried as a single daily dose as well but unfortunately it cannot be administered intramuscularly because it is highly irritant.

Quinolones including norfloxacin, ciprofloxacin, ofloxacin, enoxacin and pefloxacin have undoubtedly emerged as the drugs of choice for current treatment of typhoid fever in adults because they are highly effective, can be administered orally and are safe. Unfortunately, quinolones other than nalidixic acid, have not been approved for use in children primarily because of their potentiality to cause irreversible damage to the cartilage of weight bearing joints of immature animals (rats, rabbits, dogs). It is rather strange that nalidixic acid, the first quinolone to be marketed, is licensed for pediatric use despite its strong arthropathic potential in animals. Nalidixic acid is widely used in India for treatment of shigella dysentery and because of its widespread use in Bangladesh, 30% isolates of shigella have already become resistant to nalidixic acid. Despite liberal use of nalidixic acid in children there have been no reports of long term toxicity to the cartilage in the form of arthropathia deformans. It appears that quinolone-associated

arthropathy is species specific and dose dependent. In experimental animals, the dose of quinolone which is known to produce damage to the cartilage is at least ten times the therapeutic dose used in humans. Ciprofloxacin has been used in children with cystic fibrosis without any adverse effects on the joints.

Fluoroquinolones have great potential for the treatment of typhoid fever, infections due to *Pseudomonas aeruginosa* and shigellosis in children because of its ease of administration and excellent therapeutic efficacy. Ciprofloxacin is credited to provide 100% cure rate in patients with MDRST. It has been postulated that salmonella strains originating in Indian subcontinent may be relatively resistant to the effects of fluoroquinolones because of their prolonged and liberal exposure to nalidixic acid(13). It is, therefore, recommended to use ciprofloxacin in a dose of 10 mg/kg twice daily for optimal therapeutic efficacy. There is certainly a need to conduct careful prospective evaluation of efficacy and safety of quinolones for the treatment of typhoid fever due to MDRST in children. These multicentric drug trials are both medically indicated and ethically justified.

### Public Health Measures

Due to emergence of MDRST, typhoid fever has assumed more ominous implications both to the patients and society due to increased cost of management and greater need for hospitalization. The efforts to improve environmental sanitation, personal hygiene, availability of potable water supply, sewage disposal and promotion of communication-information-education strategies should be pursued with renewed thrust and commitment. The need

for the availability of a safe and effective vaccine against typhoid fever has become more crucial and relevant. Two new typhoid vaccines are undergoing clinical trials at present. The oral Ty21a vaccine initially appeared promising in trials in Egypt but it is perhaps not as protective as the parenteral Vi polysaccharide vaccine evaluated in Nepal. In the meantime it is recommended that acetone-killed typhoid vaccine should be made available and incorporated in the national EPI programme because 50% of children with typhoid fever are less than 5 years of age(1). The Indian Academy of Pediatrics must launch a crusade to promote the philosophy of health education to the community, inform the health professionals regarding the risks of shot gun broad spectral irrational antibiotic therapy and sensitise the Government for an urgent need to provide and promote vaccination against typhoid fever.

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