EDITORIAL

Treatment of Drug Resistant Enteric Fever with an Uncertain Destination!

Typhoid fever, also known as enteric fever, is a potentially fatal acute multi-systemic febrile illness, caused primarily by Salmonella Typhi (S. Typhi), a Gram-negative bacterium, which infects only humans. Typhoid fev-er has drawn global attention again for its increasing burden, variability of presentation and difficulties in diagnosis and emergence of antibiotic resistance.

Worldwide, enteric fever is most prevalent in areas that are overcrowded with poor access to sanitation. Incidence estimates suggest that south-central Asia, Southeast Asia, and southern Africa are regions with high incidence of S. Typhi infection (more than 100 cases per 100,000 person-years)[1,2]. It is considered to be a global public health problem, at least 250,000 deaths occur annually. Among them, almost 80% of the cases and deaths are in Asia[3,4]. Moreover, in the last two decades, the emergence and spread of Multidrug-resistant typhoid fever (MDRTF) has caused significant therapeutic and public health problems.

Multidrug-resistant typhoid fever (MDRTF) is defined as typhoid fever caused by S. Typhi strains which are resistant to all the three first-line recommended drugs for treatment i.e., Chloramphenicol, Ampicillin, and co-trimoxazole (TMP-SMX)[5,6].The first multidrug-resistant strains emerged in Southeast Asia in the late 1980s and have since spread throughout the region [7]. Asian countries where MDRTF have been reported include China (1985), Pakistan (1987), India (1988), Malaysia (1991), Singapore (1994), Bangladesh (1992), Vietnam (1995), Japan (1999), Thailand (2001), Korea (2003), Nepal (2005) and Indonesia (2009) [8-10] . A recent multi-centric study conducted across five Asian countries (China, India, Indonesia, Pakistan, and Vietnam) that are endemic for typhoid reported the prevalence of multidrug- resistant S. Typhi strains ranging from 7% to 65%[11]. To our great concern, a study conducted in ICDDR,B in 2005 among 428 culture positive cases, the prevalence of MDRTF was found to be 91.4%[12].Even developed countries such as the United Kingdom (1990), America (1997) and Italy (2000) have reported MDRTF; most of the cases were found among travellers who had returned from regions where MDR strains of S. Typhi had caused outbreaks or had become endemic [13]. Between 1999 and 2006, 13% of S typhi isolates collected in the United States were multidrug resistant[14].

The epidemiology of drug resistance has changed over years. Chloramphenicol was used universally to treat typhoid fever since 1948 until 1970s, when widespread resistance occurred. Ampicillin and trimethoprim-sulfamethoxazole (TMP-SMZ) then became treatments of choice. However, in the late 1980s, some S typhi and S paratyphi strains (multidrug resistant [MDR] S typhi or S paratyphi) developed simultaneous plasmid-mediated resistance to all three of these agents. This led to the use of fluoroquinolones in the management of enteric fever. Unfortunately, subsequent emergence of nalidixic acid resistance (NaR) and decreased susceptibility to fluoroquinolones were observe (Lynch 2009). In fluoroquinolone resistant isolates a third generation cephalosporin, ceftriaxone or Cefixima is often the drug of choice (Basnyat 2007). However, sporadic cases of third generation cephalosporin resistance have been reported[15]. It is a great concern that widespread resistance will leave treatment options severely restricted.

Risk factors for development of drug-resistance in S. Typhi

Other than overuse, misuse, and inappropriate antibiotic prescribing practices (specially in viral illness, where antibiotic is of no use), a special factor in case of typhoid fever is changing of different antibiotics unnecessarily during the treatment of typhoid fever by the treating physicians. Deffervescence of fever in typhoid usually begins after four or five days of starting appropriate treatment [16, 17].

Is there any pathognomonic clinical features at the onset of the illness that can differentiate typhoid fever due to multidrug-resistant S. Typhi strains from those caused by sensitive S. Typhi strains? Though the answer is no, still some studies have reported certain clinical features like the presence of fever >104ºF, toxaemia, hepatomegaly, splenomegaly, abdominal tenderness and abdominal distension to be more commonly associated with MDRTF as compared to typhoid fever due to sensitive strains [18,19]. The overall mortality reported during MDRTF epidemics is 7% to 16%, which is much higher than the figure of 2% seen in susceptible typhoid fever [20].

Diagnosis of MDR typhoid fever

The gold standard for the diagnosis of MDRTF is a culture isolation of the organism with susceptibility testing of the isolates[21,22]. During the first week of illness, approximately 90% of patients have a positive blood culture, which decreases to 75% in the second week, 60% in the third week, and 25 % in the fourth and subsequent weeks until the subsidence of pyrexia[23].The other samples which can be cultured are stool culture (sensitivity 30-35%), urine culture (sensitivity 7-10%) and bone marrow aspirate (sensitivity 80-95%). Newer and more rapid diagnostic modalities include the identification of a specific nucleic acid sequence of S. Typhi. The first evaluation of polymerase chain reaction (PCR) as a diagnostic tool for typhoid fever was conducted in 1993 by Song et al.[24]PCR has a sensitivity and specificity of 100% and may replace blood culture as the new gold standard. However, the cost and requirement of sophisticated instruments for performing these molecular tests is a major drawback in developing countries [25].

When to suspect MDRTF?

a) if there is failure to respond after five to seven days of treatment with a first-line antibiotic for typhoid fever b) Severe typhoid fever with shock or abnormal sensorium or other potentially life-threatening complications c) Clinical deterioration or development of a complication during conventional antibiotic treatment d) Household contact with a documented case or during an epidemic of MDRTF.[26,27]

How can we treat MDRTF?

After proper symptomatic management and sending blood for culture and sensitivity testing, according to WHO guidelines, either fluoroquinolones or third-generation cephalosporin can be used in MDRTF, depending upon the sensitivity of S. Typhi strains to quinolones.[28]

In cases of quinolone-resistant S. Typhi strains, third-generation cephalosporins are recommended as the first-line treatment[28]. There is also recommendation of use of combination of a first-generation fluoroquinolone and a third-generation cephalosporin to allow for most effective clearance of the organism. [14] However, the combination of azithromycin and fluoroquinolones is not recommended as it may cause QT prolongation and is relatively contraindicated.

Interestingly, several recent studies have found that strains previously resistant to the first-line drugs (chloramphenicol, ampicillin and co-trimoxazole) are now showing decreasing resistance[29]. Constant surveillance and vigorous audits of antibiotic sensitivity testing results are the demand of the time.

After MDRTF and enteric fever resistant to fluoroquinolone and cephalosporins, what is next? In future there we may face extended drug resistant Typhoid fever or even total drug resistant typhoid fever. We may have to use old weapons against the new threat. Either we have to reintegrate first-line drugs again or discover newer antibiotics. The future is uncertain.

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