

## REVIEW ARTICLE

# MULTIDRUG RESISTANT TYPHOID FEVER IN CHILDREN: A REVIEW

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### Introduction:

Typhoid fever is a systemic infection caused by the gram negative bacterium, *Salmonella enterica serover typhi*.<sup>1</sup> It remains a great public health problem in developing countries especially in the tropics and subtropics having substandard personal hygiene and poor sanitation<sup>2</sup>. It is endemic in many parts of the world including India and Bangladesh<sup>3,4</sup>. At least 21.7 million new cases emerge each year of which 90% occur in South East Asia, resulting in about 216000 deaths. The annual attack rate ranges from 358 to 1100 per 100,000 population<sup>5,6,7,8</sup>.

In 1948 T. Woodward introduced chloramphenicol as an effective remedy of enteric fever<sup>9,10</sup>. Subsequently, ampicillin and co-trimoxazole greatly improved the outlook as gold standards of treatment declining the fatality rate to almost one percent<sup>11,12</sup>. During the 1970s the emergence of chloramphenicol resistant strains of *S. typhi* made a wide scale change in the scenario<sup>13,14</sup>. Multidrug resistant (MDR) strains of *S. typhi* with plasmid mediated genes against the 1<sup>st</sup> line drugs is a frequent finding in many areas in these days<sup>12,15,16</sup>. Recently, fluoroquinolones, the 2<sup>nd</sup> line therapeutic option are also becoming resistant to many strains of *S. typhi* through the chromosomal mutation in DNA gyrase<sup>17,18,19</sup>.

In Bangladesh over the counter sale of drug is a common practice causing inappropriate & indiscriminate use of antibiotics<sup>6,12,20,21</sup>. The reckless use of antibiotics in typhoid fever contributes to the emergence of multidrug resistant (MDR) cases<sup>6</sup>.

In Bangladesh typhoid fever is endemic due to defective sewerage system, unsafe water and food handling with epidemic proportions quite often<sup>6,8</sup>. Recent reports from Dhaka and Khulna reveal higher incidence of MDR salmonella typhi infections with widely variable sensitivity patterns to commonly used 1<sup>st</sup> line drugs<sup>14,15,16</sup>. Some studies shows changing pattern of clinical features and complications (20 %) of typhoid fever by MDR strains<sup>17,18,19</sup>.

The present review discusses the recent developments on multi drug resistant (MDR) typhoid fever in children with a global perspective where the Bangladesh situation remains in the background.

### The Bacterium:

*Salmonella typhi* is a gram negative non spore bearing organism that is motile by means of flagellae<sup>12,23</sup>. They can survive long periods in hot, humid environment and withstand freezing<sup>1,19</sup>. Infective dose is about 10<sup>5</sup>-10<sup>9</sup> organism, with an incubation period ranging from 4-14 days<sup>19,22</sup>. The complete 4.8 Mbp genome sequence of Vietnamese strain of *S. typhi* is now available<sup>22,23</sup>. It contains the five known salmonella pathogenicity islands (SPI 1-5), plus another five genomic islands that have characteristics of Pathogenicity islands. Pathogenicity islands are genomic regions encoding for, among other things, type III secretion systems<sup>22,23,24</sup> that deliver effector molecules from the bacterial cytoplasm, across its two membranes and inject them into the host cell, there by modulating the ability of macrophage to kill the bacteria. Humans are the only reservoir of the *S. typhi*<sup>25,26</sup>.

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**Antimicrobial resistance pattern:**

Drug resistance in most cases is the result of a genetic change in the organism caused either by a chromosomal mutation or the acquisition of a plasmid or transposon<sup>23,24</sup>. Plasmid mediated resistance is more common in MDR typhoid fever. Emergence of *S. typhi* strains resistant to chloramphenicol was reported in 1970s<sup>13,14,26</sup>, and the resistance to ampicillin and co-trimoxazole followed soon<sup>27,28</sup>. MDR *S. typhi* resistant to all three first line antimicrobials (chloramphenicol, ampicillin and co-trimoxazole) emerged sporadically<sup>28</sup>. First documented outbreak in Malaysia was in 1984<sup>29</sup>. Since then MDR typhoid spread through out south-east Asia and China where the disease became endemic<sup>30</sup>. In most cases resistance to the three first line drugs was transferable on plasmid either individually or en bloc<sup>30,31,32,33</sup>.

Plasmids are extrachromosomal supercoiled loops of DNA that were probably originally derived from bacteriophages (viruses that infect bacteria)<sup>23,34</sup>. When greater than 40 kbp in size they are able to encode the machinery necessary to transfer the plasmid from host bacterium to others. The plasmids found in *S. typhi* are of two major types. First, the pHCM2, a so called cryptic plasmid, can carry genes encoding mechanisms of DNA metabolism and replication, is found widely in Asia. The second type is approximately 140-180 kbp in size and is self transferable. Plasmids are classified by size<sup>35</sup>. The large plasmids can then be transferred to and from enteric gram negative bacterium such as *Echerichia coli*, *Klebsiella pneumoniae* and *S. enterica*, especially when antimicrobials are being administered<sup>36</sup>. Chromosomally acquired quinolone resistance in *S. typhi* has been found in different parts of Asia which may be the consequence of widespread and indiscriminate use of drugs<sup>12,13,36</sup>.

**Epidemiology:**

Typhoid fever is a common infectious disease of the tropical world of which 80% occur in Asian countries<sup>6,37</sup>. It is a disorder transmitted by ingestion of contaminated food or drinks<sup>1,19,22,38</sup>. Mode of transmission, clinical

features and consequences vary widely among developed and developing countries<sup>6</sup>. It is mainly a disease of school age children and adults<sup>39,40</sup>. Symptomatology greatly varies in MDR cases<sup>1,19,22</sup>. Incidence of MDR *S. typhi* was sporadic at one time. Now it is endemic and causes large epidemics in many parts of south-east Asia including India, Pakistan, Bangladesh, Vietnam, Malaysia, Indonesia, China and Tajikistan<sup>5,6,41</sup>. Pseudo epidemic prone regions also exist which include Middle East and Egypt where infection with MDR *S. typhi* is generally related to migrant workers from the endemic zone but epidemics can result. Sporadic infection occurs in Europe and north America, most often in immigrants who have return after holiday in their country of origin<sup>42,43,44</sup>. Until recently MDR *S. typhi* was not a problem of sub-Saharan Africa<sup>1,19,40</sup>.

However since 1997, increasing number of cases have been reported from Nairobi, Kenya<sup>45,46</sup>. Recent reports from Ghana also speak of MDR cases<sup>47</sup>. Thus far, MDR *S. typhi* does not appear to have arrived in south or central America<sup>19,40</sup>. The prevalence of the disease can be very high in Pakistan and Vietnam where positive blood cultures are found in 60-70% of clinically suspected cases and 60-80% of the positive cultures show multi drug resistance<sup>47,48,49</sup>. Study in Vietnam demonstrated fluroquinolones (ofloxacin and ciprofloxacin) highly effective drug for the MDR *S. typhi*. Unregulated overuse of fluroquinolones develops resistant strains of *S. typhi* causing both sporadic and epidemic disease<sup>49,50</sup>. Treatment failure with first line drugs has been observed in 33% cases of typhoid fever in Bangladesh where prolongation of fever controlling period was also observed<sup>51,52</sup>.

**Clinical features:**

It has been recognized that MDR *S. typhi* infection is a more severe clinical entity with higher rate of toxicity, complications and case fatality<sup>1,19,22,40</sup>. This may be related to increased virulence as well as higher number of circulating bacteria<sup>53</sup>. Usual relapse rate in enteric fever is 10-15%; chronic carrier 5%; Intestinal haemorrhage 1-10%; intestinal perforation 0.5-3% and pneumonia in 10%

cases. In MDR cases all increase by 20% than the usual cases of enteric fever in the community<sup>1,19,22</sup>.

The study group of Aga Khan University Medical Centre in Karachi Pakistan working with MDR Typhoid fever in Children shows a four fold rise in the fatality rate (4.2%) with more severe clinical illness like Hepatomegaly, abdominal pain, hypotensive shock, diarrhoea, seizure, and DIC<sup>54</sup>. Similar results were observed in studies conducted in Thailand, Nigeria, and Zimbabwe<sup>55,56,57</sup>. Neuropsychiatric symptoms resembling catatonic schizophrenia were reported from Africa and many countries of Asia<sup>58,59</sup>.

#### **Treatment of MDR *S. typhi* infection:**

Emergence of drug resistance is a major challenge in the treatment of typhoid fever<sup>1,22</sup>. The first case of chloramphenicol resistance was reported in 1982<sup>9,14,60</sup>. MDR cases began to appear around 1990<sup>13,20</sup>. In 1992 40% of the isolates were multi drug resistant<sup>16</sup>. Studies from ICMH (1994) and BSMMU (1992) revealed similar pattern, while ciprofloxacin and Ceftriaxone sensitivity were common to both the groups<sup>17,61</sup>.

Ciprofloxacin and ofloxacin resistance was first reported in Bangladesh in 8% of enteric fever cases in the year 2000<sup>13</sup>. In the year 2005 a resistance pattern of 71% was observed. In year 2009 the scenario was that of 90% resistance to second generation fluoroquinolones cases<sup>6,12,20,21</sup>. Ciprofloxacin is no more a drug for empirical therapy for the treatment of enteric fever in almost all countries of the world unless a complete ciprofloxacin susceptibility is proved<sup>64,65</sup>. However WHO recommends ciprofloxacin and ofloxacin for MDR cases and azithromycin, third generation cephalosporin and high dose older generation fluoroquinolones in nalidixic acid resistant cases<sup>21,66,67</sup>. Resistance to azithromycin and Ceftriaxone is rarely reported and this is why they can be used as empirical therapy in enteric fever<sup>68,69</sup>.

Azithromycin is a macrolide azolide antibiotic with relatively poor in vitro activity against *S. typhi*. However it is concentrated 50-100 fold inside cells such as macrophages, where *S.*

*typhi* reside. It also has a long half life (68 hours) and is thus given as a once-daily regimen. In a study in Bangladesh 94% cure rate with azithromycin was observed<sup>68</sup>. An Indian study showed 88% response with once daily azithromycin for 7 days where 100% of the cases were disease free after 14 days therapy<sup>65</sup>.

#### **Approach to overcome the situation:**

Apart from public health efforts to popularize practice of safe water & sanitation facilities, much can be done by mass vaccination for the control of the total burden of enteric fever<sup>6,20,69</sup>. In institutional situations blood culture for sensitivity pattern should be a practice in each and every case of *S. typhi* infection. Azithromycin and cefixime should be the starting point in the treatment of typhoid fever where ceftriaxone should be used to treat the late appearing cases. Over The counter sale of drugs should be prohibited so that overuse and misuse of antibiotics can be controlled.

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