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Development of Antimicrobial Resistance in Salmonella Typhi and Challenges in Treatment

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Abstract: ***Salmonella typhi a human specific pathogen is known to cause a febrile condition known as typhoid or enteric fever. The proper treatment with antimicrobials is needed to save life of person infected as; in severe conditions the infection may lead to meningitis and perforations in the intestines. In the recent years development of resistance in the Salmonella typhi against various antimicrobials has emerged as a matter of concern. Combating these resistance and developing new treatment strategies against multi-drug resistant Salmonella typhi can help in lessening the human burden.***

Keywords: *Salmonella typhi*, multi-drug resistance, drug resistance, treatment strategies, enteric fever

1.Introduction

The blood related infections in the developing countries due to bacteria of *Salmonella enterica* genus has risen at an alarming levels. The *Salmonella typhi* bacteria of this genus is known to cause nonspecific febrile conditions in the humans known as typhoid or enteric fever. The patients having typhoid fever generally present the symptoms which are clinically difficult to distinguish from several other infectious diseases [1, 2]. The disease finds its prevalence in many parts of Asia and Africa and without proper treatment with antimicrobials may lead to various life threatening conditions such as meningitis and intestinal perforations [3].

Various efforts have made in estimating the global burden of the disease and the closest estimate predicts total number of cases between 13.9 and 26.9 million globally [6]. However, this estimate provides only a broad measure and number of cases. The cases that remain unreported and other regional factors have been left in these calculations [7]. The major limitation in the detection and treatment of typhoid still remains the lack of effective and precise diagnostic method [8]. Diagnostic confirmation of the disease is currently dependent on isolation of bacteria from blood cultures, but the laboratory conditions and capacity required for these tests are present in limited numbers and hence majority of patients have to rely on serological testing by Widal test, which has a negative reputation of giving high number of false positives. The consequence of this misdiagnosis may lead to the treatment of patients with the high dose of antimicrobials which itself will show side effects and also will induce drug resistance in the bacteria. This misdiagnosis will also impact the estimate of global disease incidence [9]. The antimicrobial resistance developing in the typhoid fever is a rising issue as the resistance towards first-line and second-line antibiotics in *Salmonella typhi* is linked with the treatment failure and human burden [10].

2.Epidemiological and clinical features

The clinical manifestation and severity of symptoms may vary between the patients. However, the highest number of patients presenting in the hospitals due to typhoid in developing countries are between the age group of 5-25 years [11, 12]. In the endemic areas where the disease in highly prevalent it has been observed that the patients generally present the symptoms that are not clinically recognized as typhoid [13]. Around 60-90% of the patients don't get enough medical attention and are treated as outpatients. To avoid potentially fatal complications, hospitalized patients require effective antimicrobials, appropriate nursing care, adequate nutrition, careful attention to fluid electrolyte balance, and rapid diagnosis and treatment of problems [14].

3.Antimicrobial therapy and resistance

When typhoid fever is diagnosed early and treated with effective antimicrobials, it has a low fatality rate. However, if therapy is delayed or proven ineffective due to resistance, the risk of complications and case fatality rises dramatically [14]. The first extensively used antibacterial therapy for typhoid fever was chloramphenicol. Chloramphenicol was discovered in 1947 and put into clinical practice throughout the 1950s, soon proving to be highly successful in the treatment of typhoid fever. Until resistance to chloramphenicol, ampicillin, and co-trimoxazole appeared in the late 1980s, chloramphenicol, ampicillin, and co-trimoxazole were the first-line therapies for typhoid fever over the world, until resistance against all these three emerged in the late 1980s. Multidrug-resistant bacteria (MDR bacteria) were identified, and their proliferation resulted in the widespread usage of fluoroquinolones like ciprofloxacin and ofloxacin [15-17]. Because of the extensive usage of these fluoroquinolones in the late 1990s, ciprofloxacin susceptibility was reduced [minimum inhibitory concentration (MIC) of at least 2 mg/ml]. These bacteria, which are characterised by nalidixic acid resistance in vitro, have been found in non-endemic nations and are frequently related with foreign travel to South and Southeast Asia [7, 18-20]. Reduced ciprofloxacin susceptibility has recently been followed by the emergence of high-level fluoroquinolone resistance in South Asia, which has been linked to sequential mutations in the chromosomal quinolone resistance-determining regions (QRDR) of the genes encoding DNA gyrase (gyrA) and topoisomerase IV (parC) [21]. By 2011, there have been reports of extremely fluoroquinolone-resistant S. Typhi with a new gyrA mutation from South Asia [22– 25]. Researchers discovered

a novel variety of S. Typhi that was substantially related with longer fever clearance durations and treatment failure in a randomized controlled study in Nepal [26]. An ongoing international epidemic of an antibiotic resistant S. Typhi lineage has been identified by phylogeographic research. H58 (now genotype 4.3.1) is a lineage associated with incH1 plasmids harboring genes expressing an MDR phenotype that first appeared in South Asia in the early 1990s. The common gyrA/parC mutations are also associated with lower susceptibility and resistance to fluoroquinolones, which may have been driven and selected by its ability to retain and traffic MDR plasmids. The spread of H58 S. Typhi from Asia to Africa shows that regional and worldwide transmission of a fluoroquinolone-resistant lineage is now a distinct possibility [27-29].

4.Resistance against third-generation cephalosporin

As S. Typhi becomes more resistant to fluoroquinolones, the use of third-generation cephalosporins and azithromycin in the treatment of typhoid fever has expanded across South Asia. In many endemic countries, including India, these drugs have since become the first-line therapy for simple illness [10]. Ceftriaxone has been the most extensively studied third-generation cephalosporin in recent clinical trials, however cefixime, cefotaxime, and cefoperazone have all been studied with mixed results [30]. Cefixime is the only third-generation cephalosporin that may be taken orally, making it attractive among doctors who want to avoid the hospital complications that come with intravenous antibiotic treatment. Cefixime was shown to be significantly less effective than gatifloxacin in a randomised controlled study done in Nepal prior to the establishment of high-level fluoroquinolone resistance [30]. Resistance to third-generation cephalosporins is not widespread as fluoroquinolone resistance. Extended spectrum beta lactamase (ESBL)-producing S. Typhi species, on the other hand, are becoming more common, especially among Asian patients and travellers returning from South Asia [31-34]. According to reports, the MIC for ceftriaxone in some isolates has steadily grown from less than 1mg/ml to more than 20mg/ml in some isolates [35]. S. Typhi has been linked to a number of ESBL genes, including those that code for the TEM, SHV, PER, and CTX-M enzymes, as well as Amp-C [36, 37]. The appearance of ESBL-producing organisms is exceedingly alarming, especially if they have previously acquired MDR and/or fluoroquinolone resistance-related determinants and mutations [10].

5.Azithromycin Resistance

The effectiveness of azithromycin for the treatment of typhoid fever was first questioned in clinical trials [38]. Recent studies, on the other hand, have found that it is linked to rapid remission of clinical symptoms, low rates of recurrence, and convalescent faecal carriage [17, 39-43]. However, the azithromycin dosages used in these trials ranged from 10 to 20 mg/kg/day for 5–7 days, and the best azithromycin treatment regimen for typhoid is yet unknown.

There have been infrequent reports of S. Typhi with an azithromycin MIC of at least 32 mg/ml in the recent decade, mostly from South Asia, while there is minimal published data on the clinical response to azithromycin in such infections [44-46]. Furthermore, no consensus exists on how to characterize azithromycin susceptibility in vitro. Only azithromycin disc diffusion and MIC interpretation criteria for S. Typhi were supplied by the Clinical & Laboratory Standards Institute (CLSI) in 2015 [47]. According to studies from various regions of South Asia, S. enterica serovar paratyphi A resistance to azithromycin may be more troublesome.

Only one incidence of clinical and microbiological failure caused by azithromycin in S. Typhi has been reported to yet [48]. Despite the presence of the macrolide efflux pump genes macA and macB in several S. Typhi strains prevalent in India, the mechanism for resistance was not elucidated in this investigation [48].

6.Evolving resistance and treatment options

Due to rising medication resistance, researchers are looking into new antimicrobials for typhoid, particularly in cases of severe sickness. Carbapenems (meropenem, imipenem, and ertapenem) and tigecycline, a glycylcycline antibiotic, have become the standard of care for severe typhoid [17, 49]. According to a recent study, tigecycline was very potent against S. Typhi in vitro at a dosage of 2 mg/ml, preventing the growth of more than 97 percent of isolates [49]. These findings matched those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and a separate investigation including a large number of *Salmonella* spp. isolates [49-51]. In-vitro activity of tigecycline against ceftriaxone-resistant *Salmonella* spp. isolates was shown to be good [49]. To examine the relative benefits of tigecycline in contrast to other antimicrobials for the treatment of typhoid fever, clinical trial data is currently necessary. The use of earlier antimicrobials for the treatment of uncomplicated typhoid fever, such as chloramphenicol and co-trimoxazole, has also resurfaced. Because these drugs have been avoided in therapy for the past two decades, S. Typhi sensitive to them has resurfaced, and some recent studies from Asia have indicated their effective use in typhoid fever treatment [52, 53]. According to certain research, MDR prevalence in some contexts that were previously dominated by MDR variations may now be as low as 10%. [36]. In Nepal, a trial comparing azithromycin with co-trimoxazole for the treatment of undifferentiated fever (of which about one-third is caused by S. Typhi) is in underway, and might give useful data as other treatment techniques are considered [54].

7.Conclusion

Resistance to routinely used antimicrobials continues to evolve in S. Typhi, which is a major public health problem. Fluoroquinolones should no longer be used as a first-line typhoid therapy in South Asia, due to the introduction and spread of the H58 S. Typhi genotype. Ceftriaxone and azithromycin are becoming more widely utilised, yet resistance to these antibiotics has been found in S. Typhi. Carbapenems and tigecycline may be useful in the treatment of more serious infections, but additional research is needed. Because MDR S. Typhi is becoming less common, older

medications like chloramphenicol and co-trimoxazole may provide new treatment choices, although fast re-emergence of resistance is probable if these drugs are extensively utilized. Better surveillance methods and an efficient vaccination are anticipated to be required in the future to reduce the burden of S. Typhi illness. In the future years, routine typhoid immunization in LMICs will become a reality, and Vi conjugate vaccines should be prequalified by the World Health Organization. In typhoid-endemic areas, these next generation vaccinations have the potential to make a significant difference. However, we must stay attentive and continue to study the most efficient antimicrobial therapies as well as monitor the ever-changing landscape of antibiotic resistance in S. Typhi.

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