

Extensively Drug Resistant Typhoid Fever in Pakistan – Analysis of Current Situation

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ABSTRACT

Salmonella enterica are the pathogens that causes typhoid fever and it is the major leading cause of serious systemic infection encountered in Pakistan. Many antibiotics have been used to treat typhoid infection among which chloramphenicol was the first drug, later ampicillin and combination of trimethoprim and sulfamethoxazole (co-trimoxazole) was found to be effective for treating typhoid. Those drugs were known to be the first-line anti-microbial drugs. Emergence of resistance showed by the strains of *Salmonella* species against the first-line anti-microbial agents made this infection a serious concern in Pakistan. Such strains of pathogens are termed as MDR (multi-drug resistant). Recent cases of XDR (extensively drug resistant) strains of typhoid are also reported, in which pathogens have developed resistance not only against the first-line of therapy but also against second line antibiotics *i.e.* fluoroquinolones, and third-generation cephalosporin. This review study was conducted as an awareness move on the prevalence of MDR and XDR typhoid cases reported in Pakistan and data was collected through literature search from different sources by selecting relevant keywords. This study would help us in understanding the real picture of emergence and propagation of MDR and XDR typhoid in our population.

Keywords: *Salmonella*, typhoid, prevalence, multi drug resistant, extensively drug resistant.

INTRODUCTION

Salmonella enterica serovars (*S. typhi* and *S. paratyphi*), are the pathogens only specific to humans that causes the typhoid fever which is an acute and major health problem as well as fatal systemic infection. *S. typhi* is a genus of rod-shaped gram-negative bacteria which belong to a family of *Enterobacteriaceae* that causes typhoid fever which is also known as enteric fever [1].

Entry into the epithelial cells of the intestine of host is the important step in the pathogenesis of *Salmonella* infections. *Salmonella* easily passes through

mammalian cell so that it easily gains access to mammalian cell to cause the pathogenicity. Through ingestion of contaminated food, *Salmonella* reaches the host cell and crosses the lumen of intestine and reaches the sites where it causes infection [2]. Sites at which *Salmonella* causes infection initially, is the distal ileum where the *Salmonella* interacts with lining of epithelial cells and neighboring peyer's patch cells [2, 3]. *Salmonella* interaction with epithelial cells leads to degeneration of the epithelial lining and the *Salmonella* is now able to enter enterocytes through the process of phagocytosis [4, 5]. Once entered into the enterocytes, the bacteria reside in vacuoles which are membrane bound structurally and aids in

enclosing the bacteria within the cell. Secondly, *Salmonella* expressed the bacterial proteins during the period of incubation and results in synthesis of RNA and proteins, which induces the adherence of bacteria to host cell [6]. The biochemical signals are exchanged by the interaction of the bacterium and the host. As a consequence of interaction between the organism and host, a biochemical signaling cascade is triggered in the host cell. This cascade involves the phosphorylation of tyrosine in host cell, activation of phospholipase, mobilization of calcium, rearrangement of cytoskeletal, resulting in the disarrangement of membrane and internalization of infection caused by the pathogenic organism [7].

The bacterium *Salmonella typhi*, a pathogen which causes typhoid illness in humans, is a major concern in developing countries regarding the health of the public. Typhoid fever is characterized by sign and symptoms of headache, feelings of discomfort, fever, nausea, loss of appetite, vomiting, fatigue, GI upset, abdominal bloating, pain, etc. [8].

For the treatment of typhoid, many antibiotics have been used, aging back to as far as 60 years ago, and are still continued today. Among these antibiotics, in which chloramphenicol was the first drug which were introduced in 1984. After that ampicillin was found to be effective in the treatment of typhoid but later the combination of trimethoprim and sulfamethoxazole (co-trimoxazole) worked well for the typhoid treatment. The above mentioned drugs were known to be the first-line anti-microbial drugs that worked against typhoid.

Due to the emergence of resistance showed by the *Salmonella* species against the first-line anti-microbial drugs, some other antibiotics were used to check the effectiveness of the drugs against the pathogenic organisms such as streptomycin and tetracycline but the multi-drug resistant strains of *Salmonella* also showed resistance against these two agents in many developing countries. Such strains of pathogens have been termed as MDR (multi-drug resistant) [1, 9].

Recently, some outbreak cases of extensive drug resistant (XDR) typhoid reported in Pakistan have implied that the *Salmonella* species have shown resistance to MDR as well as fluoroquinolones and cephalosporin.

The resistance developed by the bacteria to the antibiotics has become hazardous to public health and due to the drastic increase of this problem, it has become a major issue worldwide. The magnitude of

this resistance varies from country to country. Southern Asia denotes a major part in terms of MDR (multidrug-resistant) bacteria. The reported cases of MDRs are increasing by the day as the beta-lactamase producing bacteria from Enterobacteriaceae family have become prevalent and causing ineffective therapy outcomes from treatment of antibiotics. The beta-lactamase producing bacteria make them resistant to antibiotics which are usually first-line of choice for the treatment of typhoid. The ineffectiveness of antibiotic treatment causes the higher mortality and morbidity rates in infected patients [10].

Salmonella typhi shown to have developed resistance against first line of therapy for treating typhoid among which are ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole. The typhi have also developed resistance against fluoroquinolones and 3rd generation cephalosporin. But it has been observed that *Salmonella typhi* infection has been treated with meropenem (carbapenem), azithromycin (macrolide) and tigecycline. These isolates of *Salmonella typhi* referred to as extensively drug resistant (XDR) isolates of *Salmonella typhi* [11].

METHODOLOGY

Study Design

This review study is designed and built off of different articles, conducted studies and is reported on the prevalence of MDR and XDR typhoid cases within Pakistan.

Literature Search and Strategy

Literature is searched and reviewed with the help of key words such as typhoid, prevalence, *Salmonella typhi*, enteric fever, MDR and XDR typhoid in Pakistan. Literature survey is done by using the different search engines such as google scholar and PubMed. Literature searched is done under a specified range i.e. from 2016 to 2018 from above mentioned search engines. References are cited in Vancouver style and numbered for each publication with the help of the software endnote [10].

Epidemiology

The worldwide estimated death rate of typhoid is around 200,000 every year. Among the Asian countries, Pakistan is the second most prevalent country of typhoid fever and an estimated rate of

reported cases of typhoid is 412.9 per year for 100,000 individuals. As evaluated by the International Vaccine Institute in 2010, the febrile typhoid patients were 11.9 million, while 129,000 were from a lower salary fraction in Pakistan. The chances of emergence of the disease is high in low to intermediate salary income population where the typhoid caused by *Salmonella* is endemic due to the poor sanitary conditions and contaminated water supply, as observed in an investigation conducted in some regions of Islamabad, Pakistan [12].

The MDR resistant strains of *Salmonella typhi*, including the resistance showed against the quinolone antibiotics is of a major concern regarding the health of the public in Pakistan. Since the *Salmonella typhi* is not susceptible to fluoroquinolones in Pakistan, the third generation cephalosporin *i.e.* ceftriaxone, cefotaxime or cefixime has been administered parenterally and orally respectively, as a choice of agent to treat the typhoidal fever. From 2009 to 2011, data collected about MDR resistant typhoid have demonstrated an incline in MDR cases of *Salmonella typhi* and have shown a notably low resistance for ceftriaxone. To elaborate, only two children from Karachi, which were observed by conducting a survey in laboratories of Pakistan, have shown a 0.08% resistance to ceftriaxone.

A MDR case was reported in PNS Shifa Hospital, Karachi, in 2018. 22 years of age, a patient having a history of multiple symptoms like high grade fever, abdominal pain and low heart rate, was diagnosed with typhoid fever. Upon treating with ceftriaxone, there were no improvement in symptoms, so blood samples were collected and results revealed the growth of *Salmonella typhi*, which is resistant to ampicillin, co-trimoxazole and chloramphenicol. The organism produced Extended spectrum beta-lactamase and showed the resistance towards treatment with ciprofloxacin, azithromycin and ceftriaxone but showed sensitivity to the drug meropenem of carbapenem antibiotics class [13].

As time progresses the resistance of ceftriaxone has been increased, and a large number of cases have been reported from 2016, in the Sindh province of Pakistan, majority of which are from Hyderabad and Karachi. A traveler's XDR case was reported in United Kingdom, even though the person had gotten the *Salmonella* infection from Pakistan, the

Salmonella got resistant from broad spectrum antibiotics.

Few treatment options for typhoid fever have been available in Pakistan, since the *Salmonella typhi* have become resistant to first-line agents like ampicillin, co-trimoxazole, chloramphenicol as well as extended-spectrum antibiotics such as third-generation cephalosporin and fluoroquinolones which are classified as extensively drug resistant (XDR) [14].

According to the reports developed by taking blood samples of typhoid fever patients infected with *Salmonella typhi*, the reports concluded that the isolates have become resistant to 3rd generation cephalosporin and fluoroquinolone class but have showed the susceptibility pattern to carbapenems (meropenem & impanel) and macrolide antibiotic (azithromycin). In 2016, 2017, 339 isolates were found to show the XDR pattern in the Sindh province of Pakistan. The greater portion of these case were reports from Karachi and Hyderabad.

Between 2016 to 2017, over the time period of 6-months, complete genome sequences of DNA from over 80 XDR isolates of *Salmonella typhi* were determined at a single time which revealed that the isolates have preserved the genetic clones, conserved their genetic sequence and it was found that the resistant isolates had haplotype H58 genes on a single chromosome [15].

In 2018, an XDR case was reported in Pakistan. After visiting Pakistan from June to July, a young three-year old boy developed signs and symptoms of enteric fever including abdominal pain, fever, vomiting and diarrhea for two days. He was diagnosed with enteric fever while getting checked in a hospital of Toronto. The stool and blood cultures were isolated and it revealed the presence of growing *Salmonella enterica serovars Typhi (S. typhi)*.

The isolates were tested for the susceptibility to antibiotics and the *Salmonella typhi* strains showed the resistance towards the chloramphenicol, co-trimoxazole and ampicillin as well as ciprofloxacin and ceftriaxone but the strains were sensitive to meropenem and azithromycin. After the two weeks of administration of meropenem, the child was successfully treated. This was the first case of XDR typhoid of Pakistan which was reported in Canada and first pediatric XDR typhoid case treated over there [16].

The blood culture was taken from the suspected cases in 2017 from Aga Khan University Hospital laboratories to check the ceftriaxone resistant strains of *Salmonella typhi* in Hyderabad district of Pakistan. A surveillance study was also conducted through a questionnaire in the second largest city of Sindh Pakistan. Hyderabad comprises of 4 sub districts which are Hyderabad rural, Hyderabad urban, Latifabad and Qasimabad. The prevalence of XDR typhoid was tested among these 4 districts of Hyderabad. An outbreak of ceftriaxone-resistant typhoid fever caused by *S. typhi* in November 2016 was detected by Laboratory surveillance at the AKU Hospital from the city of Hyderabad of Sindh, Pakistan.

101 cases of XDR typhoid (ceftriaxone resistant strains of *Salmonella typhi*) were identified in Hyderabad city by the end of March 2017, further investigation will provide the final results. This investigation was carried out to prevent the outbreak of XDR typhoid in future. The affected sub districts of Hyderabad were Latifabad and Qasimabad [17].

DISCUSSION

The typhoid fever is diagnosed clinically in health care settings and isolates are confirmed by getting the reports of blood cultures. 80% of typhoid patients shows positive results without being treated with antibiotics. Those patients should get checked by their doctors in the early weeks of their evident symptoms. The anti-microbial therapy shows to reduce the rates of microorganisms responsible for typhoid fever caused by *Salmonella* [18, 19].

Antimicrobial drugs are frequently prescribed, so the organisms that developed resistance towards the antibiotic. In developing countries like Pakistan, immediate relief from the infections is the primary concern, so health care providers directly adopt the antibiotic therapy for an early recovery from infection. The serious concerns about MDR infection are the prolong period of stay in hospital, high cost of therapy, chances of super-infections with several other bacteria and these factors contribute to the development of resistance against therapy [20, 21].

Factors affecting the epidemiology of MDR and XDR typhoid are the following:

1. Lack of Awareness:

As the general public is not well aware about the antimicrobial resistance in Pakistan, there is a

lack of strategies to halt the development of anti-microbial resistance. For proper educational guidance of anti-microbial therapy, health care professionals should have to organize some activities like campaigns and lectures to provide education to the general public [22].

2. Irrational Use of Antibiotics:

Prescribing the antibiotics more frequently and inappropriately is a common practice in health care system of Pakistan. Irrational use of antibiotics results in development of resistance by the bacteria against the antimicrobial therapy [23].

3. Hygiene and Sanitation:

Poor sanitation conditions contribute to the infections that are spread by the resistant organisms. Bacteria spread through direct contact with infected person and by contaminated water and food [24, 25].

CONCLUSION

This review concluded that emergence of extensively drug-resistant typhoid can be reduced by rationale use of antibiotics and professionals must be properly trained through stewardship programs, so these incidences will be limited.

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