Editorial:

PAKISTAN IN ERA OF EXTENSIVE DRUG RESISTANCE ENTERIC FEVER.

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Enteric fever which is also known as typhoid fever is caused by gram-negative bacteria salmonella enteric serovar Typhi bacteria (S.Typhi), Even today enteric fever remains a global health problem and results more than 21. Approximately 6 million cases and least 250,000 deaths annually.[1] The majority of these cases and deaths (80%) occur in Asia; the remaining 20% occur in Africa and Latin America.

Enteric fever spreads through oro-fecal route by consuming contaminated food or water. Poor sanitation and poor hygienic conditions remain a major risk factor for its spread. Travelers to and from the developing world are at increased risk. At the start of 2nd millennium, Enteric fever was responsible for 21.7 million illnesses and 217,000 deaths. The majority of deaths occur in young age group of 5 to 19 years. The number of deaths attributed to enteric fever was reduced to 161,000 in 2013, as compared to 181,000 in year 1990.[2] Improvement in water sanitation and food handling in developed and industrialized countries, have largely reduced the number of cases, but situation in underdeveloped and developing nations remains alarming. Asia and Africa have the highest morbidity and mortality due to enteric fever poses the biggest challenge. A lack of access to clean drinking water, proper hygienic sanitation systems, and proper health-care facilities contribute to the spread of enteric fever in these countries.[3]

The history of typhoid fever is quite interesting. In 430 BC, an epidemic of typhoid fever emerged first time in Athens & killed their leader Pericles.[4]

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A study published in 2018 suggests that the epidemics that struck the Mexican areas in the year 1545 and 1576 and was responsible for an estimated 7 to 17 million deaths, was actually typhoid fever.[5] The 9th US President William Henry Harrison did not die of pneumonia as was thought but of enteric fever. Similarly 12th US President Zachary Taylor also died of enteric fever due to the poor sanitary conditions in Washington, DC.[6] In year 1907, Mary Mallon is also known as Typhoid Mary the most notorious carrier of enteric fever became the first carrier in the United States. She was a cook in New York and was responsible for 53 cases and three deaths.[7] In 2004–2005 an outbreak in Democratic Republic of Congo resulted in more than 42,000 cases and 214 deaths.[1]

Treatment of enteric fever revolutionized with the discovery of Chloramphenicol in 1948 and Cotrimoxazole and Ampicillin later on, but resistance to these drugs was soon reported. Rampant and indiscriminate use of these drugs was mainly responsible for emergence of resistant bacterial strains. chloramphenicol-resistant was reported from United Kingdom. However, it was not until year 1972 when chloramphenicol-resistance became a significant issue, with major outbreaks reported in Mexico in 1972, India in 1972, Vietnam in 1973 and Korea in 1977. These strains when tested were also found to be resistant to ampicillin. Co-trimoxazole was the only effective drug in the treatment of these resistant strains until the year 1975.In 1975 Co-trimoxazole was also reported in France as a resistant drug towards enteric fever. By the end of 1980s, the strains of S.Typhi that were resistant to all three first-line drugs were present.[8]

Multidrug-resistant enteric fever (MDREF) is defined as an enteric fever that is caused by S.Typhi and its strains which are resistant to all of the three first-line drugs that are recommended for treatment, i.e., chloramphenicol, ampicillin, and co-trimoxazole.

Then comes the Era of Fluoroquinolones, which emerged as the treatment of choice. The widespread use of 2nd generation of fluoroquinolones i.e. ciprofloxacin and ofloxacin-levofloxacin has now led to the reduced susceptibility of organism across the Indian subcontinent. Complete fluoroquinolone resistance, that includes the resistance to the newer generation fluoroquinolone gatifloxacin, emerged after 2010 and is now associated with treatment failures and prolonged disease.[9]

Most centers in South America, India, Pakistan, Bangladesh, Thailand, or Vietnam have switched from fluoroquinolones to third-generation cephalosporins as first-line treatment for enteric fever. For these regions, the recommendations are to use ceftriaxone as a first-line treatment. Azithromycin has recently been recommended for treating resistant typhoid in populations that are both fluoroquinolone and ceftriaxone resistant.[8] In Sindh Pakistan between the years 2016 and 2017clones of S.Typhi resistant to all first-line drugs and fluoroquinolones were reported, classified as extensively drug-resistant (XDR) Typhoid. Frequent air travel transfers these strains from one country to another within no time. In year 2018 two alerts have been triggered as XDR enteric fever cases are reported in United Kingdom and United States of America among the travelers who were returning from Pakistan.[10] Similarly another XDR case of enteric fever in Denmark was reported in 2019, April in traveler who was 15 weeks pregnant woman returning from Karachi, Pakistan. The women were treated with Cefixime for 1 week than with Ceftriaxone 2g once daily but due to deteriorated condition the treatment was changed to Azithromycin 500 mg daily and Meropenum 1g thrice daily, which later resulted in clinical improvement and decreasing C-Reactive Protein (CRP). The patient was discharged on the 15th day with oral Azithromycin with healthy fetus.[11]

Extensively drug-resistant (XDR) enteric fever is rapidly spreading in Pakistan, increasing the fears of antibiotic failure at the international level.[12] Experts consider that Pakistan's unfathomable sewage and water systems along with low vaccination rates and heavily populated cities are the main causes of the spread of extensively drug-resistant (XDR)enteric fever. In the period between 2016 and 2017, health authorities in Pakistan have detected more than 800 cases of extensively drug-resistant (XDR) enteric fever only in the city of Hyderabad.[13]

The outbreak of extensively drug-resistant (XDR) enteric fever should be considered as an alarming signal that the world is gradually moving towards a pre-antibiotic age because of unrestricted overuse of antibiotics. This has become a genuine concern in developing countries like Pakistan, where antimicrobial surveillance is in worse shape and there is an urgent need for strengthening the system. In this aspect both governmental and non-governmental organizations need to make an extensive program on promoting vaccination campaigns and adopting healthy hygienic eating and living habits. Also it is important to discourage irrational and over the counter use of antibiotics to prevent the mortality and morbidity that is linked with escalating antibiotic resistance.

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