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Original Research Article

Rise of azithromycin resistance: a study on antibiotic resistance pattern in culture positive cases of typhoid fever in a tertiary hospital in Delhi

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ABSTRACT

Background: Typhoid fever is a public health problem with a high disease burden in India. The prevalence of multidrug resistance in typhoid has nearly doubled from 1999 to 2005. The resistance against Fluoroquinlones is very high due to indiscriminate use and an increased resistance against Azithromycin, one of the first line antibiotics used is being observed. This study will evaluate the current trend of antibiotic resistance among typhoid fever cases observed in a tertiary care hospital.
Methods: A retrospective record-based analysis was carried out for all the culture-proven typhoid cases admitted to a tertiary care teaching hospital in Delhi. The blood culture reports of all patients admitted from 1 January 2016 to 31 December 2017 were analyzed. Only culture-positive typhoid fever cases which isolated *S. typhi* and *S. Paratyphi* A were included for the study. The antibiotic sensitivity pattern was done using disc diffusion method and data with regards to following antibiotics was analysed: Azithromycin, ciprofloxacins, Amikacin, Gentamycin, Amoxicillin, Cefepime, Cefixime, Cotrimoxazole, Ceftriaxone.
Results: The incidence of blood culture positive typhoid among total number of blood cultures received was 1.84%. Of these 118 blood cultures, 101 (85.6%) were *S. typhi*, and 17 (14.4%) were *S. Paratyphi A*. A total of 54 (45.8%) blood cultures were sensitive to all antibiotics. The antibiotic sensitivity testing revealed the following pattern of resistance: Azithromycin (21.2%), ciprofloxacin (16.9%), Gentamycin (10.2%), Amoxicillin (8.5%), Cefepime (1.7%), Cefixime (4%), Cotrimoxazole (4.2%), Ceftriaxone (0.8%).
Conclusions: There is an increase in the resistance against Azithromycin in the typhoid bacilli. A regular and yearly assessment of antibiotic sensitivity pattern should be undertaken by developing a registry that accumulates antibiotic resistance data from hospitals and diagnostic centers.

Keywords: Antibiotic resistance, Azithromycin, Typhoid fever

INTRODUCTION

Typhoid fever is defined as fever ≥38°C for at least three days, with a laboratory-confirmed positive culture (blood, bone marrow, bowel fluid) of *S. typhi*.[1] Typhoid Fever is caused by the bacterium Salmonella enteric subspecies enterica serovar Typhi (*Salmonella typhi*) from the family Enterobacteriacea.[1] It can also be caused by Salmonella enterica subspecies enterica, namely *S. paratyphi A*, *S. schottmuelleri* (also called *S. paratyphi B*) , and *S. hirschfeldii* (also called *S. paratyphi C*), a related bacterium that usually causes a less severe illness known as paratyphoid fever.[1] The world sees 22 million new cases of typhoid every year, and 200000 deaths every year.[1] The estimated prevalence of laboratory-confirmed typhoid and paratyphoid among individuals with fever across all hospital studies was 9.7% and 0.9% respectively.The incidence is highest in children and

young adults between 5 to 19 years old.[1] Typhoid fever is a public health problem with a high disease burden in India. The main reasons for this are the rise of antibiotic Resistance among the bacteria. The prevalence of multidrug resistance in typhoid has nearly doubled from 1999 to 2005.[1] The resistance against Fluoroquinlones is very high due to indiscriminate use and an increased resistance against Azithromycin is being observed. The resistance against ciproflocxacin and other flouroquinolones develops as a result of single point mutation in the quinolone resistance determining region (QRDR) of the topoisomerase gene gyrA, which encodes DNA gyrase. The plasmid borne mphA gene is one of the causes for azithromycin resistance. The resistance against azithromycin may arise from other mechanism such as mutation in rlpD and rlpV genes. At this time there are very few studies with regards to the mechanism of azithromycin resistance and further investigation in this topic is needed.[1]

Aim and objectives

The study is aimed to increase awareness about the rise of antibiotic resistance, judicious use of antibiotics and to understand that the alarming rate of rise of resistance against antibiotics outpaces the development of newer antibiotics and treatment modalities.

METHODS

A retrospective record-based analysis was carried out for all the culture-proven typhoid cases admitted to a tertiary care teaching hospital, Moolchand Medcity in Delhi. Due permission was sought from the hospital authorities to access the records. The blood culture reports of all patients admitted from 1 January 2016 to 1 January 2018 were analyzed. The total number of blood cultures received by the microbiology lab during these 2 years was 6379, of these 118 blood cultures were cases of Enteric fever.

Inclusion and exclusion criteria

Only culture-positive typhoid fever cases which isolated *S. typhi* and S. *Paratyphi A* were included for the study. All culture negative cases were not included in the study.

The antibiotic sensitivity pattern was done using disc diffusion method and data with regards to following antibiotics was available: azithromycin, ciprofloxacins, amikacin, gentamycin, amoxicillin, cefepime, cefixime, cotrimoxazole, ceftriaxone. All these blood cultures was analyzed and data recorded for analysis. Data has been summarized using percentages.

RESULTS

A total of 118 Typhoid positive blood cultures were isolated between 1 January 2016 to 1 January 2018. The total numbers of blood cultures received by the microbiology lab during these 2 years were 6379.

Table 1: Patient demography.

Gender	N
Males	80
Females	38
Total	118

Table 2: Trends of blood culture data.

Blood culture	Blood culture analysed; N
Typhoid positive	118
Typhoid negative	6261
Total	6379

Table 3: Number of patients with typhoid fever.

Organism	Number of patients
S. typhi	101
S. paratyphi A	17
Total	118

Table 4: Data on antibiotic sensitivity pattern.

Antibiotic	Number of resistant	%
Ceftriaxone	1	0.8
Cefepime	2	1.7
Cefixime	4	3.4
Cotrimoxazole	5	4.2
Amoxicillin	10	8.5
Gentamycin	12	10.2
Ciprofloxacin	20	16.9
Azithromycin	25	21.2

The incidence of blood culture positive typhoid among total number of blood cultures received was 1.84%. The number of male patients was 80 (67.8%) and female patients was 38 (32.2%) (Table 1). Of these 118 blood cultures, 101 (85.6%) were *S. typhi*, and 17 (14.4%) were *S. paratyphi A* (Table 2). A total of 54 (45.8%) blood cultures were sensitive to all antibiotics. The antibiotic sensitivity revealed the following pattern of resistance: azithromycin (21.2%), ciprofloxacin (16.9%), gentamycin (10.2%), amoxicillin (8.5%), cefepime (1.7%), cefixime (4%), cotrimoxazole (4.2%), ceftriaxone (0.8%) (Table 4).

DISCUSSION

The antibiotics commonly used by general practitioner for treatment of typhoid are: azithromycin (42%), ciprofloxacin (32%) cefixime (16%), amoxycillin (6%).[1,5] A combination of antibiotics is preferred by 38% of GP's cefixime + azithromycin (26%), ciprofloxacin + azithromycin (12%).[1,5] So the most commonly used antibotics are azithromycin and ciprofloxacin.

Table 5: Comparison of data with previous studies.

Pattern of resistance	Jain et al	Dahiya et al	Patel et al	Kumar et al	Mishra et al	Current study
Year	2013	2014-15	2011-13	2012	2015	2016-17
City	Delhi	Multi-centre	Varanasi	Manipal	North India	Delhi
Azithromycin	7.3	Na	21.3	Na	No resistance	21.2
Ciprofloxacin	37.9	20	25.5	29.2	19	16.9

The association of physicians of India recommends in its update that first line treatment of OPD cases should be done with cefexime 20 mg/kg/day for 14 days, azithromycin 10-20 mg/kg/day for 7 days.[1] For IPD patients the recommendations states Injection ceftriaxone 100mg/kg/day as first line treatment and switch to oral cefexime once fever resolves.[6] It has been observed that resistance against ciprofloxacin has decreased in comparison to previously reported findings. The prevalence was 37.9% in delhi in 2013 in comparison to the finding in our study which report 16.9%.[1] However Mishra et al reported 19% resistance in typhoid bacilli in 2016. There is a decreasing trend of resistance against Fluoroqinolones as reported in various studies.[4,6-10] This can be attributed to the increasing awareness about flurorqunilone resistance.[1] The resistance against Azithromycin has risen sharply from 7.3% in 2013 in Delhi to 21.2%.[6] As per latest guidelines of API for treatment of typhoid fever cefixime and azithromycin are the first line of treatment for typhoid fever. CLSI in 2015 added azithromycin MIC and disk diffusion criteria for *S. typhi* and *S. paratyphi A.*[11] reported azithromycin susceptibility during 2015-2016 by Sharma et al was found to be 98.9% for S. typhi.[12] Although this azithromycin susceptibility is promising in *S. typhi*, 62% of strains in this study had an MIC of 16 µg/ml, which is the breakpoint for susceptibility, and therefore, an early indicator of the impeding rise of resistance.[8] The resistance against cephalosporins continues to be very low however a rise in number of cases resistant to cephalosporins have been observed. In 2017, reports emerged of a large outbreak in Sindh, Pakistan, of a *S. typhi* expressing resistance to classical first-line antibiotics (chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole), as well as to both fluoroquinolones and third-generation cephalosporins. These infections can only be resolved with azithromycin, carbapenems (meropenem) and tigecycline.[1] This again brings Azithromycin to the forefront and makes it an an important antibiotic.

The widespread resistance against ciprofloxacin and rise of resistance against azithromycin is limiting the antibiotics available for use against typhoid fever. It is paramount that awareness with regards to antibiotic resistance pattern be increased among general practitioner. A regular and yearly assessment of antibiotic sensitivity pattern be undertaken by developing a registry that accumulates antibiotic resistance data from hospitals and diagnostic centers. The treatment guidelines must be updated annually with regards to changing trends of antibiotic resistance in typhoid fever.

Limitations

Limitations of current study were; it was a single centre study, MIC was not evaluated as records for the same were not available, it was a retrospective study and clinical implication were not evaluated.

CONCLUSION

There is an increase in the resistance against Azithromycin in the typhoid bacilli and a decrease on resistance against fluroquinolones. 1.84% of blood cultures were positive for typhoid fever. It is paramount that awareness with regards to antibiotic resistance pattern be increased among general practitioner. A regular and yearly assessment of antibiotic sensitivity pattern be undertaken by developing a registry that accumulates antibiotic resistance data from hospitals and diagnostic centers.

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