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ORIGINAL ARTICLE

Is Salmonella Typhi Becoming a Superbug ? A Cross-Sectional Study of the Antibiotic Sensitivity

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Abstract

Objective: To determine the antibiotic sensitivity patterns of Salmonella typhi in blood cultures of the patients attending a tertiary care hospital.

Material & Methods: This cross-sectional study was conducted in the Department of Internal Medicine, Hayatabad Medical Complex, Peshawar, Pakistan for a period of one year from 1st August, 2021 till 30 August, 2022. All adult patients of either sex, belonging to the province of Khyber Pakhtunkhwa, Pakistan between 18 to 70 years of age, whether admitted through casualty or the outpatients, having a history of fever for the past 07 days and no prior history of admission or use of antibiotics in past one month were included.

Results: The mean age of the patients was 47 ± 5.6 years with females 59.2 % (320) and the males 40.7 % (220). A total of 540 blood cultures showed a growth of Salmonella Typhi out of requested 857 cultures representing a positive culture yield of 63%. The total numbers of MDR cases were 83.6% whereas the XDR cases were 3%. The antibiotics sensitivity was 100% to Carbepenems, Tigacycline, Colistin and Polymixin, whereas between 27.7% to 16.4% in the cephalosporin class and only 16.4% to the flouroquinolones.

Conclusion: The antibiotics resistance against Salmonella Typhi is on the upswing and calls for effective programs of antibiotics stewardship, development of indigenous updated antibiotics guidelines in line with the local sensitivity patterns and actions to avert the spread of infection.

Keywords: Salmonella Typhi, Antibiotics resistance, Typhoid Fever

Cite this article: Zuhyr A, Mehr.TM, Nisa QN, Raza S, Iqbal A. Is Salmonella Typhi Becoming a Superbug? A Cross-Sectional Study of the Antibiotic Sensitivity. BMC J Med Sci. 2023. 4(2):100-104.

Introduction

In the developing world, Enteric fever triggered by Salmonella Typhi and Salmonella Paratyphi endure a prominent cause of morbidity and mortality with over 22 million cases and subsequent 200000 deaths in South Asia in year 2000.[1]The highest prevalence zones sadly continue to remain parts of Pakistan, India and Indonesia.[2]Salmonella is a Gram-negative rod-shaped facultative anaerobe that is classified in the family. Enterobacteriaceae. There are around 2600 serotypes with unique ability to adapt to hosts including humans. Food animals like poultry and cattle remain the prime source of Salmonella.[3]Typhoid fever is caused by infection with Salmonella Typhi whereas paratyphoid fever is triggered by S. Paratyphi A, B and C. Enteric fever is the term used to encompass the fevers caused by both the bacteria.[4]The blood cultures continue to remain gold standard but the facilities remain inadequate especially in the endemic regions primarily due to poor antibiotic stewardship programs. This leaves the treating physicians to retort upon the clinical signs and rapid bacteriological isolation methods which also have its inherent flaws. This approach calls for finding the most frequently occurring symptoms in retrospect in confirmed cases of typhoid fever and then using the subset to initiate the appropriate antibiotics while awaiting the culture reports.[5]

The distribution of the cases vary in different parts of the same country mainly because of the varied sanitation conditions and access to clean drinking water and has little difference in the rural and urban settings.[6]In the case of typhoid fever, multidrug resistance (MDR) stands for resistance to Ampicillin, Trimethoprim-Sulfamethoxazole, and Chloramphenicol, whereas Extensive drug resistance (XDR)

Authorship Contribution: [1-5]Substantial contributions to the conception or design of the work; or the acquisition, Final approval of the version to be published & Supervision, [3]Data analysis, Literature review, [4]Drafting the work or revising it critically for important intellectual content

Funding Source: none
Conflict of Interest: none

Received: Oct 29,2022
Accepted: Feb 19,2023
Published:Dec 20,2023

stands for Chloramphenicol, Ampicillin, Trimethoprim, Sulfamethoxazole, Fluoroquinolones, and ird-generation Cephalosporin resistance.[7] Africa and parts of Asia continue to remain the areas with highest prevalence of MDR cases of Salmonella. Ochiai et al. conducted a surveillance study amongst five Asian countries and reported highest prevalence in Pakistan, India and Vietnam compared to China and Indonesia.[8] Similar highest prevalence of MDR cases were reported in this part of the world by Chuang et al.[9] The MDR cases have spread to parts of Europe as reported by Meakins et al while doing a surveillance on 1,35,000 isolates of NTS (Non-Typhoid Salmonella) between 2000 to 2004 and reported 15% isolates presenting the MDR phenotype and 20% were established resistant to Nalidixic Acid and hence the quinolones.[10] Subsequent to the amplified resistance to the earlier used antibiotics, fluoroquinolones and third generation cephalosporins started to become the drugs of choice to treat Salmonella infection. Sadly, over a period of time, following extensive use of these antibiotics, Salmonella isolates resistance to these used antibiotics emerged.[11] Van Boeckel TP et al emphasized the gravity of the problem of increasing antibiotics resistance by quantifying an upsurge of 36% in the consumption of antibiotics over a decade between 2000 to 2010 with India and China being the highest consumers respectively.[12]

A well planned surveillance multicenter study under the title of "surveillance for enteric fever in Asia Project" (SEAP) was conducted for four years between 2016 till 2019. The enrolled study population was primarily from the provinces of Sind and Punjab with meagre representation from parts of rural and underprivileged areas of Khyber Pukhtunkhwa and Baluchistan.[13]

Because of the amplified and dissimilar prevalence of Salmonella across Pakistan and its geographical dynamism with respect to the antibiotic sensitivity, we decided to find out the antibiotic sensitivity of the Salmonella in those sick patients who present to a tertiary care referral center. The findings of the project will be quite helpful especially in the context that most of the previous studies have been carried out in the community or during specific outbreaks in the country. The results should help formulate the antibiotic guidelines for the treating doctors working in tertiary care hospitals of the country while they are awaiting the blood culture results.

Material and Methods

This cross-sectional study was conducted in the Department of Internal Medicine, Hayatabad Medical Complex, Peshawar, Pakistan for a period of one year from 1st August, 2021 till 30 August, 2022. Ethical approval from the hospital ethical committee was obtained. All adult patients of either sex, belonging to the province of Khyber Pakhtunkhwa, Pakistan, between 18 to 70 years of age, whether admitted through casualty or the outpatients, having a history of fever for the past 07 days and no prior history of admission or use of antibiotics in past one month were included. Only patients whose blood culture showed isolated growth of Salmonella typhi were included. Patients whose blood cultures showed a mixed growth alongside Salmonella or no growth were not included in the study.

At the time of admission, 10ml of blood was drawn and sent immediately to hospital main laboratory for culture and sensitivity. The blood samples were incubated on MacConkey agar followed by gram staining and morphology besides identification of the strain using the polyvalent sera (BD Difco TM Salmonella). The antibiotics sensitivity pattern was determined for all the commonly used antibiotics for Salmonella Typhi including the first, second and the third line. We used the Clinical & Laboratory Standards Institute (CLSI) 2021 standards in reporting the antibiotics sensitivity as sensitive and non-sensitive. The non-sensitive group included all "resistant", "intermediately resistant" or "non-susceptible" cases based on the diameters of the zones of inhibition using the Kirby Bauer disc diffusion method. The results of the isolated Salmonella Typhi and the sensitivity patterns along with the patients details were uploaded on the hospital automated Health-system Management and Information System (HMIS).

All the data was entered into a proforma made for the study and analyzed using SPSS version [22.] Mean and standard deviation were calculated for numerical variables like age. Frequency and percentages were calculated for categorical variables like gender. All the results were presented in the form of tables.

Results

In this randomized controlled trial study a total of 134 patients of luminal unicystic ameloblastoma and were divided into two equal groups on the basis of procedure adopted for their treatment. In Group A patients were treated with enucleation with peripheral ostectomy alone and in group B the patients were treated with enucleation with peripheral ostectomy in combination with Chemical Fixation. Female patients were in dominance in our study samples of both groups but there was no significant (P-value > 0.05) difference in both groups. The mean age of group A was similar to group B (26.097 ± 5.742 vs. 25.121 ± 5.112), without statistically significant difference. Majority of the patients in both groups were in age group of 21-30 years, consisting of 67.16% patients in group A and 62.69% patients in group B as elaborated in table I.

Table I: Antibiotics sensitivity percentages against Salmonella typhi.		
Sr No	Antibiotics	Sensitivity
01	Polymyxin	540(100%)
02	Colistin	540 (100%)
03	Tigacycline	540 (100%)
04	Ertapenem	540 (100%)
05	Meropenem	534 (99%)
06	Imipenem	534 (99%)
07	Amikacin	523(97.0%)
08	Gentamycin	523(97.0%)
09	Cefepime	127(26.4%)
10	Ceftazidime	160(28.0%)
11	Ceftriaxone	89 (16.4%)
12	Cefotaxime	150(27.7%)
13	Cefoperazone-Sulbactum	07(1.2%)
14	Ciprofloxacin	89 (16.4%)
15	Norfloxacin	110(20.3%)
16	Pipercillin-Tazobactam	106 (19.6%)
17	Fosfomycin	106 (19.6%)
18	Azithromycin	274(51.20%)
19	Co-amoxicillin	03 (0.5%)
20	Ampicillin	03(0.5%)
21	Nitrofurontoin	82(15.1%)

Discussion

The WHO has reported that the incidence of typhoid continues to escalate in parts of South Asia with sadly the highest incidence in parts of Pakistan with 451□7 per 1,00,000 individuals/year, trailed by India with 214□2 per 1, 00,000 individuals/year.[2] The blood culture positivity in typhoid fever has been reported in various studies to be between 60-80% whereas the bone marrow cultures are reported as positive in 80–95% of the cases.[14] Our results revealed the blood culture yield to be 63%, which is very much in congruence with the reported literature. The first series of cases of Salmonella resistance were reported way back in 1960 to the then most frequently used antibiotic named Chloramphenicol.[15] Travers et al reported that the MDR cases of Salmonella besides being quite difficult to treat, also results in more severe illness extra-intestinal manifestations besides the ever increasing cost incurred to effectively cure the bacteremia with the expensive and prolonged courses of antibiotics.[16]

Hyeon et al postulated that the growing resistance to the Salmonella Typhi is primarily a product of the use of various unregulated antibiotics in the animal feed to treat bacterial and non-bacterial infections. This finding is quite alarming as this raises an imperative aspect of probable zoonotic transmission of Salmonella.17Ali A et al reported 18% and 28% cases of XDR and MDR Salmonella strains respectively similar to the findings of Hussain A et al.18,19These results are far less as equated to our results with 83.6% MDR and 3% XDR cases. The primary reason such a huge difference in the results can well be explained by the fact that the enrolled patients in our study were from a large tertiary care hospital of the province and mostly seen patients were expected to be quite sick and with complications as compared to the other studies which were done on the population with enrollment from the community followed by primary interaction with the treating doctors. Wahawani et al reported that 80% of the isolated samples were XDR followed by 9% cases of MDR Salmonella in a cohort of patients from District Hyderabad, Pakistan.[20]

The figures of Imtiaz A et al are rather more alarming with 100% of the isolates were extended-spectrum β-lactamase (ESBL) producing and exhibiting MDR sensitivity patterns and only sensitive to Carbepenems group of antibiotics. The findings look in total agreement with our results with 100% sensitivity to Carbepenem and 83.6% of the MDR isolates (cephalosporin resistant) of Salmonella.[21]The ever swelling cases of MDR and XDR calls for rigorous preemptive measures to warrant that strict antibiotic stewardship programs in line with the regional antibiotics sensitivity are religiously followed in addition to ensuring the preventive side of the illness is looked in.

The data is more alarming, knowing the fact that a retrospective exploration of the records of AKU clinical microbiology revealed only 0.01% cases of ceftriaxone resistant Salmonella Typhi up until 2015, which seems to have escalated to 83.6% resistance in the year 2022 in our study population.[22]

Ali A et al in their study piloted in District Buner, Khyber Pukhtunkhwa witnessed 100% resistance against Ampicillin and Aztreonem trailed by Cotrimoxazole (98.9%), Ciprofloxacin (97%), Chloramphenicol (72%), and Ceftriaxone (52%). All the patients (100%) were found sensitive to Meropenem and Azithromycin.[18] A closely comparable study by Shah et al reported approximately analogous patterns of antibiotics sensitivity.[23] Our results reflect similarly with regard to (0.5%) Ampicillin and (0.5%) Co-amoxicillin and comparatively low sensitivity patterns with (16.4%) each to Ceftrioxone and Ciprofloxacin.

Over many years, the third generation cephalosporin remained the drugs of choice for treating cases of typhoid fever but unfortunately cases of resistance across India and Pakistan continue to be reported frequently making it a poor choice in recent times.[24,25] The problem is further compounded by knowing the fact that Salmonella typhi like other similar gram negative bacteria use the same mechanism of resurrection of extended spectrum β lactamases (ESBLs) production resulting in cross species Antimicrobial Resistance (AMR) patterns.[25] The unrelenting use of cephalosporins in the treatment of Typhoid fever calls for sensitizing the treating doctors of potentially making the other similar gram-negative bacteria less vulnerable to their

effect. The findings of increasing resistance against the various generations of Cephalosporins for treating Salmonella are reflected in our study with (26.4%) Cefepime, (16.4%) Ceftrioxones, (27.7%) Cefotaxime, (28%) Cetazidime exhibiting resistance in our study population.

The extensively prescribed fluroquinolones for the treatment are dropping their efficacy over a period of time across the globe with ever growing cases since 1992 as widely reported by the studies done by Das JK et al, Parry CM et al and Mutai WC et al. The findings are analogous rather more dismal in our population with 83.2% of the patients displaying resistance against the quinolones.[26,27,28] There is a visible jacked up resistance against quinolones up to 90% coupled with scarce availability and affordability of the expensive antibiotics for prolonged periods. The findings in our study show only 16.4% of the patients were found sensitive to Ciprofloxacin.

Qamar FN et al investigated the outbreak of Salmonella in various parts of Hyderabad and reported nearly same findings like our study with 100% sensitivity to Meropenem but findings are at odd regarding Azithromycin which was 100% in their study population whereas 51.2% in our patients.[22] Nearly similar findings were reported by Javaid N et al in their retrospective cross sectional study in Pakistan. The differences in antibiotics sensitivity can well be explained by the differences in the enrolled study population and the evolving resistance of Salmonella over a period of time.[29]

Conclusion

Antimicrobial resistance against Salmonella is on the rise especially in parts of Asia and the behavior of the bacteria continues to evolve with amplified virulence and less susceptibility to commonly available antibiotics. The antibiotic guidelines have to be indigenously devised in line with the local sensitivity patterns. There is an immense need of evolving rigorous measures for prevention of the infection as the existing rate of resistance is distressing.

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