



EXTENDED DRUG RESISTANCE IN CHILDREN WITH TYPHOID FEVER.

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ABSTRACT... In developing countries, typhoid fever is mostly seen due to poor public health and low socioeconomic indices. Currently Pakistan is going through the largest outbreak of XDR typhoid fever which has resulted in increased morbidity and mortality especially in pediatric population. **Objectives:** To see the pattern of extended drug resistant typhoid fever in different areas of Karachi. **Study Design:** Cross sectional study. **Setting:** Department of pediatrics, Ziauddin Hospital (KDLB, NORTH, CLIFTON campus). **Period:** 6 months from October 2018 till March 2019. **Material & Methods:** All patients who presented with history of fever for 3 or more days with signs and symptoms of typhoid fever were recruited. For data collection a self-structured questionnaire was used. Age, gender, socioeconomic status, personal hygiene, water supply and sanitation were taken into account. Blood samples were sent for cultures. Salmonella isolates were tested for antibiotic susceptibility. Tested antimicrobials were ampicillin, TMP/SMX, cefixime, ceftriaxone, aztreonam, ciprofloxacin, azithromycin, meropenem. For data analysis SPSS version 22 was used. **Results:** Out of 415 patients, 235 had culture proven typhoid fever. Salmonella typhi was isolated in 94.4% of the patients and salmonella paratyphi was isolated in 5.57%. Of the 235, Males were 62% and females were 42.4%. Major determinants associated with acquiring salmonella infection were young age (74%), male sex (62%), middle and low socioeconomic status (83.8%), living in west district of Karachi (54.9%) and drinking line water (79.2%). Extended drug resistance was encountered in 69.5%. Most of the isolates were sensitive to meropenem and azithromycin (96.7 %, and 95.5% respectively). Ceftriaxone resistance was prevalent in all three districts of Karachi (p value <0.001), in different age groups 1-6yrs (98%), 7-12 yrs(91%), 13-18 yrs (100%) and in males(58%) predominantly. **Conclusion:** Karachi is facing an outbreak of XDR typhoid fever. Risk of acquiring extended drug resistant typhoid fever is increased in younger age group 1-6 yrs, males, west district of Karachi and poor socioeconomic status. Drinking unboiled water is identified as one of the major culprits. Actions should be taken at all health care levels to monitor the judicious use of antibiotics, and preventive strategies like safe water supply, improved sanitation along with typhoid vaccination are suggested to overcome this outbreak.

Key words: Azithromycin, Extended-Drug Resistant, Meropenem, Typhoid Fever.

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INTRODUCTION

Typhoid fever is major public health problem in developing world. In the year 2000 there were 21.5 million cases worldwide with half of them were from southeast Asia.¹ It is prevalent in Pakistan, especially in pediatric population of < 10 years.² In 2014 the annual incidence of Salmonella typhi A and Paratyphoid A was reported to be 451/100,000 and 76/100,000 respectively in children.³

With this burden, treating typhoid fever is huge

challenge for health care provider in developing countries. Factors like nonspecific signs and symptoms⁴, variable yield of organism on blood culture⁵ and finally drug resistance⁶ are one by one increasing the complexity of managing this disease. Over the past three decades drug susceptibility against Salmonella Typhi and Paratyphi has been changed significantly.

MDR (multi drug resistant) typhoid fever is defined as resistance against three first line drugs including ampicillin, chloramphenicol and TMP-

SMX. Factually, it was first reported in late 1970 and emerge as huge outbreak in between 1980 and 1990.⁷ In Pakistan it was reported to be 44%.⁸ After that quinolones overtake as first line therapy for Typhoid fever but In early 2000, emerging resistance against quinolones was increasingly being reported.⁹⁻¹¹

In these circumstances, third generation cephalosporin both parenteral and oral become drug of choice for treatment of typhoid fever in Pakistan¹² particularly in pediatric population.

Ceftriaxone resistance was first time reported in South East Asia (Bangladesh) in 11 months old boy in 1999.¹³ From 2009 to 2011 ceftriaxone resistance was found only 0.08% in two children of Karachi by laboratory surveillance data.⁸

Currently sporadic cases of extended drug resistant typhoid (drug resistance ampicillin, chloramphenicol, cotrimaxole, flouroquinole and ceftriaxone) are frequently being reported from different centers of Sindh especially from Karachi and Hyderabad. We planned to conduct this study to determine the variation of extended drug resistant typhoid fever in all three campuses of Ziauddin Hospital in metropolitan city Karachi so that appropriate actions will be taken to monitor judicious use of antibiotics and to encourage preventive strategies according to management guidelines of typhoid fever.

MATERIAL & METHODS

Setting

Pediatric unit Ziauddin hospital (KDLB, Clifton and North campus).

Period

Six months October 2018 till March 2019.

Sample Size

One seventy two .Sample length was estimated with the use of Open epi sample size calculator as the prevalence of culture proven enteric fever was 13%¹⁴ with a confidence interval of 95%.

Inclusion Criteria

Age one year to 18 year. Both genders Individuals/

caregiver who will give consent for the study. Children who gave the history of fever, lasting for greater than three days without an apparent focus of infection. Clinical suspicion of typhoid fever (high grade fever, malaise, headache, constipation or diarrhea).

Exclusion Criteria

Children with history of fever lasting three days or more with obvious cognizance of infection like URTI, Otitis Media, and Pneumonia

Study Design

Cross-sectional study.

Data Collection

Patients who reported with the history of fever lasting for 3 days or more, without any focus of infection and clinical signs of enteric fever like toxic look headache, anorexia, abdominal discomfort, drowsy, altered consciousness, malaise, constipation, and diarrhea from outpatient department as well as admitted in all three campuses were recruited. A focal person was identified in each campus who entered Information regarding demography, socioeconomic status, signs and symptoms, diagnosis, blood cultures and antibiotic therapy on structured questionnaire. Based on the parents purchasing power parity study population was categorized into 4 socioeconomic classes, Upper, Upper middle, Middle Middle, Lower middle and Lower class. This class stratification was based on criteria provided by Pakistan Institute of development Economics.¹⁵ An informed written consent was taken from the parents before drawing the blood samples for blood culture.

Three to five ml of venous blood sample was drawn from the patient for blood culture and will be dispatched to pathology department at the time of admission before starting empirical antibiotic therapy. Later the blood was inoculated into BACTEC bottles. On the basis of visual or BACTEC machine identification, the blood culture samples had been in addition subculture onto MacConkey agar and Blood agar plates. Colonies displaying biochemical reactions indicative of salmonella were proved using

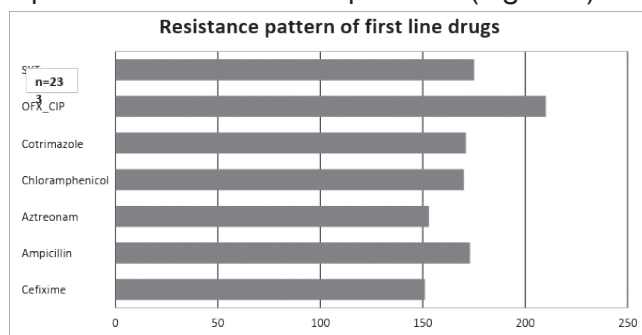
specific O and H antisera. Salmonella isolates have been tested for antibiotic susceptibility using Kirby-Bauer disc diffusion technique on Mueller Hinton agar with standard antimicrobial discs. Antibiotic susceptibility for ampicillin, TMP/SMX, cefixime, ceftriaxone, aztreonam, ciprofloxacin, azithromycin, meropenem was performed.

Data Analysis

Data was analyzed on SPSS version 22. Quantitative data is reported as mean +/- SD while qualitative data is reported as frequency and percentages. Pattern of drug sensitivity (Extended drug resistance) was compared among different age group, socioeconomic status and geographical location using chi-square test with p value < 0.05 taken as significant.

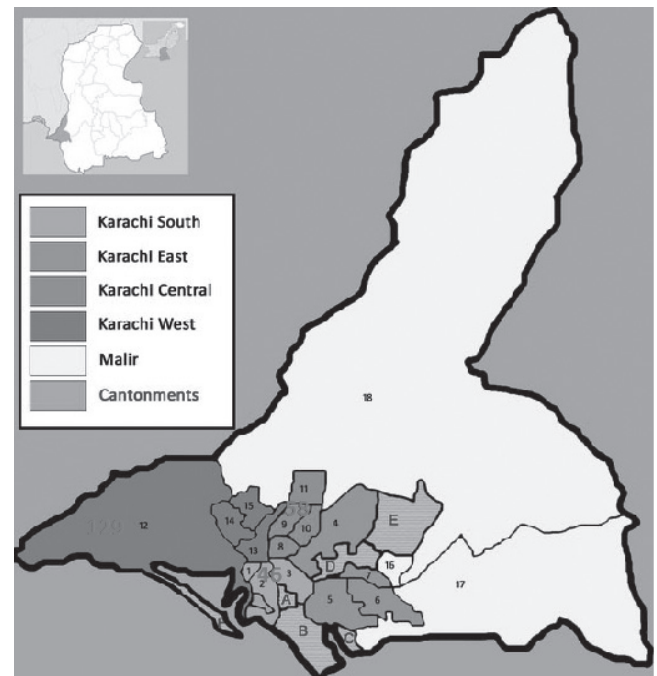
RESULTS

Over the study period from March 2018 to Sep 2018, a total of 415 patients with suspected enteric fever were included for analysis. Out of which 235 came out to be culture proven typhoid fever. Result of 233 culture proven typhoid fever were analyzed as two cases have some missing data in it. Fifty six percent of the patients were culture proven typhoid fever however 43.4% of the patients had no growth. Of the isolated bacteria 94.4% (220) were Salmonella typhi and rest 5.57% (13) were salmonella Paratyphi A. No Paratyphi B or C were isolated. Most of the patients have age group from 1-18 years, while 30 patients were taken in separate age group of more than 18 who were near to complete 19 year. Many bacterial isolates were resistant to ampicillin, cefixime, ciprofloxacin and chloramphenicol (Figure-1).



Among culture proven typhoid fever males were 134 (62%) and females were 99 (42.4%). Majority of the patients (54.9%) were from the west 19.6%

from south and 26.1% from Central district of Karachi.



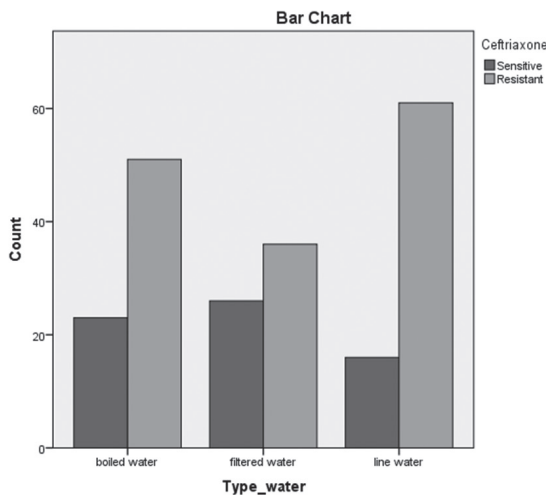
36 patients belonged to upper socioeconomic class whereas 126 and 71 were from the middle and lower socioeconomic class respectively. Fever and coated tongue were the common presentation of typhoid fever in our study population.

| Symptoms | Frequency | % |
|----------------------|-----------|------|
| Jaundice | 8 | 3.4 |
| Hepatomegaly | 91 | 38.7 |
| Tongue coating | 136 | 57.9 |
| Vomiting | 87 | 37 |
| Constipation | 25 | 10.6 |
| Abdominal pain | 86 | 36.6 |
| Diarrhoea | 50 | 21.3 |
| Fever for three days | 229 | 97.4 |

Frequency of Symptoms (n=233).

The determinants associated with acquiring salmonella typhi and Paratyphi included young children age 1-6 year (74%) male sex (62%), middle and low socioeconomic status (83.8%) and living in west district (54.9%). There's no significant difference in children acquiring salmonella from line water (35.6%) or boiled water (35.6%) while remaining were utilizing filter water (28.5%) but

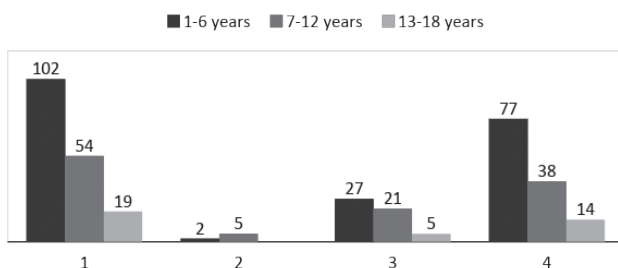
XDR typhoid fever cases are more common in consumers of line water (79.2%).



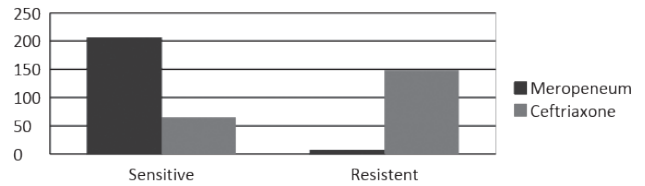
49(20.6%) isolated cases had unsatisfactory personal hygiene while 72(30.6%) had improper disposal of wastage. Family members belong to isolated cases were range from 2-15 with mean of 6.1(+_2.48).

69.5 % (148) of isolates showed extended drug resistance. Ceftriaxone resistance was prevalent in west south and central district uniformly (p value < 0.001). Regarding antibiotic sensitivity, meropenem and azithromycin were sensitive to majority of the isolates i.e. 96.7 %, and 95.5% with no significant difference among three districts of Karachi (p value 0.589 &0.516 respectively). Sensitivity to meropenem among different age groups of 1-6 year (98%), 7-12 year (91%) and 13-18 year (100%). Drug resistance to ceftriaxone is 74%, 64.4% and 73.7% in all age groups. Males were predominantly sensitive to Meropenem and resistant to Ceftriaxone (58.2%).

Comparison between Meropenem and Ceftriaxone sensitivity and resistance pattern in different age group



Comparison between Meropenem and Ceftriaxone sensitivity and resistance pattern



DISCUSSION

Drug resistance typhoid fever originates a fearsome environment not only in country, but also abroad when cases from UK and USA had reported last year. Historical sensitivity against Salmonella keeps on changing from 1970 when, for the first time, chloramphenicol resistance was reported in Indian subcontinent.¹⁶ Before 2016, ceftriaxone and cefixime was being recommended as first line antibiotics in complicated and uncomplicated typhoid fever¹⁷, but sporadic and then cluster of ceftriaxone resistant cases from Sindh province created uncertain situation regarding empirical treatment of Typhoid fever.

Every day, newspapers and social media report about the emergence of superbugs and drug resistant typhoid fever. From different districts of Hyderabad, 92% confirmed ceftriaxone resistant cases in children (under 15 y/o) were reported over a period of one year¹⁸ as compared to our study in which we have 148 (69.5%) cases of extended drug resistant typhoid fever over a period of six months. Abbasi Shaheed hospital that represents central district of Karachi also reported 96% resistance to ceftriaxone in pediatric population.¹⁹ In children aged 1-6 we had high incidence (74%) in contrast to 56% reported from Hyderabad in children (under 5 years), similar to observation from studies from India and Bangladesh.²⁰ Children are more prone to acquire resistance because they have less immune responses, receive more empirical treatment and encounter more health care providers.²¹ Similar to studies from other part of subcontinents, India²², China²³, Bangladesh²⁴ and parts of Pakistan¹⁸, male gender has predominance in XDR Typhoid fever. Among risk factors of typhoid fever, drinking unboiled water (either line water directly or after filtration) identified as a leading culprit which is

similar to previous observations in Karachi²⁵ and other parts of the developing world^{24,26}, where provision of safe water supply is a huge problem. Our study identified high incidence (54.6%) of typhoid fever in children from the west district of Karachi, but to draw global perspective regarding contaminated water supply in any specific area of city, an epidemiologic study on large scale is needed with sampling of water from main reservoir to households.

On the other hand, shift of salmonella sensitivity towards azithromycin and meropenem is evident by our observation and different observations in other parts of province^{12,19} which creates an alarming situation. Considering the current culture sensitivity of Salmonella, it is matter of great concern whether empirical treatment of typhoid fever shift towards azithromycin and meropenem in uncomplicated and complicated cases respectively or if it continues with cefixime and ceftriaxone as first line drugs. In countries like Pakistan where judicious use of antibiotics is not practiced either due to availability of over-counter medicine without any prescription or treating presumed typhoid fever with broad spectrum antibiotics without sending diagnostic test like blood culture, it is very important to design and implement comprehensive treatment guidelines at all health care levels.

The only answer to deal with this outbreak is dissemination and adaptation of preventive strategies through every possible opportunity at individual or mass level. Children under 5 years of age, which are mostly dependent on parents/caregiver for their necessities, are the most commonly affected age group so it should be the top priority of health care providers to educate parents/caregivers regarding the risk factors of this devastating illness. It is evident that typhoid immunization can reduce disease burdens, especially when given to high-risk age group in identified geographic areas.²⁷ Immunization cannot only reduce the number of circulating MDR strains but they can also decrease the incidence of undifferentiated febrile illness, thereby reducing the need for empirical antimicrobial therapy.²⁸ Unlike the significant investment required for

major infrastructure development, vaccination is relatively more affordable to governments, since it does not require substantial behavioral change and has been shown to be cost-effective.²⁹

CONCLUSION

In conclusion, to overcome this epidemic of XDR typhoid, use of conjugate typhoid vaccines should be integrated with other control strategies: access to safe water supply, sanitation improvements, hygiene education messages, community or national food hygiene measures, and appropriate case and chronic carrier detection and along with proper use of antibiotics to manage these cases and chronic carriers.

Strength of Study

Diagnosis done by gold standard blood culture. Cases were taken from three different campuses having separate catchment area.

Limitation of Study

Association of various risk factors can be further strengthened by comparing cases with matched controls.

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



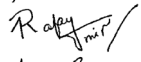
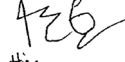

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| 2 | Heena Rais | Involved in all steps of study, Proposal writing to conclusion. |  |
| 3 | Madiha Fatima Jamil | Data collection |  |
| 4 | Saba Safdar | Data analysis |  |
| 5 | Muhammad Rafay Amir | Data collection |  |
| 6 | Ahmed Altaf | Data collection |  |
| 7 | Hira Khan | Data collection |  |