

A review of clinical profile, complications and antibiotic susceptibility pattern of extensively drug resistant (XDR) *Salmonella* Typhi isolates in children in Karachi.

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Abstract

Background: Enteric fever is a systemic infection, which can be caused by *Salmonella enterica*; Typhi and Paratyphi A. Over a period of time *Salmonella Typhi* has developed resistance to many antibiotics which has resulted in emergence of extensively drug resistant (XDR) enteric fever. WHO estimated 5274 cases of XDR Enteric fever in Karachi from November 2016 to December 2019. This study aims to determine clinical course, complications and outcomes of XDR enteric fever among the pediatric population coming to Indus Hospital

Methods: A retrospective chart review of pediatric patients (aged 1 month–15 years) seen in Indus Hospital between July 2017 to December 2018 was conducted. A pre-designed data abstraction form was used to record detailed information about seasonality and distribution of cases, demographic details, signs and symptoms, clinical course, treatment, complications and final outcomes of the cases treated for XDR Enteric fever

Results: Six hundred and eighty children were included in the study. The median (IQR) age of the patients was 5 (2-8) years. More than half (n=391, 57.5%) of the patients were males. Most common clinical manifestations included fever vomiting and diarrhea which were noted in 680 (100%), 242 (35%) and 174 patients (25%) Final outcomes of 270 (39.7%) patients have been recorded; 351 (51.6%) were lost to follow up, 52 (7.6%) were referred out and 7 (1%) left without medical advice. 266 (39.1%) patients were cured and 4 children (0.6%) expired. Seventy eight patients (82%) and 15 patients (16.3%) got cured on Azithromycin and Meropenem alone while 157 patients got cured on combination of drugs.

Conclusion: Our review indicated that children under 5 years of age were affected more with XDR Enteric fever. Meropenem and Azithromycin, either alone or in combination were the most effective antibiotics for treating XDR Enteric fever in children coming to Indus hospital

Background

Enteric fever is a systemic infection, which can be caused by two serotypes of the gram-negative bacteria *Salmonella enterica*; Typhi and Paratyphi A (1). The disease is estimated to affect approximately 11 to 21 million individuals globally on an annual basis and has a high mortality rate (2). Recent data showed that globally 200,000 deaths result annually due to enteric fever (3). The burden of disease of enteric fever is the highest in Asia; 93% of the global cases are reported from within this region (3). Southeast Asia has the third highest incidence within the region, with approximately 110 cases / 100 000 population. The estimated incidence of enteric fever in Pakistan was found to be 413 / 100 000 population in children aged 2–4 years and 573 / 100 000 population in children aged 5–15 years. (1)

Over a period of time, *Salmonella Typhi* has developed resistance to many antibiotics which has resulted in emergence of Multi-drug resistant (MDR) *Salmonella Typhi* (*S. Typhi*) strains. These strains have shown resistance to both first and second line antibiotics, namely Ampicillin, Chloramphenicol, Cotrimoxazole and fluoroquinolones (4). This strain of enteric fever has been endemic in countries like

Pakistan, India, Nepal and Bangladesh since the 1980s (5). A review of antimicrobial resistance of S. Typhi and Paratyphi A conducted in Pakistan from year 2009 till 2011, showed increasing frequency of MDR S. Typhi (91.7%) as well as two cases of S.Typhi which were resistant to cephalosporin resistance (4).

In November 2016, a massive outbreak of ceftriaxone-resistant S. Typhi was reported among children residing in Hyderabad, Pakistan. Around 486 cases were reported and consumption of contaminated drinking water was linked with the infection. These strains were called extensively drug resistant (XDR) S.Typhi as they showed resistance not only to first and second line antibiotics but also to third generation Cephalosporins. Drug sensitivity pattern of XDR Typhoid strain showed sensitivity to either Carbapenems or Azithromycin (6). Since the outbreak of XDR Enteric in Hyderabad, many other cases of XDR Enteric fever have been reported. WHO estimated 5274 cases of XDR Enteric fever in Karachi from November 2016 to December 2019 (7).

XDR Enteric fever is a new strain and may have unique clinical manifestations and outcomes compared to MDR Enteric infection. There is scarcity of data on clinical features and response to treatment in children suffering from XDR Enteric fever both nationally and in other parts of world. Therefore this study is done to determine clinical course, complications and outcomes of XDR enteric fever among the pediatric population coming to Indus Hospital. Primary end points include, clinical manifestations, complications, response to treatment and final outcome of the participants. Secondary end points included seasonality of the infection and geographic distribution of the cases.

Methods

Study design and data collection

A retrospective chart review was conducted of medical records of children who were treated for XDR Enteric fever at The Indus Hospital from 1st July' 2017 to 31st December' 2018. All children, with ages ranging from 1 month to 15 years, were included in the study. The data was extracted through the Health Management Informatics System (HMIS); data of all the children confirmed of having XDR Enteric fever, on basis of culture and sensitivity reports were included in the study.

A pre-designed data abstraction form was used to record detailed information about seasonality and distribution of cases, patient demographics, signs and symptoms, clinical course, treatment, complications and final outcomes. Laboratory parameters were also recorded to determine the severity and course of the disease; these included complete blood count (CBC), liver function test (LFTs), serum electrolytes, Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Urea and Creatinine. Data of complications like, cholecystitis, mesenteric lymphadenopathy, ascites and pleural effusion, was taken from ultrasound reports. Complications were defined as XDR infection with sign, symptoms or lab evidence of hepatitis, cholecystitis, encephalitis, mesenteric lymphadenitis, shock, ascites, pleural effusion and aphasia

Microbiological culture of venous blood was performed using 5 ml of blood, drawn under aseptic measures. BacT/Aert culture bottles were used to collect blood samples (8) Antibiotic susceptibility for a group of antibiotics was tested using Kirby-Bauerdisk disc diffusion method on Muller-Hinton agar with standard antimicrobial disks using Clinical Laboratory Standards Institute guidelines.

Case definitions

Renal impairment

Increased creatinine > 1.5 times upper limit of normal or decreased in urine output < 0.5 ml/kg/ hourr for 6 hours (9)

Hepatitis

Deranged Liver function tests with ALT more than twice the reference value with or without hyperbilirubinemia, impaired coagulation and hypoglycemia

Cholecystitis

Evidence of inflamed gall bladder sludge in gall bladder on ultrasound

Hematological complications

High or low level of hemoglobin, leucocyte or platelet count according to the given lab references.

Encephalopathy

Changes in mental status, confusion or stupor with normal CSF findings

Encephalitis

Changes in mental status, confusion or stupor or signs of meningeal irritation with abnormal CSF findings

Diarrhea

Presence of loose or watery stools 3 times or more per day (10)

Statistical analysis

Data was analyzed using SPSS version 24. Descriptive statistics were run for all continuous variables, exploring Skewness and Kurtosis. Mean with standard deviation was reported for normal distribution, while median with interquartile range was reported for skewed distribution. For normal distribution, normality was confirmed by applying T-test. For skewed distribution, Mann-Whitney test was applied to determine significance. For categorical variables, frequencies were determined. Significance of correlations was determined by applying statistical tests; p value < 0.05 was taken as significant

Results

1518 patients had blood culture positive for enteric fever during the study period. Out of these 1341 patients were children and 177 patients were adults. Out of 1341 pediatric patients, 680 met our inclusion criteria and were included in the final analysis. More than half (n = 391, 57.5%) of the patients were males. The median (IQR) age of the patients was 5 (2–8) years, with minimum and maximum 0 day to 14 years. Out of these patients, majority, 612 (90%), directly presented to ER, followed by OPD, 65(9.6%). Around a hundred (n = 101, 14.9%) patients got admitted in hospital, out of which 98 (97%) patients were admitted in ward and the rest were admitted in ICU for treatment (Table 1).

Maximum number of children, 540 (79%) came from district East (Fig. 1). 2 seasonal peaks were identified in year 2018. One was in February-May 2018 and second peak was observed in August-October 2018 (Fig. 2).

Most common clinical manifestations included fever vomiting and diarrhea which were noted in 680 (100%), 242 (35%) and 174 patients (25%) (Table 1). Most frequent complications observed included hyponatremia (n = 74, 11%), acidosis (n = 75, 9%), hypokalemia (n = 59, 9%) and bicytopenia (n = 67, 10%) (Table 2). One case of vertical transmission was observed and the newborn died of XDR enteric infection. Four cases of encephalitis were identified, out of which 3 children had aphasia on presentation. All children with encephalitis had full recovery without any residual weakness or speech difficulty. One child developed multi organ dysfunction and pulmonary hemorrhage.

Final outcomes of 270 (39.7%) patients were recorded; 351 (51.6%) were lost to follow up, 52 (7.6%) were referred out and 7 (1%) left without medical advice. 266 (39.1%) patients were cured and 4 children (0.6%) expired (Table 1). Response to antibiotics was observed in 252 patients, 95 patients got cured on single drug while 157 patients got cured on combination of drugs. Seventy eight patients (82%) and 15 patients (16%) got cured on Azithromycin and Meropenum alone (Table 2). Azithromycin was the most common antibiotic used for the treatment of XDR, it was administered to 274 (61.2%) patients, followed by Ceftriaxone and Meropenum, which were administered to 198 (44.2%) and 137 (30.6%) patients, respectively

Mortality was observed in 4 children, including a newborn. Out of those who died, two were on a single antibiotic, Meropenum, while the other two were on a combination of antibiotics (e.g. Meropenum and

Ceftriaxone). Patients who died developed complications, such as, bradycardia, respiratory distress, hypoglycemia and sepsis, electrolyte imbalance, encephalitis, and pulmonary hemorrhage.

Discussion

Enteric fever caused by *S. Typhi* continues to pose as a health burden globally, with the incidence being highest in low to middle income countries (LMIC), due to poor infrastructure of public health (11). According to World Health Organization (12), Pakistan faced the largest outbreak of XDR enteric fever, in Hyderabad in November 2016 followed by a similar outbreak in Karachi. XDR Enteric is a novel strain of *S. Typhi* which belongs to H58 lineage and has plasmid encoded resistance and extended-spectrum β -lactamase (ESBL) gene which is responsible for resistance to both first and second line antibiotics (13).

An investigation of XDR enteric fever in Hyderabad (7) and in Islamabad (14) revealed that 56% and 33% affected children were under 5 years of age. This finding is consistent with our study, since we found that the median age of affected children was 5 years (IQR: 2–8 years). This higher incidence of XDR enteric fever amongst younger children could be explained by the fact that children have lower immunity and require lower bacterial dose for development of an infection (15). Most of the participants in our study belonged to East district of Karachi, probably because Indus Hospital lies in the catchment area of this district. Many residential areas located in district East of Karachi, comprise of peri-urban slums, having unhygienic conditions, poor sewerage facilities and consumption of pipe-borne portable water supply by the people. The high burden of disease in these areas could be due to contaminated drinking water and mixing of drinking and sewage water, a finding which was also observed in Hyderabad (6).

Enteric fever has been associated with considerable seasonal variations in different parts of world (16) In Pakistan MDR Enteric peaks have been noted in May-June and in October. The seasonality was linked to increased consumption of contaminated local drinks and ice-cream during hot season and post monsoon contamination of drinking water with rain water (17). We also observed 2 peak seasons of XDR Enteric cases, one in February-May 2018 and second in August-October 2018. This observation is contrary to previous epidemiological findings of Enteric fever in Karachi, which identified clear relation of Enteric fever with monsoon rains. Epidemiological survey has shown that Sindh province, including Karachi, remained generally dry throughout 2018 (18), which makes post monsoon contamination of water less likely in our study. However timing of peak cases in our study were very similar to those observed in Lahore in 2018. In Lahore increased numbers of cases of XDR Enteric fever were observed from January - April 2018 (19), while XDR peak in our study was from February-May 2018. The most probable explanation for seasonal similarity of XDR cases between Karachi and Lahore, within same time period, could be because of intercity travelling of people.

In our study most successful, single drug was Azithromycin, which cured 78 cases (82%) followed by Meropenem, which cured 15 cases (16%). This finding is consistent with other studies, which also found better cure rates with Azithromycin and Meropenem (20, 21) Seventy six patients (48%) were successfully treated with combination of Azithromycin and Meropenem. We found synergistic effect of Azithromycin

and Meropenem in achieving fever defervescence. Synergism among various antibiotics have been observed in MDR Enteric fever also (22). Eight children were cured on single drugs although they were resistant to those antibiotics. There is a possibility that these strains were sensitive to antibiotics but had higher MIC breakpoints and were interpreted as resistant strains in our labs, since we did not determine minimum inhibitory concentration (MIC) of the antibiotics used for treatment of XDR Enteric strains.

The strength of this study is that it is the only extensive study in our knowledge which examines the clinical course and outcomes of XDR strain of S. Typhi amongst the pediatric population within Pakistan. The study also determined response to antibiotics and complications in XDR Enteric fever. The limitations of this study includes lack of use of minimum inhibitory concentration (MIC) for culture and sensitivity, along with absence of molecular mapping, which would have provided a more comprehensive picture of the disease. We did not routinely perform stool cultures and hence could not identify carriers. Retrospective data had missing information on socio demographics like drinking water quality, hygiene practices and number of people in household.

Conclusion

It can be concluded that children under 5 years of age were affected more with XDR Enteric fever. Meropenem and Azithromycin, either alone or in combination were the most effective antibiotics for treating XDR Enteric fever. We advocate increasing nation wide awareness about consumption of safe water, antibiotic stewardship and immunization practices of children.

Abbreviations

XDR: Extensively drug resistant, MDR: multi drug resistance, WHO: World health organization, IQR: Inter quartile range, S. Typhi: Salmonella Typhi, HMIS: Health Management Informatics System, CBC: complete blood count, LFT: liver function test, PT: Prothrombin Time, APTT: Activated Partial Thromboplastin Time, ALT: alanine transaminase, CSF: cerebrospinal fluid

Declarations

Ethics approval and consent to participate:

Ethical approval was taken from the Institutional Review Board (IRB) of Interactive Research & Development, registered with the U.S. Department of Health and Human Services, Office for Human Research Protections at The Indus Hospital. As per the IRB, written informed consent was not required from the patients involved in this study.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

No funding was received for this research.

Authors' contributions:

SS and MM conceived idea of the study and participated in study design and write up. SN and ND carried out data collection, MM and ND assisted with statistical analysis. All authors were involved in the coordination of the study, drafting the manuscript and approving the final version.

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Not applicable

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Tables

Table 1
Demographic characteristics, clinical features, investigations, complications
and outcome of the patients

Demographic features	Number (%)
Male	391 (57.5)
Female	289 (42.5)
Age in years Median (IQR)	5 (0–14)
Place of presentation	612 (90)
E/R	65 (9.6)
OPD	3 (0.4)
Inpatient	
Clinical features	Number (%)
Fever	680 (100)
Vomiting	242 (35.6)
Diarrhea	174 (25.6)
Anorexia	140 (20.6)
Cough	126 (18.5)
Abdominal pain	125 (18.4)
Bleeding per rectum	4 (0.6)
Rash	12 (1.8)
Urinary symptoms	14 (2.1)
Hepatomegaly	63 (9.3)
Splenomegaly	22 (3.2)
Duration of illness Median (IQR)	14 (8-26.3)
Lab investigations	Number (%)
Severe Anemia (Hb < 5 gm/dl)	9(1)
Severe Thrombocytopenia (< 50,000 × 10 ⁹ /L)	24(3.5)
Raised CRP > 5	395 (58.1)
Hyponatremia (severe + Moderate combined)	74 (10.9)
Hypokalemia (severe + Moderate combined)	59 (8.7)

Demographic features	Number (%)
Acidosis	75(9)
Raised serum creatinine	4 (0.6)
Complications	Number (%)
Bicytopenia	67(10)
Pancytopenia	16(2.4)
Hepatitis	11 (1.6)
Cholecystitis (on abdominal ultrasound)	4 (0.5)
Mesentric lymphadenopathy (on abdominal ultrasound)	11(2)
Pleural effusion (on abdominal ultrasound)	6 (1)
Peritoneal free fluid (on abdominal ultrasound)	8 (1)
Shock	5 (0.7)
Encephalopathy	16 (2.3)
Encephalitis	4 (0.6)
Aphasia	4(0.6)
Vertical	1(0.1)
Outcome	
Cured	266 (39.1)
Died	4 (0.6)
Lost to follow up	351 (51.6)
LAMA/referred out	59 (8.6)

Table 2
Response to antibiotics

Cured with single drugs	N (%)
Ceftriaxone	6(6.3)
Cefixime	6(6.3)
Meropenum	15(15.8)
Azithromycin	78(82)
Ciprofloxacin	1(1.1)
Cured with multiple drugs	N (%)
Meropenum + Azithromycin	79(50)
Other drug combinations	81(51.6)

Figures

Karachi District

Karachi District	No of cases
Karachi Central	14
Karachi East	540
Karachi South	16
Karachi West	22
Malir	99



- Karachi Central
- Karachi East
- Karachi South
- Karachi West
- Malir

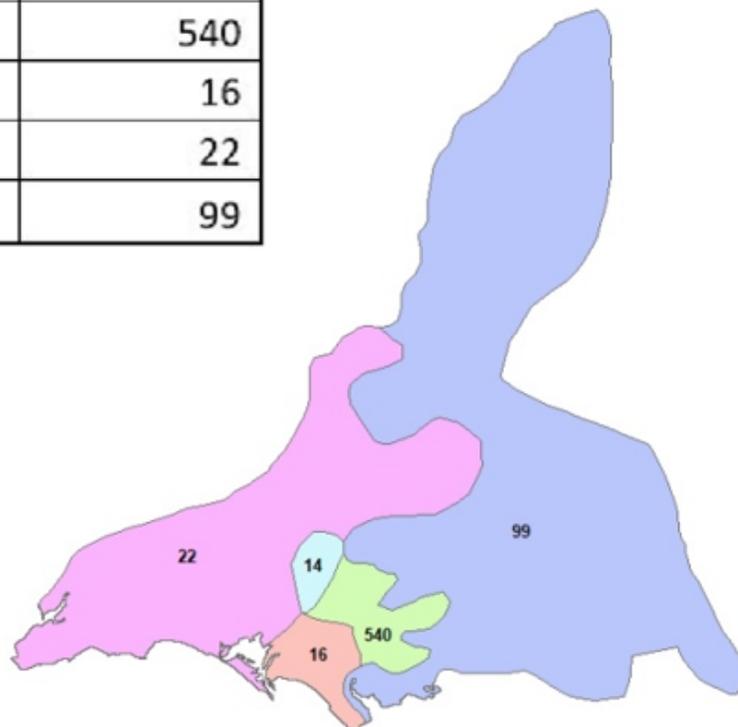


Figure 1

Geospatial map of XDR Enteric cases in Karachi

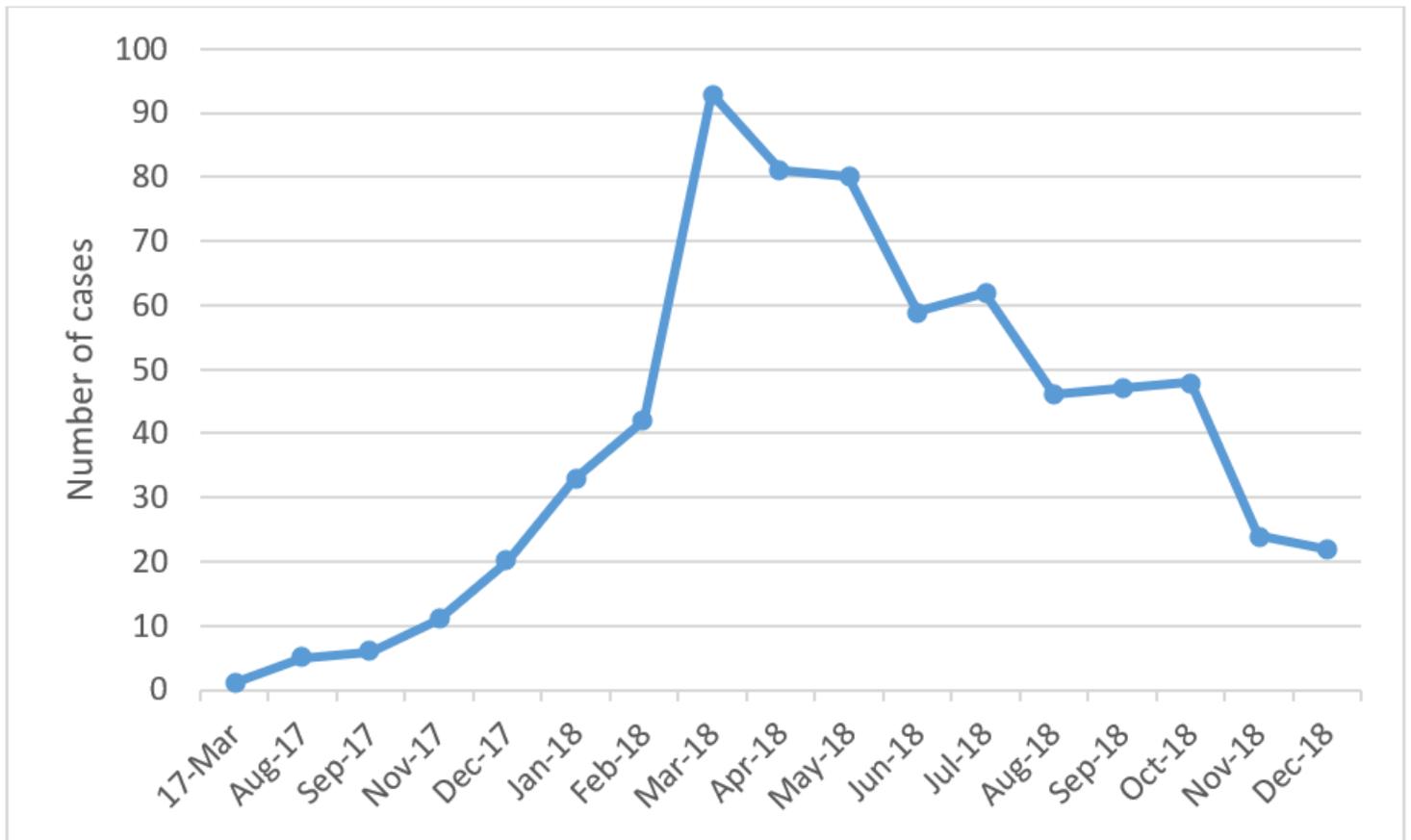


Figure 2

Seasonal pattern of XDR Enteric fever