Original article

Financial burden on the parents of children infected with extensively drug resistant Salmonella infection

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ABSTRACT

Background: Typhoid illness is a significant cause of morbidity in Pakistan. This study aimed to determine the financial burden on parents of children infected with extensively drug-resistant (XDR) salmonella infection.

Patients and methods: This observational study included 159 patients aged 6 months to 13 years admitted through OPD/ER of Karachi Adventist Hospital with the diagnosis of enteric fever and intravenous antibiotics started as per local antibiogram. To remove recall bias antibiotic cost before hospitalization was not included. All those patients who were culture positive for XDR salmonella, either continued or shifted to newer antibiotics as per susceptibility pattern were included. Depending upon the type and duration of antibiotic therapy cost was calculated in Pakistani rupee (1 USD = ~225 PKR).

Results: Total 60.4% of patients aged less than 7.5 years; 62.3% were male, 41.5% from urban areas, 15.1% had graduated mothers, 27% had graduated fathers, 5.7% uses boiled water, and 1.9% typhoid vaccination. In 54.1% of patients antibiotic cost reached >40k PKR. Patients with urban dwelling were 0.29 times less likely for higher cost, increase in duration of fever (>7 days) at admission increased the cost 5.73 times, XDR samples found 13.5 time more likely for higher cost, and TLC between 4000 – 11000/mm^3 gave negative association with higher cost.

Conclusion: The burden of XDR salmonella infection is heavy and is related to urban residence, duration of fever at admission, and length of hospital stay.

Keywords:

Financial burden, Children, XDR, Salmonella, Antibiotic

INTRODUCTION

Salmonella enterica serotype typhi (Salmonella Typhi) is a gram-negative, rod-shaped, flagellated bacterium. Salmonella Typhi infections are only found in humans and are spread through contaminated water supplies and poor hygiene practices such as fecal contamination.[2] They are characterized by a rapidly increasing, life-threatening fever, as well as a variety of clinical signs. This is especially true in impoverished areas, where one in every five children by the age of ten has typhoid fever.[3] Even with effective antibiotic therapy, S. Typhi is projected to infect at least 26.9 million individuals every year, with 1 percent dying.[4]

Out of the 16 Asian countries where typhoid is prevalent, residents of the Pakistan provinces of Punjab and Sindh have been identified to be the most at risk of becoming infected.[5] The rise of antimicrobial-resistant Salmonella Typhi strains is currently a major threat to effective typhoid fever care.[6]

MDR typhoid is resistant to three first-line antibiotics used to treat typhoid—chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole—while XDR typhoid is resistant to chloramphenicol, ampicillin, co-trimoxazole, and fluoroquinolones, as well as third-generation cephalosporins. From 2001 to 2006, a research at Aga Khan University in Pakistan found that multidrug resistance for Salmonella typhi strains increased from 34.2 percent to 48.5 percent, while resistance to quinolones increased from 1.6 percent to 64.1 percent.[7,8]

The WHO supports typhoid fever vaccination as a control method for both endemic and epidemic infections, in addition to addressing environmental deficiencies such as improving access to safe drinking water and sanitation, as well as improvements in hygiene and food safety.[9] Several typhoid conjugate vaccines (TCVs) are currently in various phases of development. TCVs are the preferred vaccine in children aged 6 months and up in endemic areas, according to the WHO[10]. Treatment options have become limited and more expensive as a result of the introduction of XDR Salmonella Typhi in Pakistan. Oral azithromycin treatment costs roughly Rs.250 per

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day in outpatients, and injectable azithromycin treatment costs around Rs.3000 per day in hospitalized patients, not considering hospital costs. The cost of meropenum therapy, on the other hand, ranges from Rs.10000 to Rs.150000 each day, depending on the patient's weight and includes hospital costs.

This research aims to address the issue of increased cost burden associated with rising XDR salmonella infection. This is especially an alarming situation for a 3rd world country like Pakistan where the poverty ratio is 39.3%[23] and where population at risk of developing typhoid do not even have access to basic necessities of life In addition to standard preventative measures, every child should be vaccinated against typhoid. Vaccination is the only way we'll be able to get rid of health problems while also reducing the family's financial load.

PATIENTS AND METHODS

In this prospective observational study we enrolled 159 children aged 6 months to 13 years brought to OPD/ER of Karachi Adventist Hospital (KAH) with history of fever for more than one week not subsided by antibiotics given by local health care practitioners. These children were admitted at KAH and after sending necessary investigations including blood culture, were started with injection ceftriaxone. If fever not subsided on 4th day of ceftriaxone therapy, azithromycin was added in a dose of 20 mg/kg/day as once daily dose. Those children who responded to azithromycin, it was continued till four days after defervescence. The children who did not respond to azithromycin even after 4 days, we added injection imipenem 30 mg/kg/dose IV 8 hourly. Meanwhile we chased blood culture and if it was XDR salmonella sensitive to imepenem and azithromycin we continued these two after 4 days of defervescence. The duration of therapy was different in different patients depending on their clinical condition. Cost of treatment was calculated in PKR and factors associated with higher costs were observed. Duration of study was 7 months (from December 1, 2020 till 30th June 2021)

Data was stored and analyzed using IBM-SPSS Version 23.0, Counts with Percentages reported for baseline characteristics of studied samples, Pearson Chi Square test was used to check the association of cost of antibiotic therapy with clinical parameters, The binary logistic regression analysis was used to model the cost using significant clinical parameters obtained after Chi Square association, p-values less than 0.05 were considered statistically significant, bar diagrams and pie charts were also used to give graphical presentation of study outcome.

RESULTS

In the present study there were 159 enrolled patients, 96 (60.4%) of them were found to be with age less than 7.5 years, 99 (62.3%) were male gender, 66 (41.5%) from urban residence, 25 (15.1%) have graduated mother, 43 (27%) have graduated father, 9 (5.7%) uses boil water, and only 3 (1.9%) had prior typhoid vaccination. Table 1 reports the baseline characteristics of studied samples. Figure 1 showed there were 86 (54.1%) samples found with more the 40,000 PKR cost on antibiotic therapy.

Table 1: Characteristics of the patients (n=159)

Characteristics	n	%
Age group		
≤7.5 Years	96	60.4
≥7.5 Years	63	39.6
Gender of patient		
Male	99	62.3
Female	60	37.7
Residence of patient		
Urban	66	41.5
Urban slums	93	58.5
Education of mother		
Illiterate	44	27.7
Primary	45	28.3
Secondary /higher secondary	46	28.9
Graduate	25	15.1
Education of father		
Illiterate	21	13.2
Primary	29	18.2
Secondary /higher secondary	66	41.5
Graduate / Post Graduate	43	27
Use of boiled water		
Yes	9	5.7
No	150	94.3
Patient status of typhoid vaccination		
Yes	3	1.9
No	156	98.1

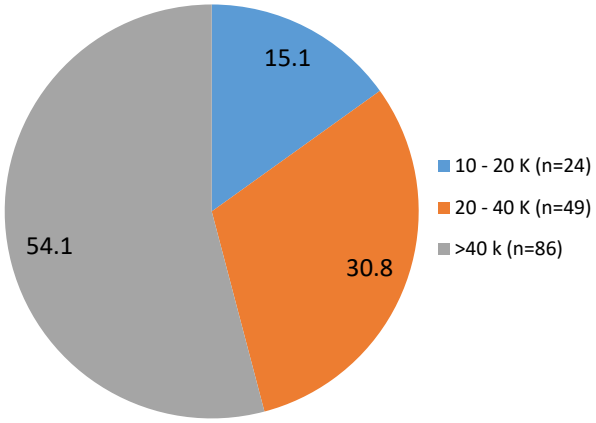

Figure 1: Cost of the antibiotic therapy

Table 2: Association of cost of antibiotic therapy with clinical parameters

Parameters	Cost of antibiotic therapy								p-value
	10-20 K		20 – 40 K		More than 40 K		Total		
	n	%	n	%	n	%	n	%	
Duration of fever at admission									
Less than 7 days	1	4.2	5	10.2	3	3.5	9	5.7	<0.01*
7-14 days	15	62.5	37	75.5	40	46.5	92	57.9	
More than 14 days	8	33.3	7	14.3	43	50.0	58	36.5	
Use of antibiotic before culture									
Iv ceftriaxone	21	87.5	13	26.5	54	62.8	88	55.3	<0.01*
Oral cefixime	3	12.5	20	40.8	30	34.9	53	33.3	
Iv ciprofloxacin	0	0.0	14	28.6	2	2.3	16	10.1	
Iv augmentin	0	0.0	2	4.1	0	0.0	2	1.3	
Duration of therapy before culture results									
3-5 days	2	8.3	14	28.6	26	30.2	42	26.4	0.18
5-7 days	20	83.3	30	61.2	56	65.1	106	66.7	
More than 7 days	2	8.3	5	10.2	4	4.7	11	6.9	
Report of blood culture sensitivity									
XDR	23	95.8	21	42.9	82	95.3	126	79.2	<0.01*
Non XDR	1	4.2	28	57.1	4	4.7	33	20.8	
Antibiotic use after culture results									
Continuation of iv augmentin / iv ceftriaxone	0	0.0	2	4.1	0	0.0	2	1.3	<0.01*
Iv ceftriaxone + iv azithro	0	0.0	11	22.4	1	1.2	12	7.5	
Iv augmentin + iv azithro	0	0.0	0	0.0	1	1.2	1	0.6	
Iv meropenum	2	8.3	6	12.2	81	94.2	89	56.0	
Iv azithromycin	21	87.5	4	8.2	0	0.0	25	15.7	
Iv augmenten	0	0.0	18	36.7	0	0.0	18	11.3	
Iv ceftriaxone	1	4.2	5	10.2	3	3.5	9	5.7	
Iv ciprofloxacin	0	0.0	3	6.1	0	0.0	3	1.9	
Duration of therapy after culture sensitivity									
3-5 days	0	0.0	1	2.0	0	0.0	1	0.6	<0.01*
5-7 days	24	100.0	10	20.4	12	14.0	46	28.9	
More than 7 days	0	0.0	38	77.6	74	86.0	112	70.4	
Fever in Clinical Examination (F)									
100-102	11	45.8	32	65.3	43	50.0	86	54.1	0.15
102.1-104	13	54.2	17	34.7	43	50.0	73	45.9	
More than 104	0	0.0	0	0.0	0	0.0	0	0.0	
HB of patient									
Less than 7 gm/dl	0	0.0	0	0.0	3	3.5	3	1.9	0.26
7-10 gm/dl	19	79.2	28	57.1	45	52.3	92	57.9	
10-12 gm/dl	4	16.7	18	36.7	32	37.2	54	34.0	
More than 12 gm/dl	1	4.2	3	6.1	6	7.0	10	6.3	
TLC of patient									
Less than 4000/cumm	14	58.3	20	40.8	25	29.1	59	37.1	0.04*
4000-11000/cumm	10	41.7	27	55.1	52	60.5	89	56.0	
More than 11000 cumm	0	0.0	2	4.1	9	10.5	11	6.9	
Platelets of Patient									
Less than 50000/cumm	0	0.0	0	0.0	1	1.2	1	0.6	0.14
50000-100000/cumm	6	25.0	3	6.1	10	11.6	19	11.9	
100000-150000 /cumm	8	33.3	14	28.6	17	19.8	39	24.5	
More than 150000	10	41.7	32	65.3	58	67.4	100	62.9	
Day of defervescence									
1 to 4 days	2	8.3	4	8.2	8	9.3	14	8.8	0.97
5 to 7 days	22	91.7	45	91.8	78	90.7	145	91.2	
Duration of hospital stay									
Less than 7 days	8	33.3	42	85.7	54	62.8	104	65.4	<0.01*
7days-14days	16	66.7	7	14.3	28	32.6	51	32.1	
More than 14 days	0	0.0	0	0.0	4	4.7	4	2.5	

*p<0.05 was considered statistically significant using Pearson Chi Square test

Table 2 gives the association of cost of antibiotic therapy with clinical parameters, results showed among samples with more than 40,000 cost on antibiotic therapy 40 (46.5%) found with 7-14 days duration of fever at admission, 54 (62.8%) uses IV ceftriaxone before culture, 56 (65.1%) have 5-7 days duration of therapy before culture results, 82 (95.3%) were XDR in blood culture sensitivity, 81 (94.2%) uses IV meropenem antibiotic after culture results, 74 (86%) have more than 7-days duration of therapy after culture

sensitivity, 43 (50%) have 102.1 – 104 fever in clinical examination, 45 (52.3%) have 7-10 gm/dl Hb, 52 (60.5%) found with 4000 – 11000 / cumm TLC counts, 58 (67.4%) found with more than 150000 / cumm platelet counts, 78 (90.7%) having 5 – 7 days of defervescence, and 28 (32.6%) have 7 – 14 days of stay in hospital, Pearson Chi Square test showed a significant association of duration of fever at admission, use of antibiotic before culture, report of blood culture sensitivity, antibiotic use after culture results, duration of therapy after culture sensitivity, TLC of patients, and duration of hospital stay with cost of antibiotic therapy, $p<0.05$. Table 3 gives the results of logistic regression analysis to model the cost of antibiotic therapy with the help of clinical parameters, results showed urban samples were 0.29 times less likely for higher cost, increase in duration of fever at admission will increase the cost 5.73 times, XDR samples found 13.5 time more likely for higher cost, and TLC between 4000 – 11000/mm^3 gives negative association with higher cost.

Table 3: Modeling on higher cost of antibiotics using binary logistic regression

Variables	B	S.E.	Wald	df	P value	Odds Ratio	95% CI	
							Lower limit	Upper limit
Residence								
Urban	-1.25	0.34	13.78	1.00	<0.01*	0.29	0.15	0.55
Duration of fever at admission								
7-14 days	0.43	0.74	0.34	1.00	0.56	1.54	0.36	6.53
more than 14 days	1.75	0.77	5.17	1.00	0.02*	5.73	1.27	25.83
Report of blood culture sensitivity								
XDR	2.60	0.57	21.22	1.00	<0.01*	13.51	4.46	40.90
Duration of therapy aster culture sensitivity								
5-7 days	-0.37	.37	1.00	1.00	032	0.69	.33	1.43
More than 7 days	-1.05	.70	2.21	1.00	0.14	0.35	.09	1.39
TLC of patient								
4000-11000/cumm	-1.81	0.82	4.82	1.00	0.03*	0.16	0.03	0.82
More than 11000 cumm	-1.16	0.81	2.06	1.00	0.15	0.31	0.06	1.53
Duration of hospital stay								
7 days-14 days	0.12	0.34	0.12	1.00	0.73	1.13	.58	2.21

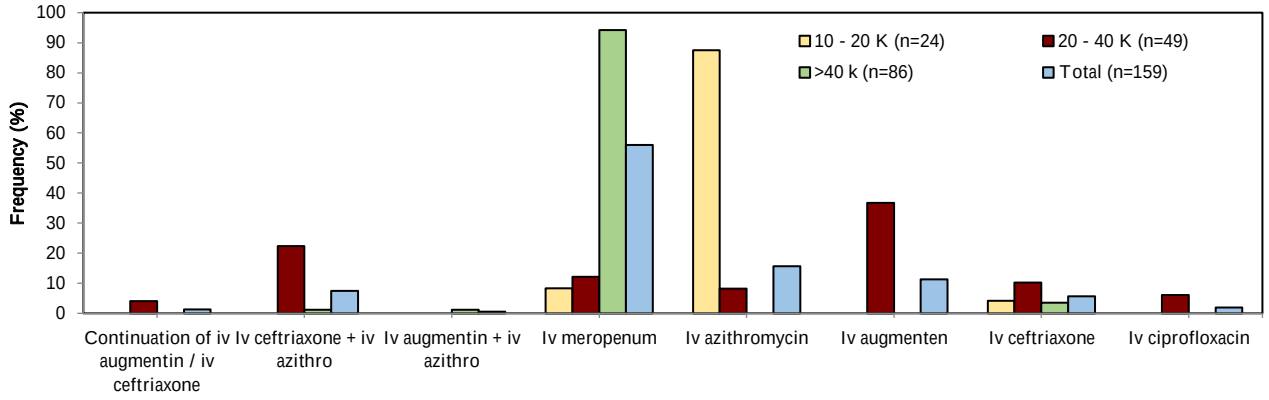

Figure 2: Relationship of cost with use of intravenous meropenum

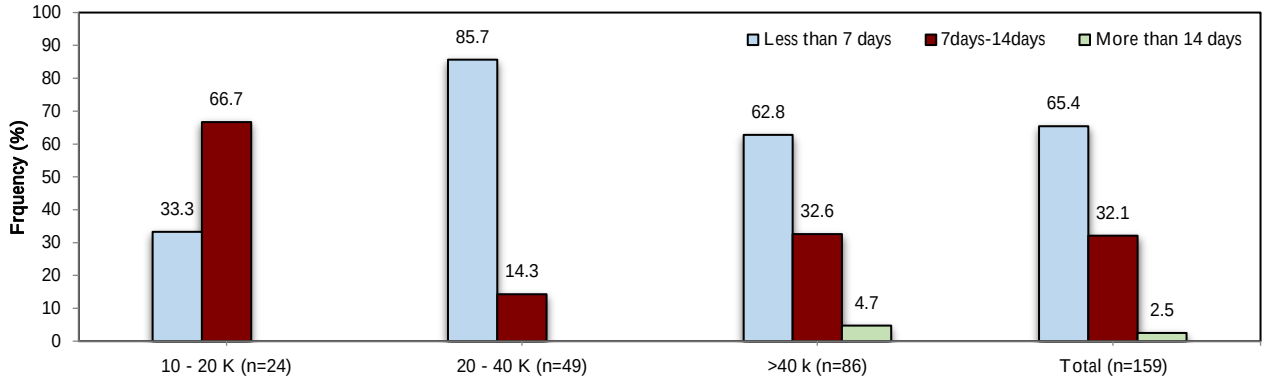

Figure 3: Relationship of hospital stay with cost of antibiotic therapy

DISCUSSION

Understanding of the household factors and typhoid disease burden is essential for making policy decisions, creating awareness regarding disease control, prevention and vaccination.

Predominant affected population in our study were males (62.3%) with mean age 7.5 years. Difference in exposure, rates of transmission, biological differences and immune response against infections between males and females result in variable clinical presentations of infections.[11] Susceptibility of males to infectious illness is higher, a phenomenon partially explained by observation of Th1 protective immune response in females.[12]

Majority of the parents of studied children had decrease literacy status, an observation which correlate with a previous study on association parental literacy with under 5 malnutrition and found that parental education especially higher maternal literacy status is directly proportional to better health and nutritional status of children under five.[13]

The commonly practiced household treatment for water is boiling to kill pathogens and make it microbiologically safe for drinking.[14] This study showed immense lack of boiled water consumption (5.7%) among culture positive enteric fever patients.

An important public health initiative to prevent bacterial infections and to minimize infectious illness complications is vaccination[15] (reference). In current study very few study subjects were vaccinated against typhoid (1.9%) suggesting logistical obstacles, inefficient health worker attitudes, parental awareness, myths and education and the influence of religious commodities[16]. Average rural monthly pay scale in Pakistan as per Pakistan Bureau of Statistics (2016).[17] was reported 30,110.000 while average urban monthly income in Pakistan was reported as 41,545.000 in 2019.[18]

As the cases of XDR enteric fever is on the rise, adding to parental anxiety and financial burden. Our study showed that majority of our participants antibiotic treatment cost >40,000 PKR, an immense financial burden where per capita monthly income is not that high. Lengthy duration of fever before admission, use of injectible 1st line antibiotics for fever add to the cost of treatment. Pakistan comes under lower middle – income countries as per new world bank country classifications by income level.[19] Pakistan have nominal GDP per capita of $1,543 in 2020-21 making us ranked 154th in the world.[20]

Patients with pure urban dwelling showed less treatment cost for XDR, an observation that is linked to better health awareness, early accessible medical care and better compliance.[20,21]

Lengthy duration of fever at presentation also accounted for increase cost in our study, a finding consistent with similar study on febrile infections cost in India in children < five year of age conducted by Pradhan HS and colleagues.[22]

Antibiotic use after blood culture sensitivity with duration of antibiotic therapy showed strong association with costing reflecting that XDR Enteric fever management put heavy load on the pocket of parents/caregivers. This observation is consistent with a comprehensive study done by Nelly Mejia and colleagues in Pakistan in 2020 where they studied cost of illness of Typhoid and paratyphoid fever.[23]

Limitation of this study was being single centered, urban setting and not including non-medical costs in terms of parental work loss and child school absenteeism.

CONCLUSIONS

XDR salmonella infection has imposed a considerable amount of burden in terms of medical cost of antibiotic treatment. Practicing appropriate hygienic measures, seeking early medical care and mass vaccination against typhoid can limit the expenditures of this dangerous infection.

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