MULTIPLE DRUG RESISTANCE, EXTENSIVELY DRUG RESISTANCE TYPHOID FEVER AND DISEASE SPECTRUM IN PEDIATRIC POPULATION PRESENTING WITH FEVER WITHOUT LOCALIZING SIGNS (FWLS): A CROSS SECTIONAL STUDY

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Abstract

Background: One of the most recurring infectious diseases in the pediatric population of Pakistan is Typhoid fever. Unmonitored overuse of antibiotics has led to multiple outbreaks of multidrug-resistant (MDR) and extended drug-resistant (XDR) typhoid in the country. This study aims to depict the typhoid disease spectrum in the pediatric population presenting with fever without localized signs (FWLS)

Objective: To find out the frequency of typhoid in patients presenting with high grade fever and to find the multiple drug resistance (MDR) and extensively drug resistance (XDR) in a diagnosed case of typhoid.

Methods: This cross sectional study was conducted at Pediatrics department Naseer Teaching Hospital, Peshawar. All the participants were enrolled using non-probability sampling, their symptoms, clinical signs, blood culture and culture sensitivities were recorded. Data was analyzed using the statistical package for social science (SPSS) version 21.

Results: A total of 166 participants were included in the study. Out of these 71 patients significantly had a positive blood culture. Fever have shown significant relation with culture report (p value = <0.001) .The study on antibiotic sensitivity across different generations revealed that Trimethoprim, Ceftriaxone, Chloramphenicol, and Ampicillin displayed lower sensitivity. In contrast, Azithromycin, Meropenem, and Imipenem exhibited greater sensitivity to the bacteria being studied. Most of patients were XDR 35 (49.3%).

Conclusion: Since in pediatric population fever is a very common complaint, typhoid disease should be suspected and ruled out as a differential especially in patients presenting with fever without localizing signs (FWLS). Also, in order to counter extensive drug resistance the importance of planned appropriate dosing of antibiotics must be emphasized at all levels of healthcare.

Key Words: Typhoid, Fever without localizing signs (FWLS), Fever, Pediatric, MDR, XDR

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Introduction

One of the most repetitive complaints faced by physicians in the pediatric population is fever, about 1/5th of which has no apparent cause[1].Fever is defined as the rectal temperature of more than 38.1°C whereas the normal temperature for the pediatric population varies between 36.1°C to 37.8°C.[2-4] Fever can be divided as fever with/ without focus, whereas fever without focus can last less than 7 days and is further organized into a fever of unknown origin (FUO) and fever without localizing signs (FWLS).[5] In such cases where the patient presents absent localizing symptoms, rapid assessments and investigations are performed for life-saving treatments especially since the target population constitutes newborns and infants.[2-5]

Diagnosing the cause of fever and essentially such a presentation is a big hurdle in the management of such patients.[6] Studies show how most of these cases do not have a defined etiology but the lesser half is constituted majorly by infectious causes, with malignancies and inflammatory diseases being the lesser accounted ones. One such infectious cause is represented by typhoid disease[7-8].

Typhoid disease, also called Enteric fever, is caused by Salmonella typhi and para typhi. In the usual presentation, the patient presents with fever and a couple of other common symptoms like abdominal pain and constipation. [9-11] However, in some cases the other symptoms might be absent, and thorough blood work is required to narrow down and diagnose the etiology. For an accurate diagnosis, a blood culture with salmonella isolated on it is pertinent.[10-11]

The disease if untreated has very high mortality and morbidity.[12] In the year 2017 alone, more than 75,000 deaths were reported in South Asia with more than five thousand being reported from Pakistan alone.[11-14] In the last five years, numbers haven't improved much and the disease's morbidity and mortality are still very high.[14] A major reason for these numbers is the emergence of drug-resistant organism species and decreased to no sensitivity to the traditional first-line and even some 2nd line antibiotic drugs.[13-14] With outbreaks of Multi-Drug Resistant (MDR) and Extensively Drug-Resistant (XDR) disease in the last few years over the world including Pakistan; its spectrum in the pediatric population warrants a closer look.

In Pakistan, there have been multiple studies conducted to study and report the incidence of drug-resistant typhoid fever. [15-16] However, a study that correlates variable presentation, such as fever without localizing signs and Salmonella typhoid detection in blood culture to both Multi-Drug Resistant (MDR) and Extensively Drug-Resistant (XDR) disease hasn't been done as per our knowledge. Along with presenting the spectrum of such patients in the pediatric population, we also present their sensitivity to various classes of antibiotics

2. Methods

2.1. Participants and study design

A cross sectional study conducted at Pediatrics department Naseer Teaching Hospital, Peshawar from October 2019 to October 2021. Assuming 50% pediatric population presenting with fever without localizing sign since there is no former estimates available in Pakistan With a 95% confidence interval, and a precision of ±7.62 the estimated minimum sample size was calculated was found to be 166. Non probability consecutive sampling technique was used. All patients presented with Fever without Localizing Signs (FWLS) were selected for this study. Inclusion criteria of sample was fever of above 100 F, willing to give sample for culture and sensitivity. Exclusion criteria was not willing to give sample for culture and sensitivity. Multidrug-resistant typhoid (MDR-Typhoid) strains are those resistant to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol) whereas XDR Typhoid are resistant to antibiotics including ampicillin, ceftriaxone, chloramphenicol, ciprofloxacin, and trimethoprim-sulfamethoxazole

2.2. Study procedure

This study was approved by ethical committee of Gandhara University. Study was carried out according to the Helsinki Declaration.

2.3. Statistical analysis

Data was entered and analyzed by using the statistical package for social science (SPSS) version 21. Mean ± SD was calculated for quantitative variables and frequency and percentages were calculated for qualitative variables. Chi square test was used for comparison.

Blood samples were taken for culture and sensitivity which were sent to laboratory specifically for study resistance of XDR and MDR

3. Result:

Total of 166 patients with fever without localizing sign enrolled, mean age of patients was 6.60 ± 3.68 years male were 107 (64.5%). 49 (29.5%) individual suffered from abdominal pain while 103 (62.0%) patients Coated tongue (Table 01).

Out of which 71 (42.77%) culture positive for Salmonella typhi, paratyphi, and gallinarum (Table 02).

Table 1. The demographic characteristics of study participants and Classification of Typhoid Fever Cases by Drug Resistance.

		Frequency/percentage	+ve Blood culture	-ve Blood culture	X^2,p value
Age	0-5 years	59 (35.5)	37 (62.7)	22 (37.3)	1.221, 0.543
	5-10 years	66 (39.8)	35 (53.0)	31 (47.0)	
	Above 10 years	41 (24.7)	23 (56.1)	18 (43.9)	
Sex	Male	107 (64.5)	61 (57.0)	46 (43.0)	0.006, 0.939
	Female	59 (35.5)	34 (57.6)	25 (42.4)	
Complaint	Abdominal pain	49 (29.5)	29 (59.2)	20 (40.8)	0.109, 0.742
	Constipation	28 (16.9)	14 (50.0)	14 (50.0)	0.719, 0.396
	Diarrhea	37 (22.3)	19 (51.4)	18 (48.6)	0.672, 0.412
Clinical Sign	Febrile	149 (89.8)	78 (52.3)	71 (47.7)	14.155, < 0.001
	Coated tongue	103 (62.0)	54 (52.4)	49 (47.6)	2.556, 0.110
	Icteric eye	5 (3.0)	0 (0.0)	5 (100.0)	6.898, 0.009
	Visceromegaly	6 (3.6)	4 (66.7)	2 (33.3)	0.227, 0.634
Resistant level	Non resistant	6(8.45)	-	-	-
	MDR-typhoid	30(42.25)	-	-	-
	XDR-Typhoid	35(49.3)	-	-	-
Organism	Salmonella typhi	71(42.77)	-	-	-
	Salmonella gallinarum	-	-	-	-
	Salmonella paratyphi	-	-	-	-
	Not detected	95(57.22)	-	-	-

Among 71 Salmonella isolated patients, 35 (55.6 %) were resistant to ceftriaxone whereas chloramphenicol 39 (86.7%), Ciprofloxacin 47 (71.2%) and Co-trimizole 60 (84.5%) resistant respectively (Table 03).

Table 02: Spectrum of antibiotics sensitivity and resistant

Antibiotics	Sensitive	Resistant
Ampicillin (5/71)	1 (20.0)	4 (80.0)
Augmentin (66/71)	25 (37.87)	41 (62.12)
Azithromycin (66/71)	65 (98.5)	01 (1.5)
Amikacin (33/71)	30 (90.9)	03 (9.1)
Cefotaxime (37/71)	17 (45.9)	20 (54.1)
Ceftriaxone (63/71)	28 (44.4)	35 (55.6)
Cefepime (38/71)	16 (42.1)	22 (57.9)
Cefixime (50/71)	19 (38.0)	31 (62.0)
Ceftazidime (56/71)	23 (41.1)	33 (58.9)
Chloramphenicol (45/71)	6 (13.3)	39 (86.7)
Ciprofloxacin (66/71)	19 (28.8)	47 (71.2)
Co-trimizole (71/71)	11 (15.5)	60 (84.5)
Gentamicin (24/71)	22 (91.7)	02 (8.3)
Imipenem (71/71)	71 (100.0)	0 (0.0)
Meropenem (71/71)	71 (100.0)	0 (0.0)
Tazocin (42/71)	20 (47.6)	22 (52.4)
Trimethoprim (18/71)	1 (5.6)	17 (94.4)

Discussion

The increase in the incidence of MDR and XDR typhoid disease across the world presents an alarming situation for public health, especially in developing countries.[13,14] In the last few years majority of the cases reported and hence the burden of typhoid disease has mostly been reported in the underdeveloped countries of Asia and Africa.[17] The impact of typhoid fever has multiplied in the last few years since the emergence of drug resistance to even 2nd generation antibiotics.[13,18] Such cases have also been reported in Pakistan and are monitored closely by the Centers for disease control and prevention (CDC).[11,12]

In our study, such cases were studied where the pediatric population presents with only complaint of fever and are later diagnosed on blood culture for drug-resistant Typhoid disease [19,20]. Various demographic variables like age, gender, and symptoms like abdominal pain, constipation, and diarrhea were studied and their relationship with positive and negative blood cultures was assessed. The most pertinent association was the relationship between febricity and blood culture, displaying how almost half of the febrile patients had a positive blood culture. Among other significant signs was the icteric eye, which even though wasn't very common all 5 patients who presented with it had a positive blood culture.

Three organisms were detected on the positive blood cultures, primarily including Salmonella typhi, while the two indifferent samples contained Salmonella gallinarum and Salmonella paratyphi. It may be of note to mention that the other two samples were both detected in males. In multiple previous studies, Salmonella Typhi has been identified as the most common organism [16,21]

In terms of antibiotic sensitivity, our results were comparable to the multitude of previously conducted studies.[12-18] Antibiotic sensitivities were also studied and the majority of the heavily used antibiotics were found to be ineffective and majorly resistant, some of the heavily resisted antibiotics included ampicillin, trimethoprim, cefixime, ceftazidime, cefepime, and augmentin. Out of the group studied, Azithromycin, Gentamicin, Imipenem, Meropenem, and amikacin were found to be most effective.

There are multiple studies available on XDR and MDR typhoid disease and sensitivity to different generations of antibiotics[14] .But with respect to assessment based on clinical signs and diagnosis based on blood cultures, this study provides a new and close outlook on MDR, XDR typhoid disease spectrum in the pediatric population who presented with Fever without localized sign (FWLS). As there is no actual way to completely stop the use of antibiotics, careful and strict guidelines must be followed for use of these higher-generation antibiotics to limit the decline in sensitivity. The present findings also support typhoid as the main differential for pediatric patients presenting with fever without localizing signs. However, the majority of the studies state no viable cause for such a presentation. Considering the present study's limitations re-investigation is a must.

What makes this study limited is its cross-sectional nature and somewhat restricted sample size. Non-adherence with the advised dose and use of multiple antibiotics may be another reason. Despite these limitations, the study provides an initial observation of the MDR, and XDR typhoid disease spectrum in a pediatric population presenting with Fever without any pertinent clinical sign

Conclusion:

One of the major threats we found in our study was the multi-Drug resistance (MDR) and extensively-Drug resistance (XDR) in the treatment of typhoid. Out of multiple antibiotics the most sensitive drug were Meropenem and Imipenem while in resitance category Trimethoprim was on the top.

Limitations: The sample was only taken from one teaching hospital

Recommendations: In pediatric population a patient with fever without localizing signs should investigate for typhoid fever.

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References:

1] Chong CY, Allen M. INVITED ARTICLE CHILDHOOD FEVER. Singapore Med J. 1996;37:96-100.

2] Bilenko N, Tessler H, Okbe R, Press J, Gorodischer R. Determinants of antipyretic misuse in children up to 5 years of age: a cross-sectional study. Clinical therapeutics. 2006 May 1;28(5):783-93.

3] Kuzmanović S, Roncević N, Stojadinović A. Fever without a focus in children 0-36 months of age. Medicinski pregled. 2006 Mar 1;59(3-4):187-91.

4] Park JW. Fever without source in children: recommendations for outpatient care in those up to 3. Postgraduate Medicine. 2000 Jan 1;107(2):259-66.

5] Ritz N. Fever without focus and fever of unknown origin in childhood. Praxis. 2013 Jan 1;102(3):157-64.

6] Chancey RJ, Jhaveri R. Fever without localizing signs in children: a review in the post-Hib and postpneumococcal era. Minerva pediatrica. 2009 Oct 1;61(5):489-501.

7] Baraff LJ. Management of fever without source in infants and children. Annals of emergency medicine. 2000 Dec 1;36(6):602-14.

8] Waddle E, Jhaveri R. Outcomes of febrile children without localising signs after pneumococcal conjugate vaccine. Archives of disease in childhood. 2009 Feb 1;94(2):144-7.

9] Mintegi S, Benito J, Pijoan JI, Marañon R, Peñalba A, Gonzalez A, Muñoz G, Luaces C, Claret G. Occult pneumonia in infants with high fever without source: a prospective multicenter study. Pediatric emergency care. 2010 Jul 1;26(7):470-4.

10] Carstairs KL, Tanen DA, Johnson AS, Kailes SB, Riffenburgh RH. Pneumococcal bacteremia in febrile infants presenting to the emergency department before and after the introduction of the heptavalent pneumococcal vaccine. Annals of emergency medicine. 2007 Jun 1;49(6):772-7.

11] Chatham-Stephens K, Medalla F, Hughes M, Appiah GD, Aubert RD, Caidi H, Angelo KM, Walker AT, Hatley N, Masani S, Nash J. Emergence of extensively drug-resistant Salmonella Typhi infections among travelers to or from Pakistan—United States, 2016–2018. Morbidity and Mortality Weekly Report. 2019 Jan 1;68(1):11.

12] Rasheed MK, Hasan SS, Ahmed SI. Extensively drug-resistant typhoid fever in Pakistan. The Lancet Infectious Diseases. 2019 Mar 1;19(3):242-3.

13] Manas P, Arfat GM, Girish S. MDR and XDR typhoid fever-a threat for the current decade?. The Pan African Medical Journal. 2021;38.

14] Appiah GD, Chung A, Bentsi-Enchill AD, Kim S, Crump JA, Mogasale V, Pellegrino R, Slayton RB, Mintz ED. Typhoid outbreaks, 1989–2018: implications for prevention and control. The American journal of tropical medicine and hygiene. 2020 Jun;102(6):1296.

15] Laghari GS, Hussain Z, Hussain SZ, Kumar H, Uddin SM, Haq A. Antimicrobial susceptibility patterns of Salmonella species in Southern Pakistan. Cureus. 2019 Apr 3;11(4).

16] Umair M, Siddiqui SA. Antibiotic susceptibility patterns of Salmonella typhi and Salmonella paratyphi in a tertiary care hospital in Islamabad. Cureus. 2020 Sep 3;12(9).

17] Qamar FN, Yousafzai MT, Dehraj IF, Shakoor S, Irfan S, Hotwani A, Hunzai MJ, Thobani RS, Rahman N, Mehmood J, Hemlock C. Antimicrobial resistance in typhoidal Salmonella: surveillance for enteric fever in Asia project, 2016–2019. Clinical Infectious Diseases. 2020 Nov 1;71(Supplement_3):S276-84.

18] Zakir M, Khan M, Umar MI, Murtaza G, Ashraf M, Shamim S. Emerging trends of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Salmonella Typhi in a tertiary care Hospital of Lahore, Pakistan. Microorganisms. 2021 Nov 30;9(12):2484.

19] Wattal C, Goel N. Pediatric blood cultures and antibiotic resistance: an overview. The Indian Journal of Pediatrics. 2020 Feb;87:125-31.

20] Joshi RD, Khadka S, Joshi DM, Shrestha B, Dangal G, Acharya KP, Shrestha S, Dongol Y. Antimicrobial sensitivity trend in blood culture positive enteric fever.

21] Dharmapalan D, Shet A, Yewale V, Sharland M. High reported rates of antimicrobial resistance in Indian neonatal and pediatric blood stream infections. Journal of the Pediatric Infectious Diseases Society. 2017 Sep 1;6(3):e62-8.