Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023 || PP. 241-247

https://doi.org/10.55544/jrasb.2.2.34

Drug Utilization Study in Pediatric Patients with Typhoid Fever

Prakruti K. Jadav[1], Pinal H. Sukharamwala[2] and Nirmal T. Mehta[3]

[1]Assistant Professor, C.K. Pithawalla Institute of Pharmaceutical Science and Research, Dumas Road, Surat-395007, Gujarat, INDIA.

[2]Assistant Professor, C.K. Pithawalla Institute of Pharmaceutical Science and Research, Dumas Road, Surat-395007, Gujarat, INDIA.

[3]Assistant Professor, C.K. Pithawalla Institute of Pharmaceutical Science and Research, Dumas Road, Surat-395007, Gujarat, INDIA

[2]Corresponding Author: pinalckpipsr@gmail.com

www.jrasb.com || Vol. 2 No. 2 (2023): April Issue

Received: 12-04-2023	**Revised:** 03-05-2023	**Accepted:** 13-05-2023

ABSTRACT

Drug utilization study was observational concurrent study in which 75 pediatric patients with culture or serologically proven typhoid fever were enrolled from 5 private children hospitals of Surat region during September to December, 2021. Information like age, sex, weight, treatment history, presenting symptoms, haematological and diagnostic test data, pattern of use of antibiotic including type, route, dose, frequency, duration and response of patient to drug in term of fever clearance time were collected in patient data collection form. The typhoid fever was predominantly found in patients of age between 2 to 10 years. Ceftriaxone was used in 86.6% of patients. Only 18.3% patients had received dose of Ceftriaxone in range recommended by IAP and WHO i.e. between 75-100mg/kg. Rest patients had received drugs like cefixime, azithromycin, ofloxacin, ciprofloxacin, gatifloxacin or chloramphenicol alone or in combination. The clinical resistance with ceftriaxone was observed in 6% of patients. Mean fever clearance time with ceftriaxone used as single therapy was found to be 3.30 days, which was not significantly different from that of those patients who received its combination with other drugs. Anemia, moderate thrombocytopenia and leukocytosis were found in 50.7%, 9.3% and 14.7% of patients respectively. The predominant features were fever (100%), anorexia (63.33%) followed by cough (25.33%), abdominal pain (24%) and diarrhea (18.6%). In Surat region, ceftriaxone is commonly used antimicrobial in hospitalized children with typhoid fever. Treatment protocol is not matched with IAP guideline but matched with trend of antibiotic used in another region. Indiscriminate use of drug is one of the important factors leading to drug resistance.

Keywords- Typhoid fever, Drug utilization study, Pediatric, Response to antibiotic.

I. INTRODUCTION

Typhoid fever is a systemic infection caused by the bacterium Salmonella Typhi (S.Typhi) and Salmonella Paratyphi (S. Paratyphi) which causes bacteremia and inflammatory destruction of the intestine and other organs, is endemic in most countries especially Indian subcontinent and South East Asia [1]. The best global estimates are of at least 21.6 million cases of typhoid fever each year with 200,000 deaths [2]. The incidence of typhoid in endemic areas is typically considered to be low in the first few years of life, peaking in school-aged children and young adults and then falling in middle age [3].

Historically, the infection was treated with chloramphenicol, ampicillin, or trimethoprim-sulfamethoxazole. The first major epidemic of multidrug-resistant S. Typhi was reported in Mexico. S. Typhi resistant to chloramphenicol was reported from Britain in 1905 and from India in1972 [4]. Since then, multidrug-resistant strains are endemic in many parts. The use of gold standard antimicrobial drugs like chloramphenicol, ampicillin, and co-trimoxazole become infrequent. Fluoroquinolones when first introduced in the early 1990s were very effective but the past decade has seen a progressive increase in MIC of ciprofloxacin and quinolone-resistant strains of S. Typhi reported [5]. They are also restricted to use in children [6].

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023 || PP. 241-247

https://doi.org/10.55544/jrasb.2.2.34

Ceftriaxone, a third-generation cephalosporin, is highly effective against S. Typhi, recommended by WHO, and has become the standard of care for the treatment of typhoid fever in many parts of the world. There has been a report of high-level resistance to ceftriaxone in S. Typhi in Bangladesh, the Philippines, and Vietnam Clinical strains with higher Minimum Inhibitory Concentration (MIC) are found in India [7, 8].

Antibiotic resistance is further accelerated due to the irrational use of antibiotics. The high degree of resistance to other first-line drugs probably reflects their overuse or irrational use in the treatment of typhoid as well as in other unrelated infections [9]. Drug utilization studies can document the extent of inappropriate prescribing of drugs (e.g. antibiotics, NSAIDs) and even the associated adverse clinical, ecological, and economic consequences [10].

Therefore objectives of the study are to evaluate the drug utilization pattern of antibiotics, to check its rationality, to evaluate response to antimicrobial therapy, and to study clinical and laboratory profiles in pediatric patients with typhoid fever.

II. METHOD

In a concurrent study Patients of age between 1 to 17 years who had positive blood culture, Widal test, or Typhidot test were included in the study. Patients with comorbidities or whose diagnosis was based on the clinical ground were excluded from the study. Information like age, sex, weight, treatment history, presenting symptoms, hematological and diagnostic test data, pattern of use of antibiotic including type, route, dose, frequency, duration, and the response of the patient to the drug in terms of fever clearance time was collected in the patient data collection form.

2.1 Definition

Response: It is defined as the patient becoming afebrile within 5 days of starting the treatment.

Fever clearance time: Time from start of treatment until the body temperature reached ≤37.5◦C and remains at ≤37.5◦C for 48 h [11].

2.2 Analysis of data

Data were grouped as required using Epi-info version 7 software. Statistical Analysis was done using PSPP software. Independent sample t-test was used for comparison of mean fever clearance time of patients who had taken antibiotics before hospitalization to that of those who had not taken antibiotics and for comparison of mean fever clearance time of patients who had taken ceftriaxone alone and that of those who had taken a combination of antibiotics. A p-value less than 0.05 were considered significant.

III. RESULT

Total 75 cases were studied.

3.1 Age and gender distribution

The mean age of patients was 6.36 years (SD ±3.26). The cases were predominantly in the age group 2-5 years (41.3%) and then 6-10 years (40%) (Table 1). More than half (58.5%) were males (Table 2). The majority of male patients from the studied cases were in the age group 2-5 years and 6-10 years and the majority of female patients are in the age group 2-5 years (Figure1).

Table 1: Age distribution

Age(years)	Number of patients	Percentage
≤1	3	4%
2-5	31	41.3%
6-10	30	40%
11-15	11	14.7
>15	0	0%

Table 2: Gender distribution

Gender	Number of patients	Percentage
Male	44	58.7%
Female	31	31.3%

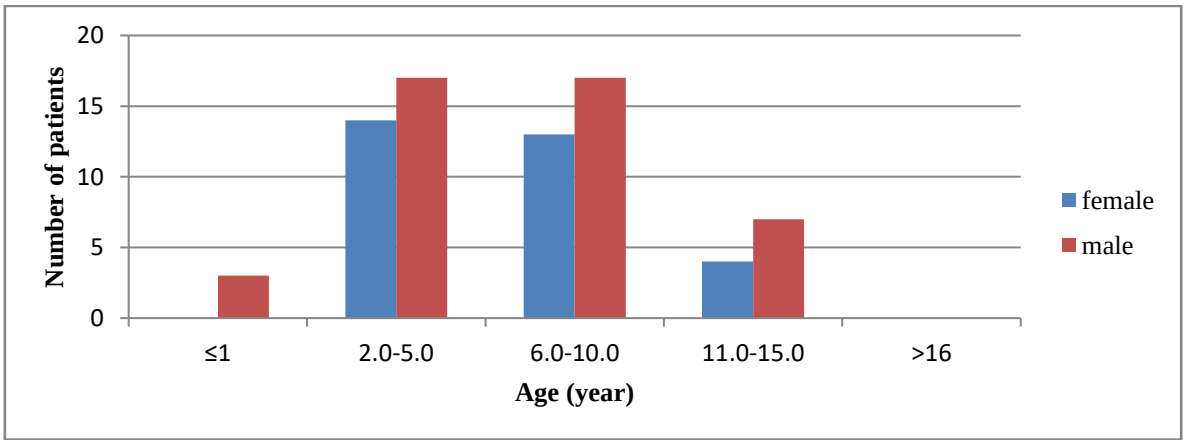

Figure 1: Number of male and female in each age group

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023 || PP. 241-247

https://doi.org/10.55544/jrasb.2.2.34

3.2 Drug utilization pattern

3.2.1 Drug used before hospitalization

The majority of patients had taken antibiotics from local doctors. 12.2% of patients had not taken antibiotics before hospitalization. 25% of patients had taken antimicrobial while 10.9% of patients had taken antimalarial (Table 3).

Table 3: Utilization of antibiotic before hospitalization

Antibiotic	Number of patients	Percentage
Not known	32	43.2%
Not taken antibiotic	9	12.2%
Amoxicillin+clavulanic acid	5	6.8%
Azithromycin	5	6.8%
Ofloxacine	5	6.8%
Cefixime	4	5.4%
Chloroquine	4	5.4%
Pyrazinamide+sulfamethxazole	3	4.1%
Cefpodoxime	2	2.7%
Cefuroxime	2	2.7%
Arteether	1	1.4%
Azithromycin	1	1.4%
Cephalexin	1	1.4%
Doxycycline	1	1.4%

3.3 Overall antibiotic used during hospitalization

As shown in Table 4, among the drug used for treatment during hospitalization, ceftriaxone emerged as the most commonly used (77.3%). Total 7 patients were treated with ceftriaxone including beta-lactamase inhibitor. The rest of the patients were treated with other antibiotics singly or in combination.

Table 4: Overall utilization of antibiotics during hospitalization

Antibiotics	Number of patient	Percentage
Ceftriaxone	58	77.3%
Ceftriaxone + tazobactam	4	5.3%
Ceftriaxone+sulbactam	3	4.0%
Cefuroxime	2	2.7%
Ceftriaxone+azithromycin	1	1.3%
Ceftriaxone+cefixime	1	1.3%
Ceftriaxone+chloramphenicol	1	1.3%
Ceftriaxone+ciprofloxacin	1	1.3%
Ceftriaxone+ofloxacin	1	1.3%
Ceftriaxone+tazobactam+azithromycin	1	1.3%
Gatifloxacin	1	1.3%
Ofloxacin	1	1.3%

More than half of the patients received a dose of ceftriaxone in the range of 76 to 100mg/kg (WHO recommended dose of ceftriaxone is 50-75 mg/kg/day). In 13(17.33%) of cases, antibiotics were shifted to another antibiotic at the 3rd day (mean) (range 2-5 days). Among them, 11 patients have received ceftriaxone previously. Other antibiotics used were azithromycin, chloramphenicol, ciprofloxacin, ofloxacin, and cefixime either single or in combination.

3.4 Antibiotic used after discharge

The mean duration of hospitalization was 4.61 days (SD ± 1.83, range 2-12). The table shows antibiotics used after discharge. The mean duration of receipt of antibiotics after hospitalization was 3.73, SD ± 1.91days (range 2-5 days). Table 5 shows antibiotics used after discharge.

Table 5: Antibiotic use after discharge

Antibiotics	Number of patients	percentage
Ceftriaxone	22	31.0%
Cefixime	15	20.0%
Ceftriaxone + cefixime	10	13.3%
Cefixime + azithromycin	10	13.3%
Ceftriaxone + tazobactam + cotrimoxazole	3	3.9%
Ceftriaxone + tazobactam	3	3.9%
Cefpodoxime	2	2.7%
Azithromycin	1	1.3%
Ceftriaxone+ chloramphenicol	1	1.3%
Ciprofloxacin+ azithromycin	1	1.3%

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023 || PP. 241-247

https://doi.org/10.55544/jrasb.2.2.34

3.5 Response pattern

As shown in Table 6 fever of 3 patients out of 58 patients treated with ceftriaxone was not cleared within 6 days. Among them blood culture of one patient showed sensitivity to ceftriaxone but showed clinical resistance.

Table 6: Response to antibiotic

Antibiotic	Number of patients treated	Number of patients responded	Percentage
Ceftriaxone	58	55	94.82%
Ceftriaxone + tazobactam	4	4	100%
Ceftriaxone + sulbactam	3	3	100%
Cefuroxime	2	2	100%
Ceftriaxone + ofloxacin	1	1	100%
Ceftriaxone + cefixime	1	1	100%
Gentamicin	1	1	100%
Ceftriaxone + azithromycin	1	1	100%
Ceftriaxone + ciprofloxacin	1	0	100%

Mean FCT is shown in Table 7.

Table 7: Mean FCT

Antibiotic	Mean FCT (day)
Ceftriaxone	3.30
Ceftriaxone+tazobactam	3.36
Ceftriaxone+sulbactam	3
Cefuroxime	2.5
Ceftriaxone+ofloxacin	5
Ceftriaxone+cefixime	3
Gentamicin	4
Ceftriaxone+azithromycin	2

There was no significant difference in the mean FCT of a patient who received ceftriaxone and that of those who take a combination of antibiotics (p=0.308).

3.6 Laboratory finding and clinical features

Hemoglobin <11gm% was found in 50.7% of patients (Table 8). The platelet count is shown in Table 9. Leukocyte counts are shown in Table 10.

Table 8: Heamoglobin level

Hemoglobin (gm%)	Number of patient	Percentage
<11	38	50.7%
11-16	37	49.3%
>16	0	0

Table 9: Platelet count

Platelet count (lakh/cmm)	Number of patients	Percentage
<1.0	0	0%
1.0-1.4	7	9.3%
1.5-4.5	64	85.3%
>4.5	4	5.33

Table 10: Leukocyte count

Leukocyte (/cmm)	Number of patient	Percentage
<4000	5	6.7%
4000-11,000	59	78.7%
>11,000	11	14.7%

In 58 cases typhoid fever was confirmed by Widal test, in 15 cases typhoid fever was confirmed by typhoid test and in 2 cases typhoid and blood culture were done. All the patients had complained of fever for 4.43 days (SD ±2.75). Table 11 shows the clinical features of patients. Another predominant feature was anorexia followed by cough, abdominal pain, and diarrhea.

Table 11: Clinical feature in male and female.

Clinical feature	Male	Female	Total (%)	Percentage
Fever	44	31	75	100%
Vomiting	5	5	10	13.33%
Headache	5	5	10	13.33%
Abdominal pain	10	8	18	24%
Rash	1	0	1	1.33%
Diarrhea	6	8	14	18.6%
Constipation	5	6	11	14.66%
Cough	12	7	19	25.33%
Anorexia	34	18	52	63.33%

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023 || PP. 241-247

https://doi.org/10.55544/jrasb.2.2.34

IV. DISCUSSION

In the present study, typhoid fever was predominantly found in patients of age between 2 to 10 years. It was found that 10.9% of patients had taken antimalarial before diagnosis and hospitalization because of empirical diagnosis of typhoid fever as malaria.

The recent guideline for the treatment of typhoid fever in pediatric patients by the Indian Academy of Pediatrics (IAP) recommends treatment with third-generation cephalosporin e.g., Cefixime (dose 15-20mg/kg/day) for uncomplicated typhoid and ceftriaxone (dose 50-75 mg/kg/day) for severe typhoid fever as the first-line agent 12. In the present study, ceftriaxone is used in 86.6% of patients. 18.5% of patient had received dose between 50 to 75 mg/kg/day, 18.3% patient had received dose between 76-100mg/kg and 52.3% patient had received dose more than 100mg/kg/day. In other cases, ceftriaxone was used in combination with other drugs like ciprofloxacin, chloramphenicol, azithromycin, or cefixime. The protocol used is not matched with the IAP task force report but matched with the trend of antibiotic use reported by other authors 13. In 3 cases, there was no clinical improvement by 5 days and then azithromycin was started which is in accordance with the IAP report. In the other 10 cases, antibiotics were shifted on the 2nd or 3rd day.

Fluoroquinolones are not approved by the Drug Controller General of India to be used under 18 years of age unless the child is resistant to all other recommended antibiotics and suffering from a life-threatening infection. It was found that fluoroquinolones were used in four patients.

Polypharmacy is found to be low (the number of drugs per prescription is less than 3). However, ant-vomiting was used in 54.4% of patients while 13.33% of patients had complained of vomiting.

The clinical resistance (fever was not clear within 6 days) with ceftriaxone was observed in 6% of patients. The mean fever clearance time with ceftriaxone used as single therapy observed in the present study was 3.30 days. Results of our present study suggest that combination therapy may not be superior to single-drug therapy, as it was not observed that any significant difference in the mean FCT in those patients who received ceftriaxone alone or in combination with other drugs. Receipt of antibiotic therapy prior to admission was found no significant impact on mean FCT.

Anemia was found in about half of the patients. Anemia is attributed to myeloid maturation arrest, a decrease in the number of erythroblasts, and increased phagocytic activity of histiocytes in the bone marrow. Significant Thrombocytopenia (<1.0 lakh/cumm) was not there in any patient. Moderate thrombocytopenia (<1.5 lakh/cumm) was found in 9.3% of patients against one-third of the patient showing moderate thrombocytopenia in literature 14. The etiology of thrombocytopenia is uncertain. It may be due to bone marrow depression as organisms localize in the bone marrow. Buter et al suggested intravascular coagulation may account for the thrombocytopenia but cautioned that evidence was not conclusive. Leucopenia was found in 6.7% of patients while Leukocytosis was found in 14.7% of patients which is in accordance with the results of literature15. Platelet count and leukocyte count have no value in the early diagnosis of typhoid fever in children.

Fever was the main presenting feature in all the cases similar to other studies. Another common feature was anorexia which was found in 63.3% of patients. Abdominal pain and cough were found in 25.33% and 24% of patients respectively. Diarrhea (18.6%) was somewhat more common than constipation (14%). Vomiting and headache were reported in 13.33% of patients.

V. CONCLUSION

Typhoid fever continues to be a major health problem resulting in a significant number of children requiring hospitalization. It is predominantly founded in children of age between 2 to 10 years and is more common in males than females. In the Surat region, ceftriaxone is a commonly used antimicrobial in hospitalized children. The treatment protocol is not matched with Indian Pediatric Association guidelines for the treatment of typhoid fever in children but is matched with the trend of antibiotics used in other regions. Clinical resistance to ceftriaxone is found in the study. Indiscriminate use of the drug is one of the important factors leading to drug resistance.

Hematological investigations are poorly specific and of no value in the early diagnosis of typhoid fever in children. Fever, anorexia, abdominal pain, and cough are common symptoms found in a pediatric patient with typhoid fever.

Public Health investigations to minimize human carrier contact, improved personal hygienic measures including health care behavior strategies, typhoid vaccination, and rational antibiotic selection based on sensitivity patterns to proven resistance will help to reduce the morbidity and mortality of this global health problem.

LIMITATION

The main limitation of study is its inability to detect a difference in efficacy of various antimicrobial regimens chiefly single versus combination therapy may be due to the small sample size.

ACKNOWLEDGEMENT

Extremely thankful to Dr. Hitesh Jariwala for giving me permission to carry out study in his hospital. I am also thankful to Shashibhai, Shital and Mittal for

ISSN: 2583-4053

Volume-2 Issue-2 || April 2023 || PP. 241-247

https://doi.org/10.55544/jrasb.2.2.34

their support in the hospital. I extend my thanks to Dr. Digant Shah (Vatsalya Children Hospital), Dr. Ketan Shah (Ketan Children Hospital), Dr. Chetan Shah (Anand Children Hospital) and Manager of Vankawala Children Hospital. I am also thankful to all Nurses and R.M.O.s of hospitals.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Zhou Z, McCann A, Weill FX, Blin C, Nair S, Wain J, Dougan G and Achtman M: *Transient Darwinian selection in Salmonella enterica serovar Paratyphi A during 450 years of global spread of enteric fever*. Proceedings of the National Academy of Sciences 2014; 111: 12199-204.

[2] Nithya M, Jamdade S, Kannan N and Mitra N: *Reliability of Typhidot-M in diagnosis of typhoid fever in children.* Asian Journal of Medical Sciences 2021; 13:136-9.

[3] Antillón M, Warren JL, Crawford FW, Weinberger DM, Kürüm E, Pak GD, Marks F and Pitzer VE. *The burden of typhoid fever in low-and middle-income countries: a meta-regression approach.* PLoS neglected tropical diseases 2017; 11: e0005376.

[4] Makkar A, Gupta S, Khan ID, Gupta RM, Rajmohan KS, Chopra H, Gupta M, Bansal S, Poonia B, Malik M and Panda PS: *Epidemiological Profile and Antimicrobial Resistance Pattern of Enteric Fever in a Tertiary Care Hospital of North India–a Seven Year Ambispective Study*. Acta Medica 2019; 61:125-30.

[5] Maharjan A, Dhungel B, Bastola A, Thapa Shrestha U, Adhikari N, Banjara MR, Lekhak B, Ghimire P and Rijal KR: *Antimicrobial susceptibility pattern of Salmonella spp. isolated from enteric fever patients in Nepal*. Infectious disease reports 2021;13: 388-400.

[6] Fasugba O, Gardner A, Mitchell BG and Mnatzaganian G: *Ciprofloxacin resistance in community-and hospital-acquired Escherichia coli urinary tract infections: a systematic review and meta-analysis of observational studies*. BMC infectious diseases 2015; 15:1-6.

[7] Tanmoy AM, Westeel E, De Bruyne K, Goris J, Rajoharison A, Sajib MS, van Belkum A, Saha SK, Komurian-Pradel F and Endtz HP: *Salmonella enterica serovar Typhi in Bangladesh: exploration of genomic diversity and antimicrobial resistance*. MBio 2018; 9: e02112-18.

[8] Kokare RS, Bari AK, Pereira JV, Patel K and Poojary A: *Minimum inhibitory concentration (MIC) of Ceftriaxone and Azithromycin for blood culture isolates of Salmonella enterica spp*. The Journal of Infection in Developing Countries 2021;15: 538-43.

[9] Dhingra S, Rahman NA, Peile E, Rahman M, Sartelli M, Hassali MA, Islam T, Islam S AND Haque M: *Microbial resistance movements: an overview of global public health threats posed by antimicrobial resistance, and how best to counter*. Frontiers in Public Health 2020 ;8:535668.

[10] Wettermark B, Vlahović-Palčevski V, Lee D and Bergman U: *Studies of Drug Utilization*. Pharmacoepidemiology 2019; 6: 373-410.

[11] Toure OA, Landry TN, Assi SB, Kone AA, Gbessi EA, Ako BA, Coulibaly B, Kone B, Ouattara O, Beourou S and Koffi A: *Malaria parasite clearance from patients following artemisinin-based combination therapy in Côte d'Ivoire*. Infection and Drug Resistance 2018; 11: 2031.

[12] https://iapindia.org/standard-treatment-guidelines/

[13] Wong VK, Baker S, Connor TR, Pickard D, Page AJ, Dave J, Murphy N, Holliman R, Sefton A, Millar M and Dyson ZA: *An extended genotyping framework for Salmonella enterica serovar Typhi, the cause of human typhoid*. Nature communications 2016 ;7: 1-1.

[14] Jin C, Gibani MM, Pennington SH, Liu X, Ardrey A, Aljayyoussi G, Moore M, Angus B, Parry CM, Biagini GA and Feasey NA. *Treatment responses to azithromycin and ciprofloxacin in uncomplicated Salmonella Typhi infection: a comparison of clinical and microbiological data from a controlled human infection model.* PLoS neglected tropical diseases. 2019; 13:e 0007955.

[15] Dheer G, Kundra S and Singh T. *Clinical and laboratory profile of enteric fever in children in northern India*: Tropical doctor 2012; 42:154-6.