

# A clinical audit to evaluate antibiotic prescribing practice in pediatric patients admitted for enteric fever. Rationalizing antibiotic stewardship program

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**Abstract:** To evaluate the antibiotic prescribing practice in pediatric patients for enteric fever, and to assess the need of developing and implementing the Antibiotic Stewardship Program (ASP) for the hospital. A prospective audit was completed in the pediatric ward of tertiary care hospital of Lahore for one year. Blood culture reports were collected from microbiology department and clinical data were assessed regarding the choice of antibiotics, frequency, dosage and clinical outcome. All the statistics were analyzed using SPSS software and compared with the guidelines. Out of 157 cases hospitalized with suspicion of enteric fever, 137 cultures were positive for salmonella. Monotherapy of ceftriaxone (70%) was prescribed mostly as empirical therapy. About 20% of patients received a combination of antibiotics empirically. Susceptibility reports showed only 7 cases were of non-resistant typhoid, 15 multi-drug resistant and 115 extensively drug-resistant. Nearly 46% of patients were discharged earlier whose empirical therapy was changed either before or promptly after susceptibility reporting. Commonly used definitive antibiotics (32%) were a combination of azithromycin and meropenem. Inappropriate use of antibiotics was noted frequently as compared to the guidelines. However, recommendations themselves need to be reviewed as antibiotic resistance patterns are changing drastically.

**Keywords:** Clinical audit, antibiotic protocols, typhoid fever.

## INTRODUCTION

An exponential rise in antibiotic resistance is an emerging threat globally due to the unnecessary misuse of antibiotics leading to terrific multidrug-resistant strains making them inept. Overuse of antibiotics accounts for a financial burden on an individual as well as on the hospital. As it is estimated, In Brazil, 50% of physicians prescribe either the wrong drug or improper dosage for the inappropriate duration. Thereupon, an upsurge in antibiotic resistance has been observed over the past years, which makes treatment complex for many infectious diseases including typhoid. Control of antibiotic misuse is needed for an hour. Hence, in 2016, Pakistan has started an antibiotic stewardship program to combat drug resistance (Atif *et al.*, 2021; Fonseca and Conterno 2004).

Developing countries are facing a substantial challenge in the treatment of typhoid fever due to antimicrobial resistance with constrained choices left for empirical treatment. Multidrug-resistant strains are prevailing worldwide. In a study done in India, about 10% of the patients required a combination of antibiotics for enteric fever (Dahiya *et al.*, 2019).

Meanwhile, it is crucial to look for the current burden of disease by surveilling enteric fever which occurs mainly in low-income countries (Luby *et al.*, 2015). Also, timely reporting of Gram stain results from blood cultures, combined with early clinical liaison, results in more rational and cost-effective treatment (Cunney *et al.*, 1997).

In Pakistan, the current dismay of anti-microbial failure is alarming at a global level due to the spread of extensively drug-resistant typhoid fever. In Hyderabad alone, between 2016-2017 health regularities had found approximately 800 cases of extensively drug-resistant typhoid. A study done in Rawalpindi showed resistance to conventional antityphoid drugs in *S. paratyphi* has increased from 14% to 44% (Butt *et al.*, 2005; Rasheed *et al.*, 2019).

It is the need of the hour that medical staff should be aware of antibiotic agents which are sensitive and resistant to many different bacteria to escalate or deescalate the use of antibiotic therapy according to Antibiotic Sensitivity Testing (AST) report. We also need to know the cause of these emerging multi-drug resistant organisms and how to tackle the situation. This can only be done by developing antibiotics stewardship programs at local hospital levels.

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Thus, this study aims to evaluate the antibiotic prescribing practice in pediatric patients for enteric fever and to assess the need of developing and implementing the Antibiotic Stewardship Program (ASP) for the hospital by providing a clinical audit.

## MATERIALS AND METHODS

A cross-sectional study was carried out in the pediatric ward of tertiary care hospital in Lahore after ethical approval from the institutional review board. Data was collected for one year from 30<sup>th</sup> April 2019 to 28<sup>th</sup> April 2020.

The pediatric patients with the suspicion of enteric fever were admitted to the wards either through the emergency or outpatient department. Blood samples for culture and susceptibility were taken and empirical antibiotics were started within the first hour of hospital admission. The samples were submitted to the microbiology department for drug susceptibility testing.

Blood cultures were properly processed and identified manually in a microbiological laboratory by applying standard microbiological techniques of culture & sensitivity by Clinical & Laboratory Standard Institutes (CLSI) guidelines. (James *et al.*, 2007) Culture and susceptibility reports were reviewed by members of the clinical microbiology team. During the study period of one year, all the patients with clinically significant isolates for *Salmonella enterica*, serovar *Typhi* and *Salmonella enterica* serovar *Paratyphi A, B and C* recovered from blood were recognized and included in the study. Patients admitted with suspicion of enteric fever but culture reports showed no growth were excluded from the study. Organisms were classified into susceptible strain, multidrug-resistant, and extensively drug-resistant according to the national guidelines. (11) In addition to demographic and microbiological data, the potential source of bacteremia was noted together with any significant underlying illness. Choice of the empirical antimicrobial agent (s), dose, frequency and route of administration of antibiotic treatment was noted. The appropriateness of this treatment was assessed concerning the organism (s) isolated, the underlying source and the standard recommendations made by WHO to treat enteric fever. (12) Details were also recorded of changes in treatment recommendation based on Gram stain and culture and susceptibility results.

## STATISTICAL ANALYSIS

Data were analyzed by computer software; Statistical package for social sciences (SPSS version 21). Appropriate statistics were applied. For quantitative variables, the mean and standard deviation were calculated. For qualitative variables, frequency and

percentage distribution tables were generated. The data presentation diagrams (bar diagrams) were also made.

## RESULTS

Over a year, 157 pediatric cases were evaluated. Demographic data showed that there were 96 boys (61.15%) and 61 girls (38.85%) with a mean age of 3.36 years and SD of 0.625. (Range neonates to 15 years). Among these 157 patients, 146 were admitted to pediatric wards with the suspicion of Enteric fever. The remaining 11 patients were hospitalized with other working diagnoses, however, their culture came out positive for *Salmonella enterica*.

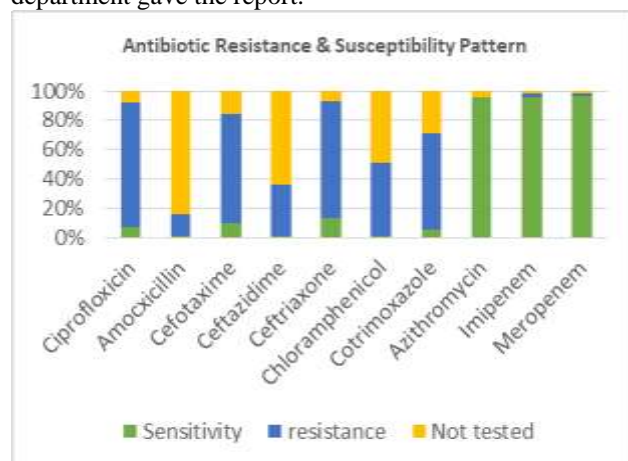
All the admitted patients received the first dose of antibiotic within the first hour of hospital presentation. The most commonly prescribed empirical therapy was Ceftriaxone with a dosage of 75mg/kg. It was prescribed in 84 cases (53.5%). Few other dosages of ceftriaxone were also noted including 50mg/kg in 6 (3.8%) and 100mg/kg in 21 (13.4%) patients. Besides this, Ciprofloxacin 20mg/kg was also tried empirically in 9 children. Only 2 cases received Azithromycin 20mg/kg while 3 patients had Meropenem 60mg/kg. The remaining 32 of 157 patients took different combinations of antibiotics empirically including ceftriaxone, azithromycin, meropenem, vancomycin, tazocin, metronidazole, and linezolid. Table 1 shows the frequency distribution of empirical antibiotics prescribed in suspected enteric fever cases.

**Table 1:** Showing frequency distribution of different empirical antibiotics for enteric fever

Empirical Antibiotics	
	Frequency
Ceftriaxone:	111
Optimal dose	84
Inappropriate dose	27
Ciprofloxacin	09
Azithromycin	02
Meropenem	03
Combination of antibiotics	32

The majority of patients 101 (64.3%) received their culture sensitivity reports within 4 days of blood sampling, while 56(35.6%) patients had to wait for greater than 4 days. However, few (3%) reports were delayed for more than 8 days. The working diagnosis of enteric fever was confirmed by culture growth showing *Salmonella enterica* in 137(87.3%) cases. A small number of other organisms were also isolated among suspected enteric fever cases. These mainly included *Pseudomonas* in 11(7%) cases followed by *Klebsiella*, *E. coli*, *Serratia*, *Staphylococcus aureus* and coagulase-negative *Staphylococcus*.

The empirical regime was changed in 56 (35.7%) cases after reviewing the culture susceptibility reporting. Although in 41 (26.1%) patients, it was changed even before the susceptibility analysis was provided. In the rest of the 60 cases (38%) the change in empirical treatment was delayed for a few days even when the microbiology department gave the report.



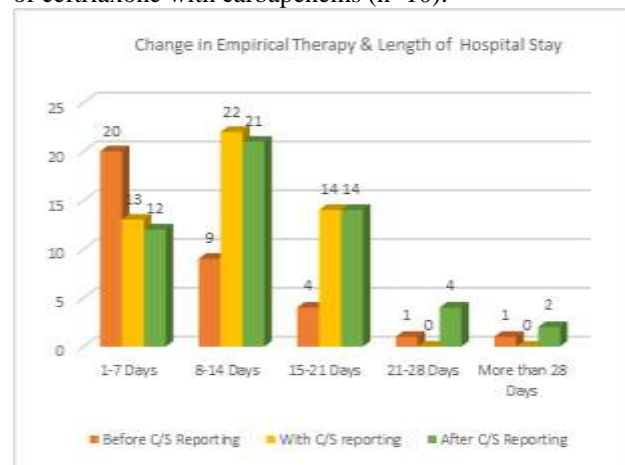
**Fig. 1:** Showing percentage distribution of sensitivity and resistance pattern of antibiotics.

CST reports showed that the microbiology team assessed blood samples with almost all the relevant drugs for susceptibility and resistance. Ciprofloxacin was tested in major ( $n=127$ ) *salmonella*-positive cultures and it was found to be resistant in 92% of cases. The organism also showed resistance to many of the important drugs like ampicillin (95%), cefotaxime (88%), and ceftriaxone (85%). Few drugs which particularly showed susceptibility were azithromycin (100%), imipenem (97%), and meropenem (98%) as seen in fig. 1.

After the CST reporting, the empirical medication was continued in 42 cases (30%). The monotherapy of azithromycin and meropenem was used in 20 (14%) and 11(8%) patients respectively, while vancomycin was used in 3(2%) cases as definitive therapy. The most commonly used altered antibiotics were the combination of meropenem and azithromycin among 44 cases (32%) in variable doses. Besides this, azithromycin was also used along with imipenem in 6(4%), with ceftriaxone and ciprofloxacin in single cases each. The other significant combination seen was vancomycin and meropenem in 4 (3%) children. A total of 3 pediatric patients received triple antibiotic therapy of vancomycin, meropenem, and azithromycin. Only 2 patients received ciprofloxacin as definitive therapy after culture susceptibility reporting.

Only one patient expired out of 137 patients admitted with enteric fever, the rest of 136(99%) patients were discharged after successful treatment. However, the duration of hospital stay was variable for different patients.

The patients discharged earlier (within two weeks) had their empirical therapy susceptibility to bacteria ( $n=39$ ), or those whose CST reports were given at an appropriate time and changes in empirical therapy were done promptly ( $n=25$ ). On the other hand, 19 patients were admitted for a longer period (more than 2 weeks), who kept receiving inappropriate antibiotics even after a susceptibility analysis reported resistance to those antimicrobial agents as described in fig 2. The patients discharged within two weeks had either susceptible ceftriaxone ( $n=19$ ) treatment empirically or a combination of ceftriaxone with carbapenems ( $n=10$ ).



**Fig. 2:** Bar diagram to compare length of hospital stay with change in antibiotic therapy in accordance to culture sensitivity reporting.

## DISCUSSION

*Salmonella enterica* subspecies *enterica* serovar *Typhi* (*Salmonella typhi*) causes typhoid fever in humans through the fecal-oral route. Typhoid fever was always a major public health concern globally. There are an estimated 16.6 million cases and 600 000 deaths annually with most deaths occurring in Asia (440 000) and Africa (130 000). The majority of those affected are 3-19 years of age (Pang *et al.*, 1998). Our data shows 137 patients were admitted with enteric fever in the pediatric ward of tertiary care hospital for one year. Statistics also show that males (61%) were affected more and the age group affected the most was 6 months to 6 years (58%). The figs. are correspondent to the ones seen in North Indian Hospital with males affected more (62.5%) and the mean age of admission was 6 years (Dheer *et al.*, 2012). In endemic areas, an early stage of typhoid fever may mimic many common febrile illnesses due to lack of any typical signs and it may be confused with other differential diagnoses, such as acute gastroenteritis, bronchopneumonia, meningitis, pyrexia of unknown origin as described in this study. Empirical antibiotics were started in all cases within the first hour of admission following the WHO guidelines. (WHO-typhoid-fever Appendix)

There is a rapid change in the distribution as well as antimicrobial susceptibility of *salmonellae* typhoid in Pakistan (Butt *et al.*, 2005). As per national guidelines, only 70% (n=111) of patients received suitable empirical antibiotics which are monotherapy of ceftriaxone. The rest of the patients received either an inappropriate antibiotic group (n=14) or a combination of antibiotics (n=32) that is against guidelines. Variation in drug doses was also noted which affected the overall management. Only 84 patients received the correct dose of ceftriaxone while 27 cases had a suboptimal dose. Azithromycin and ciprofloxacin doses were prescribed correctly (Typhoid Management Guidelines - 2019 - MMIDSP).

Many patients (n=56) had to wait for more than the usual period (4 days) for culture and susceptibility review, besides this, few of the relevant drugs were not tested in many samples. Amoxicillin, ceftazidime, chloramphenicol and co-trimoxazole were tested the least. These two factors not only prolonged the hospital stay but also affected the choice of prescribing definitive treatment.

Only 7 cases of non-resistant typhoid fever were noted in the microbiology report which showed susceptibility to first-line drugs, and the rest of 130 samples showed multi-drug resistance. 115 out of 137 were proven to be extensively drug-resistant samples, which are resistant to first-line antibiotics and third-generation cephalosporin including ceftriaxone and cefotaxime. (Typhoid Management Guidelines - 2019 - MMIDSP) But the susceptibility rate of ceftazidime was found out to be higher (35%). Although included in the WHO guidelines (WHO Communicable Disease Surveillance and Response, 2003), the evidence from the Systemic reviews does not support listing cefixime (Dolecek *et al.*, 2019). In comparison with fluoroquinolones, cefixime exhibits a higher number of failures. So, this drug was not tested for susceptibility in any blood sample. The only drug which showed no resistance is azithromycin, even carbapenems exhibited resistance in few cases of enteric fever.

The empirical therapy was changed timely with concordance to culture sensitivity reporting in a quarter of patients. The pediatricians also changed antibiotics even before the microbiology report was issued (35.7%), based on the poor response of a patient to empirical drugs after 48 hours. In 60 cases empirical antibiotics were continued for few days even when pathology reports showed resistance to the drug.

Patients (n=32) were discharged within a week whose empirical therapy was found susceptible to bacteria and then continued as definitive treatment. Conversely, patients who kept receiving the resistant drugs (n=19) remained admitted for more than two weeks. Similarly, patients (n=17) receiving a combination of empirical therapy, using ceftriaxone along with other relevant groups were discharged earlier within two weeks.

The most commonly preferred definitive monotherapy after culture sensitivity reporting was azithromycin, followed by carbapenems and vancomycin. About 53 patients received the combination of two antibiotics. Azithromycin and meropenem were used the most (32%). 6 patients also received a combination of triple antibiotics, details about which are not present in any guidelines.

The strength of the study lies in its novelty as it provides recent data of all the hospitalized cases (n=157) of suspected enteric fever collected throughout a year. It provides information about antimicrobial resistance patterns and inappropriate antibiotics use. It also brings attention to develop antibiotic stewardship programs at local levels to minimize drug misuse and tackle growing resistance in microbial. The study is limited in its implication as it only included data of admitted pediatric patients who had culture-positive blood samples of *Salmonella enterica*. Patients who presented to the outpatient department with suspicion of enteric fever were not included in the data. Also, the antibiotic response of admitted patients was not recorded who showed no growth on culture reports.

## CONCLUSION

There is emergent resistance of many microorganisms to available antibiotics. There is a dire need to develop an antibiotic stewardship program at a local level to restrain the misuse of antibiotics. This program is structured to assess the available data to devise guidelines about prescribing antibiotics based on culture sensitivity analysis. It also helps to teach physicians/pediatricians to prescribe correct antibiotics in appropriate doses for the effective management of infectious diseases. Microbiologist also needs to revamp its testing methods to provide effectual reports in due time. The communication between the departments needs to be effective to optimize patient care.

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## REFERENCES

- Atif M, Ihsan B, Malik I, Ahmad N, Saleem Z, Sehar A and Babar Z (2021). Antibiotic stewardship program in Pakistan: A multicenter qualitative study exploring medical doctors' knowledge, perception and practices. *BMC Infect. Dis.*, **21**(1): 1-1
- Butt T, Ahmad R, Salman M and Kazmi S (2005). Changing trends in drug resistance among typhoid

- salmonellae in Rawalpindi, Pakistan. *East Mediterr. Health J.*, **11**(5-6): 1038-1044.
- Cunney R, McNamara E, Alansari N, Loo B and Smyth E (1997). The impact of blood culture reporting and clinical liaison on the empiric treatment of bacteraemia. *Clin. Pathol. J.*, **50**(12): 1010-1012.
- Dheer G, Kundra S and Singh T (2012). Clinical and laboratory profile of enteric fever in children in northern India. *Tropical Doctor*, **42**(3): 154-156.
- Dolecek1 C, Pokharel S, Basnyat B and Olliaro1 P, (2019). Review of antibacterial medicines for the treatment of enteric fever for the WHO model list of essential medicines 2019 Update. Who.int. 2019. (online) Available at: <[https://www.who.int/selection\\_medicines/committees/expert/22/applications/s6.2\\_typhoid-fever.pdf](https://www.who.int/selection_medicines/committees/expert/22/applications/s6.2_typhoid-fever.pdf)> (Accessed 29 March 2021).
- Fonseca L and Conterno L (2004). Audit of antibiotic use in a Brazilian University Hospital. *Braz. J. Infect. Dis.*, **8**(4): 272-280.
- Gavi.org (2018). New typhoid vaccine to receive Gavi support. (online) Available at: <<https://www.gavi.org/library/news/statements/2018/new-typhoid-vaccine-to-receive-gavi-support/>> (Accessed 29 March 2021).
- Jorgensen J, Hindler J, Reller L and Weinstein M (2007). New consensus guidelines from the clinical and laboratory standards institute for antimicrobial susceptibility testing of infrequently isolated or fastidious bacteria. *Clin. Infect. Dis.*, **44**(2): 280-286.
- Kapil A, Dahiya S, Malik R, Sharma P, Sashi A, Lodha, R, Kabra S, Sood S, Das B, Walia K and Ohri V (2019). Current antibiotic use in the treatment of enteric fever in children. *Indian J. Med. Res.*, **149**(2): 263.
- Luby S, Saha S and Andrews J (2015). Towards sustainable public health surveillance for enteric fever. *Vaccine*, **33**: C3-C7.
- Mmidsp.com. (2022). *Typhoid Management Guidelines – 2019 – MMIDSP*. (online) Available at: <<https://www.mmidsp.com/typhoid-management-guidelines-2019>> (Accessed 20 March 2021).
- Pang T, Levine M, Ivanoff B, Wain J and Finlay B (1998). Typhoid fever-important issues still remain. *Trends Microbiol.*, **6**(4): 131-133.
- Rasheed M, Hasan S, Babar Z and Ahmed S (2019). Extensively drug-resistant typhoid fever in Pakistan. *Lancet Infect. Dis.*, **19**(3): 242-243.
- Who.int. (2012). (online) Available at: <[https://www.who.int/selection\\_medicines/committees/expert/22/applications/s6.2\\_typhoid-fever\\_Appendix.pdf?ua=1](https://www.who.int/selection_medicines/committees/expert/22/applications/s6.2_typhoid-fever_Appendix.pdf?ua=1)> (Accessed 29 March 2021).