Original Article

Current Trends of Empirical Treatment of Typhoid Fever among General Practitioners in District Kohat, Khyber Pakhtunkhwa, Pakistan

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ABSTRACT

Objective: To determine the current trends of empirical treatment of typhoid fever among General Practitioners (GPs) in district Kohat, Khyber Pakhtunkhwa, Pakistan.

Study Design: Prospective questionnaire-based cross sectional study.

Place and Duration of Study: This study was conducted at the hospitals i.e. District Headquarter Hospital, KDA, Kohat and Liaqat Memorial Hospital, Kohat from November 2017 to April 2018.

Materials and Methods: Well-designed and structured questionnaires were distributed amongst 100 general practitioners who gave consent to participate in the study. They were briefed about the study and were requested to fill the questionnaires by responding to the questions in predetermined order. The questionnaires were collected by one of the authors and results were analyzed.

Results: Eighty five percent of the GPs diagnosed typhoid fever clinically, without taking any help from laboratory investigations. Eighty percent of the GPs prescribed empirical antibiotic treatment for typhoid fever and only 3% advised blood culture for diagnosis. The most common antibiotics prescribed by GPs as empirical treatment were flouroquinolones in 30 %, cefixime in 42% and ceftriaxone in 14 % of cases. Seventy five percent of GPs prescribed empirical treatment for 11-14 days duration. Combination of antibiotics was prescribed by 40 % of GPs.

Conclusion: Empirical treatment is commonly prescribed by GPs in the treatment of typhoid fever and Cefixime, flouroquinolones and ceftriaxone are most frequently prescribed antibiotics in our set up.

Key Words: General practitioner, Infectious disease, Empirical treatment, Typhoid fever

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INTRODUCTION

Typhoid fever is one of the commonest infectious diseases in tropical countries[1].Worldwide, approximately 13-17 million cases are reported every year with 600,000 deaths per annum. Eighty percent of reported typhoid fever cases with subsequent deaths belong to Asia alone[2].Most of the cases of typhoid (enteric fever) are caused by Salmonella enterica subsp. enterica serovar Typhi **(**S.Typhi). Although S. Paratyphi A and B and occasionally other serotypes (such as, S. Dublin,S. Newport and S.Virchov are also culprits. S. Typhi is the only human pathogen having no animal reservoir.

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However, typhoid fever is a rare imported infection in western communities[3, 4] while in developing countries like Pakistan where clean water provision, environmental hygiene and food cleanliness are not ideal, typhoid is still a main health issue. The global incidence of typhoid in 1985 was estimated to be 12.5 million cases per annum leading to over 0.3 million deaths subsequently[5]. The significance of better sanitation was well demonstrated in Singapore in 1980 where the incidence of typhoid steadily decreased from there 10/100, 000 population in the 1950sto 1/100**,**000 in the 1980s[6]**.**

Contrarily, in developing countries much dependence is upon chemotherapy because of the problems in adopting preventive steps like public health measures or immunization. The death rate of untreated typhoid has been reported approximately30%, while with use of proper antibiotics it is <1%.

Commonly used antibiotics for typhoid fever in developing countries are ampicillin, chloramphenicol and co-trimoxazole but unfortunately S. Typhi is resistant to all[7]**.**The emergence of resistance to multiple anti typhoid drugs has excessive repercussions as far as typhoid treatment is concerned [8]such as kids having such strains are more sick, have extended duration of

ailment and show a considerably higher death rate[9]. Nevertheless, there are no distinguishing pathognomonic manifestations to such resistant infections from those which completely sensitive to S. Typhi. The available treatment choices for typhoid fever include fluoroquinolones like ofloxacin or ciprofloxacin[8,10,11,12] and expanded-spectrum cephalosporin such as Ceftriaxone[12].In Pakistan, S.typhi multi-drug resistant strains were reported for the first time in 1987[13] and an increased prevalence (approximately 90%) of S. Typhi isolates was observed[10, 14].

Majority of suspected typhoid fever cases are treated by general practitioners (GPs) by prescribing empirical treatment without a confirmatory test of blood culture and sensitivity and there is an increasing incidence of multi-drug resistance typhoid fever in Pakistan. So an appropriate and effective empirical treatment should be prescribed to cover multi-drug resistant typhoid fever. Therefore, we conducted a questionnaire-based prospective cross sectional study to determine the current trends of empirical treatment of typhoid fever by general practitioners in the hospitals and clinics of district Kohat, Khyber Pakhtunkhwa, Pakistan. It is expected that this survey will help the health professionals to develop an effective protocol of empirical treatment of typhoid fever in order to avoid treatment failures.

MATERIALS AND METHODS

This prospective questionnaire-based cross sectional study was carried out in hospitals and clinics of Kohat district, Khyber Pakhtunkhwa, Pakistan from November 2017 to April 2018. GPs who were full-time registered practitioners, who belonged to urban areas of district Kohat, showed their willingness to participate in the study and were treating cases of typhoid fever irrespective of its duration and age of patient, were included in study. The house officers, specialists and GPs working in rural areas, who were treating typhoid fever were excluded from the study.Convenient sampling technique was used for collection of data. Well-designed and structured questionnaires were prepared and distributed amongst 100 general practitioners who gave informed consent to participate in the study. They were briefed about the study and questionnaires in person by one of the authors and any ambiguity was clarified. They were requested to fill the questionnaires by responding to the questions in predetermined order as per their current practice without any influence. The questionnaires were collected by one the authors and results were manually checked before computerized analysis of the empirical treatment of typhoid fever. The results of the data were recorded as percentages.

RESULTS

Total of 85% of the GPs diagnosed typhoid fever clinically, without taking any help from laboratory investigations. Eighty percent of the GPs prescribed empirical antibiotic treatment for typhoid fever and only 3% advised blood culture for diagnosis.(Tablel I).

Table No.I: Response of GPs regarding empirical treatment of typhoid fever

Sr. #	Question	Yes %	No %	Occasionally %
1	Do you diagnose typhoid fever solely on clinical basis?	85	5	10
2	Do you prescribe antibiotics as empirical treatment of typhoid fever?	80	5	15
3	Do you advise blood culture & sensitivity test to diagnose typhoid fever?	0	97	3

Table No.2: Response of the GPs about the trend of empirical antibiotics to treat typhoid fever

Question 1	Which antibiotic you prescribe as first choice as empirical treatment for typhoid fever patients?
Responses	a. Flouroquinolones (30 %) b. Cefixime (42 %) c. Azithromycine (4 %) d. Ceftriaxone (14 %) e. Chloramphenicol (1 %) f. Amoxicillin (2 %) g. Sulphamethoxazole-Trimethprim (3 %) h. Others (4 %)
Question 2	For how many days you prescribe antibiotics as empirical treatment of typhoid fever?
Responses	a. 1-6 days (2 %) b. 7-10 days (20 %) c. 10-14 days (75 %) d. More than 14 days (3 %)
Question 3	Do you prescribe antibiotics combination in typhoid fever?
Responses	Yes (40 %) No (60 %)
Question 4	If yes, which combination?
Responses	a. Cefixime + Quinolones (26 %) b. Quinolones+Azithromycin (12 %)

The antibiotics prescribed by general practitioners as empirical treatment were flouroquinolones 30%, cefixime 42%, azithromycine 4 %, ceftriaxone 14%, chloramphenicol 1%, amoxycilline 2%, sulpha-methoxazole + trimethoprim 3 % and others 4 %. The duration of empirical treatment prescribed was 1-6 days 2 %, 7-10 days 20 %, 11-14 days 75 % and more than 14 days 3%. Combination of antibiotics was prescribed by 40 % of general practitioners in which 26 % was cefixime + quinolones and in 12 % it was quinolones + azithromycin(Table 2).

DISCUSSION

Typhoid fever is common systemic infectious disease in South Asia including Pakistan. The clinical features and severity of typhoid fever differ in various age groups along with geography. Most cases of typhoid fever belong to age group ranging from 5 to 25 years [15, 16, 17]. But, it has been observed in typhoid endemic areas that numerous patients (predominantly children) manifest as suffering from "non-specific fever", which at the end are proved to be wrong leading to fatal outcomes oftenly [18, 19, 20].

The antimicrobial resistance is a serious worldwide issue nowadays and it has perpetually been produced due to extensive use of antibiotics[21]. Additionally, injudicious use of broad spectrum antibiotics due to their low cost, easy administration as empiric treatment of suspected typhoid cases and multiple courses of antibiotic therapy. So judicious use of antibiotics for typhoid fever will help to reduce the antimicrobial resistance and will have favorable effect on patient centered outcome and health related expenditures It is becoming challenging task to treat typhoid fever due to emerging resistant strains of S. Typhi. There is lack of availability and affordability of confirmatory tests like blood culture and sensitivity in these poor countries so the disease is commonly treated by GPs with Empirical antibiotic treatment. Although, culture of bone marrow is the gold standard diagnostic tool[18] but blood culture is commonly practiced as first choice test for patients with typhoid fever. However, most cases of enteric fever are seen in low-income countries where blood cultures are frequently unavailable, too expensive, or incoherently applied[19]. Hence due to these limitations in low-income countries with limited diagnostic resources, antibiotics are prescribed empirically in suspected cases of typhoid fever. Antimicrobial resistance in enteric fever is another major health concern which made the treatment of typhoid fever a great challenge. Furthermore, timely treatment with suitable antibiotics is vital for reduction of enteric fever associated mortality[20].

World Health Organization (WHO) guidelines recommended flouroquinolones (ciprofloxacine & Ofloxacine) and 3rd & 4th generation cephalosporin antibiotics as first-line antimicrobial agents for treatment of typhoid fever[22]. There are no clear-cut guidelines for the prescription for usage of single and multiple antibiotics for the treatment of typhoid fever. Combination of antibiotic treatment can be considered when single drug treatment fails. Usually, a fluoroquinolone is the drug of first choice. If there is inadequate response, then cefixime, a 3rd generation oral cephalosporin, is added. If there is no improvement in the condition of patient, then Cefixime is replaced by azithromycin [22].

In our study 85% of the GPs diagnosed typhoid fever clinically, without advising any investigations and eighty percent of them prescribed empirical treatment of typhoid fever. Most common prescribed antibiotics were cefixime (42%), flouroquinolones (30 %) ceftriaxone (14 %) and azithromycine (4 %). These antibiotics were prescribed for 10-14 days duration by majority of GPs (75%). Prescription of combination of two antibiotics was also observed in 40 % of GPs in our study and most common combination was quinolones & Cefixime. A study on knowledge, attitude and practice of general practitioners (GP) regarding treatment of typhoid fever by Paul et al in 2016 revealed that the antibiotics used by GPs for treatment of typhoid are: Azithromycin (42%), Fluoroquinolones (32%), Cefixime(16%), Amoxycillin (6%) and Choramphenicol (4%). A combination of antibiotics is preferred by 38% of GPs and the preferred combinations of antibiotics are Cefixime + Azithromycin (26%) and Ciprofloxacin +Azithromycin (12%). Parenteral antibiotic is preferred in most cases when the patient is unable to consume orally usually due to excessive vomiting [22].

The observations of our study are in accordance with WHO recommendations of first line antibiotics treatment of typhoid fever [21] .The findings of our study regarding empirical antibiotics treatment of typhoid fever are in consistent with similar studies conducted by other researchers in India [22] but the main difference is that this study was conducted at different places of India while our study was carried out in one district only.

The limitations of our study are small sample size, non-inclusion of specialists and sampling of convenience type. Moreover, well-designed studies are recommended in order to study the latest trends for typhoid chemotherapy in lager population. Moreover, continued surveillance of resistance rates and antibiotics combinations is desirable to guarantee suitable recommendations for the treatment of typhoid especially in endemic areas.

CONCLUSION

GPs commonly prescribe antibiotics empirically for treatment of typhoid fever without performing confirmatory blood culture test. Most frequently used antibiotics are cefixime, flouroquinolones and

ceftriaxone. However large scale, well-designed studies highlighting antibiotic susceptibility of S.typhi in typhoid fever are recommended to know effective antibiotics in order to avoid treatment failures.

Author's Contribution:

Concept & Design of Study:	Muhammad Ashraf
Drafting:	Sohail Aziz Paracha
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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