Infection and Drug Resistance

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ORIGINAL RESEARCH

Comparison of Single vs Combination Drug Therapy in Extensively Drug Resistant *Salmonella typhi*: An Observational Study from Pakistan

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Introduction: Antibiotic resistance has become a significant problem in typhoid fever due to the emergence of extensively drug resistant (XDR) *Salmonella enterica* serovar *typhi*. In Pakistan, an outbreak of ceftriaxone-resistant typhoid was first reported in November 2016.

Methods: A retrospective chart review was conducted at Liaquat National Hospital and Medical University, in Karachi, Pakistan. Patient records were identified from the microbiology laboratory data of all admitted patients who had blood culture positive for XDR *Salmonella typhi* from January 2017 to December 2019.

Results: Out of 254 patients, 179 (70%) were male with an average age of 11.7 ± 10.9 years. Around 190 (74%) patients were treated with combination therapy, 126 (49%) were given azithromycin and meropenem and 61 (24%) received azithromycin and imipenem. A total of 64 (25%) patients received single drug therapy, 33 (12%) were given azithromycin, 23 (9%) meropenem, and 8 (3%) imipenem. Analysis indicated that single drug therapy resulted in an earlier onset of defervescence compared with combination therapy (5.03±2.98 days vs 3.45±2.48 days; P <0.001), with a decreased occurrence of pancytopenia (P <0.001).

Conclusion: Single antimicrobial therapy achieved defervescence earlier than combination therapy, with carbapenems performing better than azithromycin.

Keywords: extensive drug resistant, Salmonella typhi, drug therapy, carbapenem, azithromycin

Introduction

Typhoid fever is one of the major public health problems in low- and middle-income countries with 20 million cases and around 161,000 deaths annually.[1] Symptoms include high grade fever, abdominal pain, and headaches. If not treated, it can lead to intestinal hemorrhage and perforation with significant mortality.[2]

In the mid-1980s, *Salmonella typhi* developed resistance to chloramphenicol, ampicillin, and trimethoprim; the first-line therapy for typhoid fever. This multidrug resistant strain caused several outbreaks in the Indian subcontinent, Southeast Asia, and Africa.[3] Up to 2014, sporadic cases of resistance against third-generation cephalosporin were also being reported worldwide.[4]

In November 2016, an outbreak of ceftriaxone-resistant typhoid was first reported in Hyderabad city of province Sindh, Pakistan.[5] The organism identified was *Salmonella enterica* serovar *typhi* 4.3.1 (H58) clade. It was resistant to not only chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, and fluoroquinolones but also to third-generation cephalosporin and hence named as XDR typhoid. This isolate was found to harbor a $bla_{CTX\text{-}M\text{-}15}$ extended-spectrum β-lactamase (ESBL) gene conferring resistance to ceftriaxone.[6] Since then, XDR typhoid has spread to other cities in the province of Sindh, including Karachi. Around 20,000 cases have been documented in Hyderabad and Karachi alone as of August 2021.[7]

Received: 24 April 2022
Accepted: 1 August 2022
Published: 21 October 2022

Later from 2018 onwards, XDR typhoid infection has been reported across the globe from the United States, England, Canada, and China.[6,8] The whole-genome comparison revealed that it belonged to the Pakistan-originating H58 lineage, which had the potential to replace local strains and spread globally through travel-associated international transmission.[8]

The management of XDR typhoid is challenging with very limited treatment options. The Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP) worked out management guidelines in 2019 based on the antimicrobial sensitivity patterns and recommended azithromycin and carbapenem as treatment of choice.[9] However, studies are needed to assess the outcome of patients treated with such a limited number of antibiotics, particularly questions regarding single or combination therapy. Qureshi et al found no difference in single versus combination therapy and they recommend use of lower cost oral azithromycin as first-line treatment.[10] We aimed to compare the treatment outcome between those who received single drug therapy (azithromycin, meropenem, or imipenem) versus combination drug therapy (azithromycin plus meropenem or azithromycin plus imipenem). To the best of our knowledge this is the first study from Pakistan where we compared single versus combination drug therapy. Our objective is to contribute to the existing guidelines on the management of this emerging and difficult to treat infection.

Materials and Methods

A retrospective chart review was conducted at Liaquat National Hospital and Medical College, a tertiary care hospital, in Karachi, Pakistan. From January 2017 to December 2019, medical records of patients admitted to adult medicine, pediatric wards, intensive care, and high dependency units with a diagnosis of XDR typhoid were retrieved. All patients with confirmed blood culture positive for XDR strain of *Salmonella typhi* and treated with either azithromycin or carbapenem or both, were included in the study. Patients with culture-proven XDR typhoid, but with incomplete medical records, missing information, or those that received ceftriaxone for any period of time before switching to either azithromycin and/or carbapenem were excluded. Only charts were examined in this retrospective observational study. So, there was no need for patient consent. However, there are ethical concerns with retrospective research; for this reason, the approval of the study was taken from the institutional review board (IRB) and ethical review committee (ERC) of Liaquat National Hospital (ERC No 0464–2019). This study complies with the Declaration of Helsinki.

Structured pro-forma was filled. Demographics, co-morbidities, symptoms and signs, complications if any, antimicrobial therapy received and duration, time to defervescence of fever in days, duration of hospital stay, outcome whether discharged or died were noted. The patients were divided into two groups, those who received combination drug therapy and those on single drug therapy. The above variables were compared between the two groups.

The primary outcome was time to defervescence of fever while on the antimicrobial therapy and secondary outcome was the duration of hospital stay or death.

Fever was defined as oral temperature ≥100°F. Defervescence was defined as the return of oral temperature from documented fever to less than 100°F for more than 48 hours. Time to defervescence was calculated from the point of start of appropriate antimicrobial therapy until defervescence was reached. Single drug therapy was defined as patients who received either azithromycin or carbapenem (meropenem or imipenem) and combination drug therapy was carbapenem plus azithromycin. Patients received carbapenem intravenously (IV) at a dose of 20–40 mg/kg three times a day and azithromycin (IV as well as oral) 10 mg/kg/day according to the hospital protocol.

Data Collection and Analysis

All the data were entered and analyzed in SPSS version 22.0. Continuous variables such as age, duration of fever, defervescence of fever and hospital stay in days were presented as means and standard deviations and their mean difference was evaluated using Student's *t*-test between groups. Categorical variables: gender, type of treatment, complications, outcome, and symptoms at presentation were reported as counts and percentages. Their proportion differences were determined using Chi-square or Fisher's exact tests between groups as appropriate. 95% confidence interval was also computed for the duration of treatment. P-value <0.05 was considered significant.

Results

Three hundred patients were identified with a blood culture positive for XDR *Salmonella typhi*, during the three-year study period. Out of 300, 46 were excluded, 35 received ceftriaxone and/or had < 24 hours hospital stay, and 11 had hospital stay of < 24 hours. A total of 254 records were assessed (Figure 1).

The mean age was 11.7 ± 10.5 years and 70% were male. Of 254, 73.2% were less than 18 years of age. The most common presenting symptoms were fever and chills. The median duration of fever before presentation was 10 days. Around 85% presented with fever higher than 101°F. Of 254 patients, 29 (11%) developed complications (clinical characteristics and outcomes are shown in Table 1).

A total of 190 (75%) patients received combination drug therapy, of whom 127 (66%) received a combination of azithromycin and meropenem and 63 (33%) azithromycin and imipenem. While 64 (25%) received single drug therapy, 33 (51%) were given azithromycin, 23 (36%) meropenem, and 8 (12.5%) imipenem. A significant number of patients presented with vomiting (P = 0.023) and loose stools (P = 0.02) who were given combination drug therapy as compared with single drug therapy. Those patients who presented with complications were put on combination drug therapy more than single drug therapy (Table 2)

Table 3 shows the outcome. Defervescence occurred in 239 (94%) patients. The mean time to defervescence was 4.6±2.9 days with most patients (87%) defervescing within a week of initiation of antimicrobial therapy. As

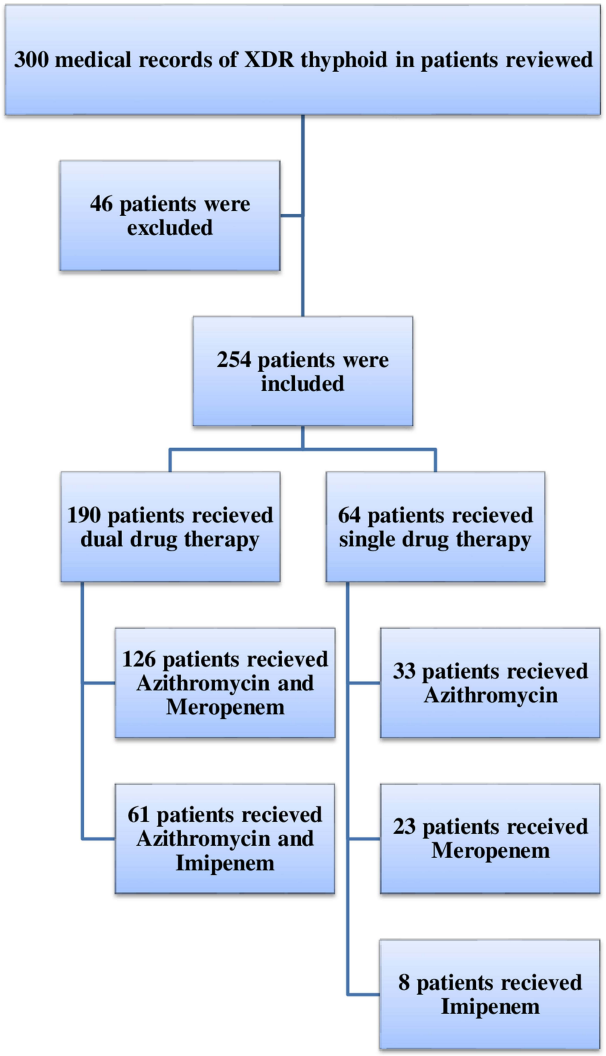

Figure 1 Patient stratification.

Table 1 Clinical Characteristics and Outcome of Patients Admitted with XDR Typhoid

Variables	Total n=254	Combination Drug Therapy n=190	Single Drug Therapy n=64	*p*-value
Age				
Age Mean ± SD	11.741 ± 10.565	11.61 ± 10.35	12.12 ± 10.06	0.735
≤ 5 years	77 (30%)	61 (32.1%)	16 (25%)	0.285
5–10 years	81 (31%)	58 (30.5%)	23 (35.9%)	0.422
≥10 - ≤18 years	28 (11%)	23 (12.1%)	5 (7%)	0.343
>18 years	68 (26.7%)	48 (25.2%)	20 (31.2%)	0.350
Gender				
Male	179 (70.4%)	134 (70.5%)	45 (70.3%)	0.974
Female	75 (29%)	56 (29.4%)	19 (29.6%)	
Symptoms at Presentation				
High grade fever ≥101°F	216 (85%)	164 (86.3%)	52 (81.2%)	0.326
Fever Duration Mean ± SD	12.37±10.22	12.37±9.89	12.38±11.22	0.995
Chills	162 (63.7%)	118 (62.1%)	44 (68.7%)	0.339
Abdominal pain	97 (38.1%)	75 (39.4%)	22 (34.3%)	0.468
Vomiting	57 (22.4%)	50 (26.3%)	7 (10%)	0.023*
Loose motions	44 (17.3%)	38 (20%)	5 (7.81%)	0.02*
Defervescence				
Yes	239 (94%)	184 (96.8%)	55 (85.9%)	0.001*
Defervescence of fever Mean ± SD	4.63 ± 2.9	5.03 ± 2.98	3.45 ± 2.48	0.000*
Defervescence within 1 week				
Yes	222 (87%)	162 (85.2%)	60 (93.7%)	0.05
Outcome				
Hospital stay Mean ± SD	6.01± 3.94	6.55±4.164	4.42±2.66	0.000*
Discharged	253 (99.6%)	189 (99.7%)	63 (98.4%)	0.084
Expired	1 (0.39%)	0	1 (1.56%)	

Note: *Statistically significant.
Abbreviations: XDR, Extensively Drug Resistant, SD, Standard Deviation.

compared with combination drug therapy, single drug therapy resulted in an earlier onset of defervescence (5.03 ±2.98 days vs 3.45±2.48 days; P <0.001) (Figure 2). Also a significant number of patients defervesced in less than 1 week who received single drug therapy (P = 0.05). Those patients who received azithromycin only, defervesce in an average of 3.85 days (95% CI: 2.86–4.84), while those on intravenous carbapenem defervesce in 4.4 days

Table 2 Complication Occur in Patients with XDR *Salmonella typhi*

Complication	Total (n=108)	Combination Therapy (n=190)	Single Therapy (n=64)	*P*-value
Thrombocytopenia	63 (58.3%)	49	14	0.531
Pancytopenia	28 (25.9%)	26	2	0.02*
Lower GI bleed	15 (13.8%)	11 (5.78%)	4 (6.25%)	0.892
GI perforation	8 (7.4%)	7 (3.68%)	1 (1.56%)	0.401
Altered sensorium	6 (5.5%)	6 (3.15%)	0 ()	0.172

Note: *Statistically significant.
Abbreviations: XDR, Extensively Drug Resistant, GI, Gastro-Intestinal.

Table 3 Length of Hospital Stays in Patients with XDR *Salmonella typhi*

Variable	Mean	Combination Therapy	Single Therapy	*P*-value
Hospital stay	6.01± 3.94	6.55 ± 4.164	4.42 ± 2.66	0.000*
Fever duration	12.37 ± 10.22	12.37 ± 9.89	12.38 ± 11.22	0.995
Defervescence of fever	4.63 ± 2.9	5.03 ± 2.98	3.45 ± 2.48	0.000*

Note: *Statistically significant.
Abbreviation: XDR, Extensively Drug Resistant.

(95% CI: 3.07–4.47) (P = 0.31). In patients receiving combination therapy, defervescence occurred in 5.14 days (95% CI: 4.59–5.7) for those on meropenem and azithromycin and 4.76 days (95% CI: 4.09–5.43) for those on imipenem and azithromycin (P = 0.44) (Figure 3).

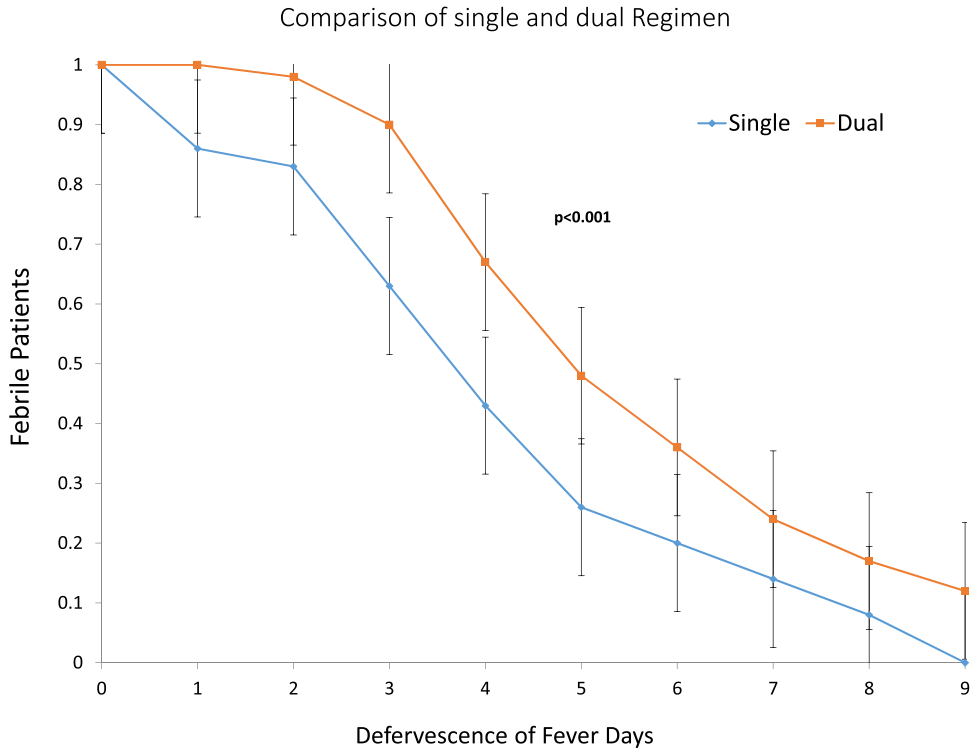

Figure 2 Single vs Dual combination therapy relationship to defervescence of fever days.

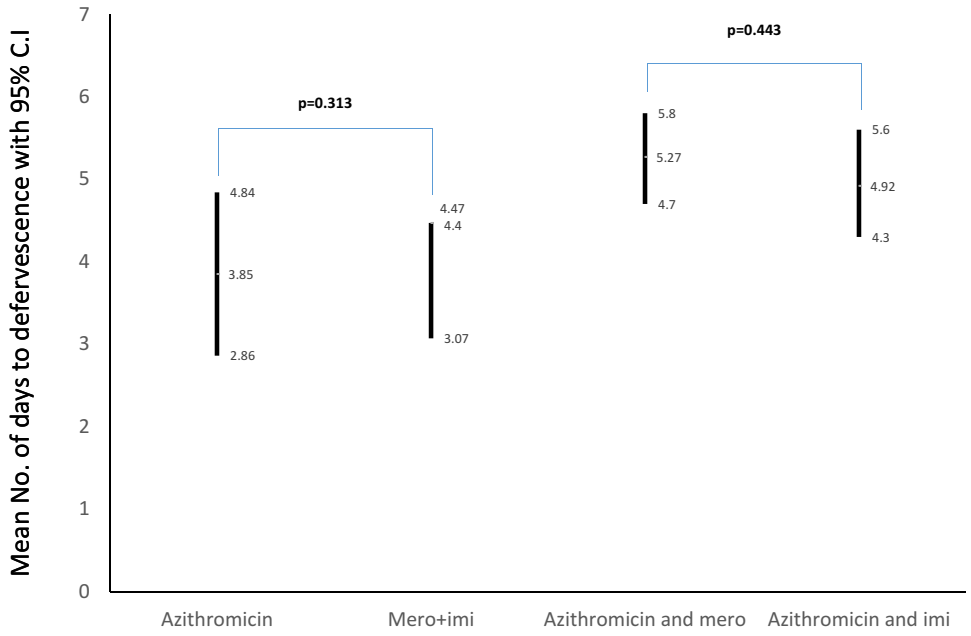

Figure 3 Defervescence time in relationship to administrated drugs.

Length of hospital stay was shorter on single drug therapy (6.55±4.16 vs 4.42±2.66; P <0.001). Only 1 patient died due to CNS infarct with a hemorrhagic component whereas all other patients were discharged home.

Discussion

The findings of our study demonstrate that fever defervescence occurred effectively within one week of either azithromycin or carbapenems. Qureshi et al also demonstrated that response of azithromycin and/or meropenem is effective with less than 5% treatment failure.[10] The time to defervescence of fever also seemed to be like non-XDR typhoid cases. The average defervescence among non-XDR typhoid cases reported previously was 3–4 days.[11,12] We found an average of 4–6 days, like Qureshi et al where they reported 6–7 days.[10] This shows that azithromycin or carbapenems are effective in treating XDR typhoid infection.

The most important observation we found was that single-drug antimicrobial therapy had a significant earlier defervescence as compared with combination therapy. We did not find any significant difference in outcome between carbapenems or azithromycin when used as a single agent. Randomized trials and a systematic review showed oral azithromycin for typhoid fever is effective and even better compared with fluoroquinolones, chloramphenicol, or ceftriaxone.[13,14] Although these studies were done on non-XDR strains, we found azithromycin to be very effective in fever defervescence and cure of XDR typhoid also. This has also been endorsed by many studies.[10,11,15] Azithromycin is effective since it can accumulate intracellularly more than 50 times that of blood, it has a long half-life, and it is rapidly absorbed from the gut.[13,14] Importantly, azithromycin retained sensitivity among XDR salmonella strains, and it can be safely used in these patients with good results. However, it is expensive and intravenous formulation may not be readily available in resource-poor settings. Carbapenems whether meropenem or imipenem can also be used as an alternative to azithromycin; although expensive, they both found to be very effective in fever defervescence. Excellent response to treatment with meropenem was also reported. In 2016, Munir et al reported a case in which all first-line antibiotics, as well as fluoroquinolones and third-generation cephalosporins, were ineffective against *Salmonella enterica* serovar *typhi*. Consequently, the patient had to be treated with meropenem, a carbapenem antibiotic that is not used to treat typhoid fever.[16]

Since XDR *Salmonella* strains have very limited sensitivity patterns, there are concerns regarding the use of single drug therapy in such cases. However, we found that single drug therapy whether azithromycin or carbapenems can be used with excellent outcome.

With typhoid fever treatment options diminishing, XDR typhoid presents itself as a severe threat that requires urgent attention. In Pakistan, azithromycin is the last oral treatment for patients with XDR typhoid. Carbapenems are costly and require parenteral administration, which is challenging in resource-poor settings where typhoid is endemic. Hence, the increasing use of carbapenems for XDR typhoid in Pakistan is of concern. Carbapenem resistance has already been found in non-typhoidal *Salmonella* serovars, indicating that, as evolution predicts, *Salmonella typhi* may not be far behind. Furthermore, there are several reports of azithromycin-resistant *Salmonella typhi* strains in South Asia. At least six cases have been reported from Nepal, India, and Pakistan.[17] According to the WHO, *Salmonella* species is a target for the development of novel antibiotics since the spread of such a resistant microbe on a global scale would be significant.[18]

Preventive measures are of utmost importance to curtail the spread of this highly resistant organism. *Salmonella typhi* is spread via feco-oral transmission. Vigho et al found community water supply and street food are the main risk factors for XDR typhoid.[19] Focus on the supply of safe potable drinking water and strict policy of street food safety should be implemented by the authorities. Vaccination against salmonella is also imperative. Pakistan implemented a Typhoid Conjugate Vaccine (Typbar-TCV®) vaccination campaign for children aged 6 months to 10 years old in high-risk regions of Hyderabad in 2018. A total of 207,000 children were immunized. This was followed by the introduction of TCV through its expanded program on immunization in 2019 and more than 9.5 million children aged 9 months to 15 years were vaccinated in 2019.[20]

The limitations of our study are that it is a retrospective chart review. Because patients were excluded from our study due to inadequate data, there may have been selection bias. Additionally, even though none of the patients had received either azithromycin or meropenem, the average duration to defervescence may have been impacted due to the antibiotics received prior to hospital presentation. Only patients who were hospitalized were included. To assess the optimal duration of antimicrobial therapy and the effectiveness of oral vs IV azithromycin, more clinical research, including randomized control studies, are required. However, the inclusion of blood culture-proven XDR typhoid is the strength of our study rather than relying on clinical judgment.

Conclusion

Our study has demonstrated that in patients with XDR typhoid receiving azithromycin or carbapenems, whether in single or combination therapy, the time to defervescence was comparable with the majority becoming afebrile within one week. Single antimicrobial therapy achieved defervescence earlier than combination therapy. Single drug azithromycin or carbapenems (whether meropenem or imipenem) can be used with excellent results.

Summary

- Mainly pediatric population.
- Single drug therapy resulted in an earlier onset of defervescence (5.03±2.98 vs 3.45±2.48; P <0.001).
- Length of hospital stay was also shorter in those on single drug therapy (6.55±4.16 vs 4.42±2.66; P <0.001).
- Low mortality (0.3%).

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on a reasonable request.

Ethics Approval and Consent to Participate

Only charts were examined in this retrospective observational study. So, there was no need for patient consent. However, there are ethical concerns with retrospective research; for this reason, the approval of the study was taken from institutional review board (IRB) and ethical review committee (ERC) of Liaquat National Hospital (ERC No. 0464-2019). This study complies with the Declaration of Helsinki.

Funding

There is no funding to report.

Disclosure

The authors declare no conflicts of interest in relation to this work.

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