Original Article

Salmonella typhi: Antibiotic sensitivity pattern in Dubai, United Arab Emirates

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ABSTRACT

Objective: Drug resistant typhoid fever is a major clinical problem. The object of this study was to determine the sensitivity pattern of various drugs used for treatment of typhoid fever.

Methodology: This was a hospital based descriptive study, conducted from April 2007- May 2009 at the Infectious Diseases Unit and Medical wards, Rashid hospital Dubai, UAE. Only those patients whose blood culture yielded *Salmonella typhi* were included in the study. The antibiotic susceptibility testing was performed on pure culture by two available methods; broth dilution by VITEK II automated Microbiology system and Disc Diffusion technique. The results were interpreted using Clinical and Laboratory Standards Institute (CLSI) standards. Sensitivity results were reported as sensitive or resistant based on CLSI criteria.

Results: A total of 118 patients fulfilled the inclusion criteria with the mean age + SD 29.2+7.9 years, 86.4% were males and 13.5% females. Most (94.9%) of the patients were expatriates and belong to the developing countries. The history of recent travel (within a month) to endemic areas was positive in 79.6%. The sensitivity pattern showed that the resistance rate was highest for Nalidix acid (71.5%), followed by Chloramphenicol (37.5%), Ampicillin (34.8%), Co-trimaxazole (30.7%), Augmentin (14%) and Ciprofloxacin (6%). Among the sixty four *S.typhi* tested for Chloramphenicol sensitivity; 30.2% isolates were found to be multi-drug resistant (i.e. resistant to Chloramphenicol, Ampicillin and Co-trimaxazole). Whereas, all the *S.typhi* isolates were sensitive to third generation Cephalosporins, Amikacin, Gentamycin, Tazocin and Meropenem.

Conclusion: In this study, we observed that the significant percentage of *S.typhi* is still resistant to the primary drugs. Whereas, the Quinolones and third generation Cephalosporins are potentially effective drugs against S.typhi, however, the increasing resistance to the Quinolones is a matter of concern.

KEY WORDS: *Salmonella typhi*, Antibiotics, Sensitivity, Resistance.

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INTRODUCTION

Typhoid fever is caused by *Salmonella Typhi* and it is usually acquired through the ingestion of water or food contaminated by the urine or feces of infected carriers.[1] Typhoid fever constitutes a major public health problem in many developing countries of the world and it has also been increasingly reported from the developed countries.[2] Typhoid fever causes 20 million cases annually with at least 70000 deaths and almost 80% of deaths occur in Asia.[3,4] It predominantly affects children and young adults[5] and if not treated appropriately has mortality rate of 30%, whereas, with proper treatment the mortality reduces to as low as 0.5%.[3]

Drug resistance is fast becoming a major problem in the management of this infection and the emergence of multi-drug resistance has great implications for the therapy, for example, patients infected with such strains are more ill at presentation, have a longer duration of illness and higher mortality. However, there are no pathognomic features to distinguish such infections from infections with fully sensitive *S.typhi* at presentation.[6] Chloramphenicol resistance became established globally in the *S. typhi* population after 1972 on plasmids of incompatibility group Inc H and Multi drug resistance (defined as resistance to all the first line antibiotics used to treat typhoid fever, i.e chloramphenicol, amplicillin and co-trimaxazole) has been endemic, particularly in Indian sub-continent and South East Asian countries since 1984.[7] Though initially, individual plasmids were known to code for multi drug resistance to each of these antibiotics, since 1988 a single plasmid was known to code for multi drug resistance. This plasmid belongs to incompatibility group H 11 and is highly permissible. In addition to Multi Drug Resistance (MDR) *S.typhi*, now resistances to floroquinolones have emerged as the newer challenges to the treatment of typhoid fever.[8] This study was undertaken to determine the frequency and pattern of *S.typhi* drug resistance in adult patients admitted to Rashid Hospital with typhoid fever.

METHODOLOGY

This was a hospital based descriptive study, conducted during the period from April 2007 to May 2009 at the Infectious Diseases Unit and Medical wards, Rashid hospital Dubai, UAE. Rashid hospital is one of the main tertiary care hospitals in Dubai and is Joint Commission International (JCI) accredited. Only those patients whose blood culture yielded *Salmonella typhi* were included in the study. The study was designed to include demographics (age, sex, nationality and travel history), clinical information, biochemical and hematological changes, and pattern of antibiotic sensitivity for *Salmonella typhi* observed in each patient. The data was entered into a structured proforma separately.

On admission, blood samples were aseptically collected from all the study patients for blood culture in aerobic and anaerobic blood culture bottles (Bact-Alert blood culture system), 5ml in each, all bottles were incubated at $37C^0$ up to 7 days. Once a positive culture bottle was detected, a Gram stain slide was prepared from the bottle and then a loopful of the positive blood culture bottle content was sub-cultured on blood agar, MacKonkey agar, Chocolate agar and Sabouraud agar and each was incubated at $37C^0$ for 18-24 hours. If lactose non fermenting colonies were detected then biochemical identification tests were performed using Biomerieux VITEK II automated system in addition to inoculation on triple sugar iron (TSI) slants. Final identification of isolates was confirmed serologically according to Kauffman-White classification using "Mast Assure" Salmonella (somatic and flagellar) antisera[9].

The antibiotic susceptibility testing was performed on pure culture using methods depending on availability; broth dilution by VITEK II automated Microbiology system or by Disc Diffusion technique. For broth dilution (VITEK II) the following antibiotics were tested: Ampicillin, Cefuroxime, Ceftriaxone, Ceftazidime, Gentamycin, Co-trimoxazole, Ciprofloxacin, Levofloxacin, Tazocin and Augmentin (Amoxicillin + Clavulinic acid). Whereas, for disc diffusion Meuller-Hiton agar was used and isolates were tested against the following antibiotics (Mast Diagnostics-Mast Group Ltd. Merseyside, UK): Ampicillin (10µg), Chloramphenicol (30µg), Cefuroxime (30µg), Ceftriaxone (30µg), Gentamycin (30µg), Co-trimoxazole (25µg), Nalidixic Acid (30µg), Ciprofloxacin (5µg) and Augmentin (30µg). The results were interpreted using Clinical and Laboratory Standards Institute (CLSI) standards. Sensitivity results were reported by both broth dilution and disc diffusion as sensitive or resistant based on CLSI criteria. Further blood tests included liver function test, full blood count, coagulation profile, malaria parasite, urea, electrolytes and random blood sugar.

The therapeutic intervention was planned as per the standard protocols for the management of typhoid fever. While awaiting the culture and sensitivity results, the empirical antimicrobial therapy was initiated with either Ceftriaxone (2gm/day) or Ciprofloxacin (400 mg IV/ 500mg oral BD), considering the likely antibiotic sensitivity pattern. The antimicrobial therapy was continued/changed accordingly after receiving the culture and sensitivity report. The majority of patients received antimicrobial therapy for the period of 10-14 days, whereas patients with complicated and drug resistant typhoid fever were treated for a longer period. The patients were discharged from the hospital once they became symptom free and their hematological and biochemical parameters returned to normal or near normal levels. Data was analyzed by SAS Enterprise Guide 4.1.

RESULTS

A total of 118 patients were recruited into the study. The mean age + SD of the patients under the study

Table-I: Clinical information of 118 study patients.

Clinical Parameter	*No (%)*	*Clinical Parameter*	*No. (%)*
Males	102(86.4%)		
Female	16(13.5%)	Signs:	
History of travel	94(79.6%)	Fever	118(100%)
Antibiotic history (+ve)	66(59.9%)	Relative bradycardia	52(44%)
Symptoms:		Anemia	54(45.7%)
Fever	118(100%)	Jaundice	24(20.1%)
Vomiting	64(54.7%)	Abd.tenderness	42(35.6%)
Abd. Pain	56(47.4%)	Splenomegaly	86(72.8%)
Diarrhea	52(44%)	Hepatomegaly	44(37.2%)
Headache	20(16.9%)	Rose spots	18(12.9%)
Cough	48(40.6%)	Confusion	10(8.4%)
Constipation	13(11%)		
Bleeding/rectum	6(6%)		

was 29.2+7.9 years (12-52 years) with male predominance, 102 (86.4%) vs 16 (13.5%) and there was no significant age difference between the two groups. Most (94.9%) of the patients were expatriates who visited or lived in the UAE and were working as laborers in the construction companies or agricultural fields. Among the study population; 72(61%) patients were from India, 16(13.5%) Bangladesh, 10 (8.4%) Pakistan, 6 (5%) Nepal, 6 (5%) UAE and 8(6.7%) from the other counties. The history of recent travel (within a month) to the endemic areas was positive in 94 (79.6%) of the patients. The duration of illness was 3-30 days before the patients attended the accident and emergency department of the hospital. Fever, vomiting, abdominal pain, diarrhea, were the main presenting symptoms, whereas; fever, relative bradycardia, anemia, abdominal tenderness, hepatomegaly, splenomegaly and jaundice were the main clinical signs (Table-I).

All *Salmonella typhi* isolates identified as gram negative lactose non-fermenting rods. They all showed alkaline slant and acid with little H2S and no gas production on Triple Sugar Iron slants. VITEK identification gave *Salmonella typhi* and then biochemical identification was confirmed by serological typing. All isolates showed positive agglutination with Poly H (flagellar), Poly O (somatic), mono d flagellar (dh) and mono d somatic (O9) antisera (Mast Assure). The sensitivity pattern shows that the resistance rate was highest for Nalidixic acid (71.5%), followed by Chloramphenicol (37.5%), Ampicillin (34.8%), Cotrimaxazole (30.7%), Augmentin (14%) and Ciprofloxacin (6%). Among the sixty four *S.typhi* isolates tested for chloramphenicol sensitivity, 20 (30.2%) were found to be multi-drug resistant (i.e. resistant to Chloramphenicol, Ampicillin and Co-trimaxazole). A summary of the antibiotic susceptibility tests is shown in Table-II.

The main hematological derangements included; decreased hemoglobin (Hb. 5-15.4 gm/dl) and thrombocytopenia (Plat. 3-636x10^3/µl). Whereas, disturbances in the liver function tests and prothrombin time beyond the reference range were also observed in the significant proportion of the patients (Table-II). Serum ALT levels were above the acute hepatitis range

Table-II: Antibiogram of S. Typhi isolated in the study patients.

Antibiotic	*Total isolates.*	*Sensitive Isolates (%)*	*Resistant isolates (%).*
Ampicillin	115	75 (65.2%)	40 (34.8%)
Cotrimaxazole	114	79 (69.3%)	35 (30.7%)
Ciprofloxacin	118	111 (94%)	7 (6%)
Nalidixic Acid	91	26 (28.5%)	65 (71.5%)
Gentamycin	118	118 (100%)	0
Amikacin	109	109 (100%)	0
Tazocin	116	116 (100%)	0
Chloramphenicol	16	10 (62.5%)	6 (37.5%)
Augmentin	43	37 (86%)	6 (14%)
Meropenem	104	104 (100%)	0
Cefuroxime	118	118(100%)	0
3rd Generation Cephalosporin	118	118 (100%)	0

(>10 times of normal) in 12(10.1%) patients (Range 14-1804 U/L).

In addition to the supportive treatment, all the patients received intravenous antibiotics at the time of admission and were discharged on oral antibiotics (Cefuroxime or Ciprofloxacin), if they required continuing antibiotics at home after the discharge from the hospital. The fever subsided on average by 8th day of admission (2-18 days), whereas the average hospital stay was 11.3 days (3-28 days). The course of the disease remained uneventful and all the patients were discharged in good health.

DISCUSSION

Typhoid fever continues to be a global health problem and it is an endemic in developing countries particularly the Indian subcontinent, south and Central America.[10] In this study; we also have the same observation. Dubai being a cosmopolitan city, people are visiting or living in Dubai from all over the world, but in our study most (>96%) of the patients belonged to developing countries and the majority (79.6%) of them had a positive history of recent travel to their countries, which shows high prevalence of this disease in those countries. In the past, typhoid could be treated successfully with inexpensive, widely available antimicrobial agents but the resistance to multiple antimicrobial agents in *S.typhi* has been a major problem, especially in Asia.[4] The emergence of antibiotic resistant strains of bacteria is closely related to the irrational use of antibiotics in treating human infections.

Drug resistance in typhoid fever is considered as one of the important factors in the morbidity and mortality of the disease. Since the introduction of Chloramphenicol in 1948, it has been the drug of choice in the treatment of typhoid fever in most parts of the world.[10] However, due to development of resistant to Chloramphenicol its use has declined significantly, particularly in developed countries where third generation Cephalosporins or Ciprofloxacin are used preferably. Therefore the sensitivity pattern of *S.typhi* is changing and there is re-emergence of sensitivity to Chloramphenicol but rising resistance to Ciprofloxacin.[12] The Chloramphenicol resistant rate has been reported variably, Khosla et al and Adalet et al have reported resistant rate of 83% and 100% respectively.[13,14] In other studies, Chloramphenicol resistance was found in 63.6% and in 33% *S. typhi* isolates[15,16], whereas, in this study we noted Chloramphenicol resistance in 37.5% isolates. Since the late 1980, cases of multi-drug resistant typhoid fever have rapidly increased and currently endemic zone in Asia stretch from Pakistan in the west and China in the east.[17] In addition, there is pseudo-epidemic zone in the Middle East. More than 40% of the populations of Persian Gulf states, especially of United Arab Emirates are expatriate workers, mainly from Indian subcontinent and the Far East. These workers travel repeatedly from their home countries to work and 70-80% multi-resistant *S.typhi* strains are imported and in this region 5-30% of *S.typhi* isolates are multi-drug resistant.[18] In our study, most of our patients were also workers from Indian subcontinent and majority of them had positive history of recent travel to their counties. Furthermore, the multi-drug resistance was observed in 31.2% which is quite consistent with the above report, however it was significantly lower than reported by Khosla et al (50-52%)[13], Misra et al (100%)[19] and Ijeoma et al (100%)[20] but higher than noted by Dash et al (16%).[21]

The floroquinolones group of drugs emerged as useful drugs for the treatment of multi-drug resistant S.typhi. But unfortunately, same factors of indiscriminate antibiotic use and cross resistance within the antibiotic group which lead to the emergence of Chloramphenicol resistant organism are still operative. Resistance to Ciprofloxacin is being reported both from the Indian Subcontinent as well as West.[22] The resistant to Ciprofloxacin has been reported variably from 5%-18.1%.[15,23] In this study, 6% of the isolates were resistant to Ciprofloxacin. Nalidix Acid resistance is a marker for predicting low-level resistance to Ciprofloxacin among S.typhi and also an indicator of treatment failure to Ciprofloxacin. Therefore, it is suggested that all S.typhi isolates should be screened for Nalidixic acid resistance along with Ciprofloxacin and it is advised to change the antibiotic if the isolate found to be is Nalidixic acid resistant.[23] In our study, the resistance to Nalidixic acid was observed in 71.5% *S.typhi* isolates, whereas only 6% isolates were

Table-III: Hematological and biochemical changes observed in 118 study patients.

Parameters	*No. (%)*	*Parameters*	*No. (%)*
Anemia	54(45.7%)	Low Albumin	48(40.6%)
Leucopenia	4(3.4%)	Raised ALT	94(79.6%)
Leucocytosis	6(5%)	Raised Alk.Phos	50(43.3%)
Thrombocytopenia	46(39%)	Raised T.Bil.	38(32.2%)
Raised B. Urea	12(10.1%)	Raised PT	74(62.7%)

resistant to Ciprofloxacin. The resistance rate is reported higher in the other studies; Lakshmi et al has reported 92-96% and Rodregues et al noted 82-88% resistance rate.[16,25]

The interesting finding in this study was that the none of *S.yphi* isolates were resistant to third generation Cephalosporin and Aminoglycoside, an observation which is also supported by Chowta et al[15] and Misra at al[19] who have reported 100% sensitivity to the above groups. Brian et al has also reported that the resistances to third generation Cephalosporins occur uncommonly.[26]

Furthermore, the other important finding in our study as mentioned earlier in the discussion was that the multi-drug resistance rate and resistance to Chloramphenicol was significantly lower than reported by many previous studies. Although, most of our patients were from the Indian subcontinent where resistance to primary drugs is still high and it was likely that they acquired infection in their home countries. The low prevalence of drug resistance to primary drugs most likely indicates that *S.typhi* is regaining its sensitivity to these drugs.

CONCLUSION

In this study, we observed that the significant percentage of *S.typhi* is still resistant to the primary drugs. Although, in comparison to most of the earlier reports the resistant rate was low, this reflects that the bacteria are regaining its sensitivity against the primary drugs. Whereas, the Quinolones and third generation Cephalosporins are potentially effective drugs against *S.typhi*, however, the rising resistance rate to the Quinolones is a matter of concern. To decrease the resistance rate, the rationale use of antibiotics should be encouraged.

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