Doi: 10.32677/IJCH.2016.v03.i02.009

Original article

Current antibiogram pattern of *Salmonella typhi* and *paratyphi* isolates and response to treatment in a tertiary care centre

S Udayakumar[1], P M Swathi[1], K Pushpalatha[1], G S Ravi[2]

From Departments [1]Paediatrics and [2]Microbiology, ESI Medical College and Postgraduate Institute of Medical Science and Research, Bengaluru, Karnataka, India

Correspondence to: S Udayakumar, No. 818, 13th Cross, Mahalaxmi Layout, Bengaluru - 560 086, Karnataka, India. Phone: +91-9448061125. E-mail: uday0908@gmail.com

Received – 16 April 2016 Initial Review – 03 May 2016 Published Online – 31 May 2016

ABSTRACT

Objective: The objective of this study is to study the current antibiotic sensitivity pattern of *Salmonella typhi* and *paratyphi* isolates and the clinical response of children with culture positive enteric fever (EF) to the specific antibiotic used as suggested by the sensitivity pattern. **Materials and Methods:** This is a retrospective study analyzing the records of 197 children treated for blood culture positive EF during 3 years from January 2013 to December 2015. Antibiogram pattern of *S. typhi*/*paratyphi* and response pattern to the antibiotic used as per antibiogram were analyzed. Kirby Bauer's disc diffusion method was used for antibiotic sensitivity using closed-loop stripping analysis standards. Temperature charts of the patients analyzed for response pattern of fever to the antibiotic started. **Results:** 197 culture positive cases were included in the study (*S. typhi*=190 and *paratyphi*=7). Sensitivity pattern to 9 out of 10 antibiotics tested was high and was low only to nalidixic acid (6.3%). There were 184 (93.4%) children whose antibiogram showed high sensitivity to cephalosporins and were treated with intravenous ceftriaxone (Group 1). The majority of children in this group (172/184, 93.5%) became afebrile by 7 days of therapy. 13 (6.6%) children whose antibiogram showed resistance to cephalosporins were treated with intravenous ciprofloxacin (Group 2). 9 of this group became afebrile by 7 days. 12 children from Group 1 and 4 children from Group 2 were considered as either reduced susceptibility or resistance to respective antibiotics and were treated with either azithromycin or piperacillin-tazobactam over the next 5-7 days successfully. **Conclusion:** Appropriate diagnosis using blood cultures and using 3rd generation cephalosporins as the first line of the drug in treating children with EF can reduce the duration of treatment, promote better compliance, reduce relapse rates, and may help decrease multi-drug resistant *S.typhi/partyphi* strains in the community..

Key words: *Culture positive, Enteric fever, Multi-drug resistant Salmonella typhi, Salmonella paratyphi, Salmonella typhi*

Enteric fever (EF) (typhoid fever) is an acute infectious disease due to infection with *Salmonella typhi* and *Salmonella paratyphi* bacteria. It has become rare in developed nations (with the incidence of <10/100000 population/year) due to improvement in food handling and water/sewage treatment. However, it remains a major public health issue in developing world like South Central and South East Asia (>100/1,00,000 population/year) [1]. An estimated 26.9 million typhoid cases occur annually, of which 1% result in death [2]. In addition, an estimated 5.4 million cases of paratyphoid occur each year [2]. *S. typhi* and *S. paratyphi* A are the predominant types responsible for infection in India, particularly during the summer months [3].

Although EF is effectively treated with antibiotics, drug resistance has been reported since the 1960s [4]. First, outbreak of multi-drug resistant *S. typhi* (MDRST), defined as resistance to first three commonly used antibiotics *viz*., chloramphenicol, ampicillin, and co-trimoxazole, was reported in 1989 [5]. With the worldwide emergence of these strains, and increasing morbidity and mortality due to infection with these strains, search for more effective antibiotic/s became a necessity. Fluoroquinolones such as ciprofloxacin and ofloxacin emerged as ideal candidates, but their efficacy was also short lived as their wide spread, and indiscriminate use in the 1990s led to emergence of resistance [1,2,6-12]. Cephalolosporins, especially 2nd and 3rd generation drugs, were next tried and today, these are used as the drugs of choice against EF world over. However, with the widespread use of these agents, there is an emerging trend of fully or partially resistant strains of *Salmonella* to these drugs too [2,13-15]. More and more antibiotics such as azithromycin and aztreonam are being suggested by various authorities to treat these truly multidrug-resistant isolates [2,16,17]. The result of this is twofold: (1) The cost of therapy has steadily increased, and (2) the probability of domiciliary management is steadily diminishing. Hence, this study was undertaken to know the current antibiogram pattern of *S. typhi* and *paratyphi* isolates and the clinical response of children with culture positive EF to the specific antibiotic used as suggested by the antibiogram.

MATERIALS AND METHODS

This is a retrospective study involving analysis of data of children admitted and treated for EF over a period of 3 years from January 2013 to December 2015 at ESI Medical College and Postgraduate Institute of Medical Sciences and Research, Bengaluru, Karnataka, India. A total of 197 records of children admitted and treated for culture positive EF were analysed for the antibiogram pattern and their pattern of response to treatment to the antibiotics used as per the antibiogram. Kirby-Bauer disc diffusion method was used for antibiotic sensitivity using closed-loop stripping analysis standards.

Children between 1 and 18 years of age with EF whose blood cultures were positive for *S.typhi* or *paratyphi* included in the study. Children, who received antibiotic therapy before admission to our hospital or where incomplete records were available, were excluded from the study. Temperature charts of the patients were analyzed to assess the response pattern of fever to the antibiotics used and duration to defervescence noted.

RESULTS

Analysis of antibiograms of 197 children treated for culture positive EF revealed that the isolates of *S. typhi* (n=190) and *S. paratyphi* (n=7) were sensitive to 9 out of 10 antibiotics tested. Sensitivity to ciprofloxacin was 94.4% in comparison to sensitivity to nalidixic acid which was only 6.3%, thus showing discordance in patterns of sensitivity to fluoroquinolones. Surprisingly, sensitivity to primary three antibiotics *viz*., ampicillin, chloramphenicol, and co-trimoxazole was high (Table 1).

A total of 184 children were treated with intravenous ceftriaxone as their antibiogram showed sensitivity to cephalosporins (Group 1). 172 children among this group had become afebrile by 7 days of treatment. The remainder, i.e,. 12 children were considered as either having reduced susceptibility or resistance to this drug and were treated with either azithromycin or piperacillin-tazobactam over the next 5-7 days successfully. 13 children were treated with intravenous ciprofloxacin as their antibiogram showed resistance to cephalosporins (Group 2). 9 children from this group had become afebrile by 7 days of treatment. The remainder, i.e. 4 children were considered as either having reduced susceptibility or resistance to this drug and were treated with either azithromycin or piperacillin-tazobactam over the next 5-7 days successfully (Table 2).

DISCUSSION

In this study, we found high levels of sensitivity of *S. typhi* and *S. paratyphi* to both cephalosporins and fluoroquinolones, whereas, in a recent study, Narain and Gupta have reported intermediate to low sensitivity to both these groups of antibiotics [18]. Our study revealed high sensitivity pattern to the primary three antibiotics in contrast to low sensitivity pattern reported in the above study (Table 3). We found low levels of MDRST and high levels of resistance to nalidixic acid. Kumar et al. [12], Madhulika et al. [19], Nagshetty et al. [20], Bhattacharya et al. [21], and Shetty et al. [22] have all reported similar results in their respective studies.

The Indian network for surveillance of antimicrobial resistance in its large multicenter study of 3275 isolates of *S. typhi* and *S. paratyphi* all over India over a period of 3 years have reported re-emergence of susceptibility to ampicillin, cotrimoxazole and chloramphenicol, a decline in MDR strains, and a high resistance to nalidixic acid [23]. This study also has reported continued high efficacy of 3rd generation cephalosporins against these organisms. The present study is largely in concurrence with these findings (Table 4).

Table 1: Antibiogram showing sensitivity

Drugs	*S. typhi* (n=190)		*S. paratyphi* (n=7)	
	Sensitivity in numbers	Percentage	Sensitivity in numbers	Percentage
Ampicillin	170	89.5	3	42.8
Cotrimoxazole	171	90	4	57.1
Cephalosporins	178	93.5	6	85.7
Furazolidone	169	88.9	6	85.7
Nalidixic acid	12	6.3	2	28.6
Ciprofloxacin	152	80.0	5	71.4
Chloramphenicol	166	87.4	7	100
Piperacillin-Tazobactam	178	93.7	7	100
Azithromycin	190	100	7	100
Tetracycline	190	100	6	85.7

S. typhi*: *Salmonella typhi*, *S. paratyphi*: *Salmonella paratyphi

In this study, 93% of the children in Group 1 were afebrile by 7 days of treatment with ceftriaxone (Table 2). This demonstrates that ceftriaxone used as first line drug continues to be very effective in inducing defervescence quickly thereby reducing the duration of hospital stay. There was only one child coming back with relapse indicating using ceftriaxone as the first line of therapy has almost 0% relapse rates. Hence, authorities recommend 3rd generation cephalosporins as the drug of choice in treating EF [1,2,6,16].

Table 2: Pattern of response to antibiotic therapy

Treatment Groups	Day of defervescence of fever [days (%)]		
	3-5	5-7	>7
Group 1 (n=184)	48 (26.0)	123 (67.0)	13 (7.0)
Group 2 (n=13)	-	9 (69.2)	4 (30.8)

Kumar et al. in their article have suggested that a significant decrease in the proportion of MDR strains indicates that the MDR typhoid epidemic in the country is waning [12]. This may also be due to preferential use of 3rd generation cephalosporins as the first line of therapy by clinicians to treat EF in the recent times. The present study has shown high sensitivity pattern to the primary three antibiotics which throw up the possibility of using these drugs for managing EF

Table 3: Comparison of sensitivity patterns with Narain and Gupta study

Drugs	*S. typhi*		*S. paratyphi*	
	Narain and Gupta study (n=220)	Present study (n=190)	Narain and Gupta study (n=5)	Present study (n=7)
Ampicillin	131 (59.5)	170 (89.5)	3 (60)	3 (42.8)
Cotrimoxazole	148 (67.3)	171 (90)	4 (80)	4 (57.1)
Cephalosporins				
Ceftriaxone	164 (74.5)	178 (93.7)	3 (60)	6 (85.7)
Cefotaxime	64 (29.4)	165 (93)	0 (100)	6 (85.7)
Cefuroxime	135 (61.4)		4 (80)	
Ceftazidime	205 (93.2)		4 (80)	
Cefperazone/salbactam	220 (100)		5 (100)	
Furazolidone		169 (88.9)		6 (85.7)
Nalidixic acid		12 (6.3)		2 (28.6)
Ciprofloxacin	133 (58.6)	152 (80)	4 (80)	5 (71.4)
Ofloxacin	133 (60.5)		4 (80)	5 (71.4)
Chloramphenicol	205 (93.2)	166 (87.4)	3 (60)	7 (100)
Piperacillin-Tazobactam	220 (100)	178 (93.7)	5 (100)	7 (100)
Azithromycin	120 (54.5)	190 (100)	3 (60)	7 (100)
Tetracycline		190 (100)		6 (85.7)
Gentamicin	116 (52.5)		2 (40)	
Tobramycin	198 (90.0)		5 (100)	
Amikacin	164 (74.5)		5 (100)	
Nitrofurantoin	137 (62.3)		5 (100)	
Meropenem	204 (92.7)		5 (100)	

S. typhi*: *Salmonella typhi, S. paratyphi*: *Salmonella paratyphi

Table 4: Comparison of INSAR study with the present study

	INSAR study [23] - antibiogram of *S. typhi* (2511)			Present study (n=197)		
Year	2008 (n=430)	2009 (n=694)	2010 (n=1387)	2013 (n=56)	2014 (n=63)	2015 (n=71)
Antibiotics		% Sensitive			% Sensitive	
Ampicillin	95	96	89	87.5	90.5	90.1
Chloramphenicol	96	97	95	87.5	85.7	88.7
Cotrimoxazole	96	95	94	86.4	92.5	90.4
Ceftriaxone	100	97	100	89.3	93.7	97.2
Ciprofloxacin	99	75	59	79.3	82	80
Nalidixic acid	23	22	8.3	3.5	9.5	5.6

***S. typhi*: *Salmonella typhi,* INSAR: Indian Network for Surveillance of Antimicrobial Resistance**

in resource-poor settings, as also suggested by Kumar et al. in their study [12].

Treatment with cephalosporins on empirical basis needs to be checked both by general practitioners and specialists caring for children and adults to maintain the susceptibility pattern of Salmonella to this drug. The cost and route of administration make ceftriaxone less suitable in resource-poor settings. The oral 3rd generation cephalosporin cefixime has been reported to be inferior to other oral agents in terms of fever clearance time and treatment failure [24].

Indian Academy of Pediatrics task force on management of EF recommends azithromycin for oral therapy where initial treatment for uncomplicated EF has failed and, advocates use of aztreonam or imipenem as the second line for treatment of complicated EF [16]. Our study has shown high sensitivity pattern to azithromycin which can, therefore, be used as an effective alternative oral agent for management of uncomplicated EF when the cheaper oral agent is needed as also suggested by Crump and Mintz in their article [1].

India being a high incidence country for EF, continued vigilance regarding appropriate diagnosis, rational use of antibiotics is needed to sustain the gains. Although with the improving living standards and general hygiene there is a declining trend in incidence and prevalence, there is probably still a necessity for typhoid vaccine to be made part of the national immunization schedule.

Our study has certain limitations; it is a retrospective study done in a single centre and sample size is small. Minimum inhibitory concentration trends of isolates could not be estimated as this facility was not available in our setup; hence, reduced susceptibility strains could not be identified.

CONCLUSIONS

Appropriate diagnosis using blood cultures and using 3rd generation cephalosporins as the first line of drug in treating children with enteric fever can reduce the duration of treatment, promote better compliance, reduce relapse rates, and may decrease multidrug resistant S.typhi/paratyphi strains in the community.

REFERENCES

1. Crump JA, Mintz ED. Global trends in typhoid and paratyphoid fever. Clin Infect Dis. 2010;50(2):241-6.
2. Salmonella BZ. In: Kliegman RM, Stanton BF, Schor NF, St. Geme JW, editors. Nelson Text Book of Pediatrics. 1st South Asia Edition. New Delhi: Reed Elsevier India Pvt, Ltd.; 2016. p. 1382-93.
3. Gautam V, Gupta NK, Chaudhary U, Arora DR. Sensitivity pattern of *Salmonella* serotypes in Northern India. Braz J Infect Dis. 2002;6(6):281-7.
4. Agarwal SC. Chloramphenicol resistance of *Salmonella* species in India, 1956-61. Bull World Health Organ. 1962;17:331-5.
5. Murti BR, Rajyalakshmi K, Bhaskaran CS. Resistance of *Salmonella typhi* to chloramphenicol. I. A preliminary report. J Clin Pathol. 1962;15:544-51.
6. Pegues DA, Miller SI. Salmonellosis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw Hill; 2012. p1274-81.
7. Lynch MF, Blanton EM, Bulens S, Polyak C, Vojdani J, Stevenson J, et al. Typhoid fever in the United States, 1999-2006. JAMA. 2009;302(8):859-65.
8. Rahman BA, Wasfy MO, Maksoud MA, Hanna N, Dueger E, House B. Multi-drug resistance and reduced susceptibility to ciprofloxacin among *Salmonella enterica* serovar Typhi isolates from the Middle East and Central Asia. New Microbes New Infect. 2014;2(4):88-92.
9. Harish BN, Menezes GA. Antimicrobial resistance in typhoidal *Salmonella.* Indian J Med Microbiol. 2011;29(3):223-9.
10. Maskey AP, Basnyat B, Thwaites GE, Campbell JI, Farrar JJ, Zimmerman MD. Emerging trends in enteric fever in Nepal: 9124 cases confirmed by blood culture 1993-2003. Trans R Soc Trop Med Hyg. 2008;102(1):91-5.
11. Brown JC, Thomson CJ, Amyes SG. Mutations of the gyrA gene of clinical isolates of *Salmonella typhimurium* and three *Salmonella* species leading to decreased susceptibilities to 4-quinolone drugs. J Antimicrob Chemother. 1996;37(2):351-6.
12. Kumar Y, Sharma A, Mani KR. Antibiogram profile of *Salmonella enterica* serovar Typhi in India - A two year study. Trop Life Sci Res. 2013;24(1):45-54.
13. Parry CM, Threlfall EJ. Antimicrobial resistance in typhoidal and nontyphoidal Salmonellae. Curr Opin Infect Dis. 2008;21(5):531-8.
14. Saha SK, Talukder SY, Islam M, Saha S. A highly ceftriaxone-resistant *Salmonella typhi* in Bangladesh. Pediatr Infect Dis J. 1999;18(4):387.
15. Medalla F, Hoekstra RM, Whichard JM, Barzilay EJ, Chiller TM, Joyce K, et al. Increase in resistance to ceftriaxone and nonsusceptibility to ciprofloxacin and decrease in multidrug resistance among *Salmonella* strains, United States, 1996-2009. Foodborne Pathog Dis. 2013;10(4):302-9.
16. Kundu R, Ganguly N, Ghosh TK, Yewale VN, Shah RC, Shah NK. Management of enteric fever in children. Indian Pediatr. 2006;43(10):884-7.
17. Butler T. Treatment of typhoid fever in the 21st century: Promises and shortcomings. Clin Microbiol Infect. 2011;17(7):959-63.
18. Narain U, Gupta R. Emergence of resistance in community-acquired enteric fever. Indian Pediatr. 2015;52(8):709.
19. Madhulika U, Harish BN, Parija SC. Current pattern in antimicrobial susceptibility of *Salmonella typhi* isolates in Pondicherry. Indian J Med Res. 2004;120(2):111-4.
20. Nagshetty K, Channappa ST, Gaddad SM. Antimicrobial susceptibility of *Salmonella typhi* in India. J Infect Dev Ctries. 2010;4(2):70-3.
21. Bhattacharya SS, Das U, Choudhury BK. Occurrence & antibiogram of *Salmonella typhi* & S. Paratyphi A isolated from

Rourkela, Orissa. Indian J Med Res. 2011;133:431-3.
22. Shetty AK, Shetty IN, Furtado ZV, Antony B, Boloor R. Antibiogram of Salmonella isolates from blood with an emphasis on nalidixic Acid and chloramphenicol susceptibility in a tertiary care hospital in coastal Karnataka: A prospective study. J Lab Physicians. 2012;4(2):74-7.
23. Indian Network for Surveillance of Antimicrobial Resistance Group. Antibiogram of *S. enterica* serovar Typhi and *S. enterica* serovar Paratyphi A: A multi-centre study from India. WHO South-East Asia J Public Health. 2012;1(2):182-8.
24. Pandit A, Arjyal A, Day JN, Paudyal B, Dangol S, Zimmerman MD, et al. An open randomized comparison of gatifloxacin versus cefixime for the treatment of uncomplicated enteric fever. PLoS One. 2007;2(6):e542.

Funding: None; Conflict of Interest: None Stated.

How to cite this article: Udayakumar S, Swathi PM, Pushpalatha K, Ravi GS. Current antibiogram pattern of *Salmonella typhi* and *paratyphi* isolates and response to treatment in a tertiary care centre. Indian J Child Health. 2016; 3(2):120-124.