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SENSITIVITY PATTERN OF SALMONELLA TYPHI IN PATIENTS WITH TYPHOID SMALL BOWEL PERFORATIONS

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ABSTRACT

Background: Enteric fever caused by Salmonella Typhi, gram negative bacilli, is counted as a major public health problem, especially in underdeveloped countries of tropic region. One of the notorious and potentially lethal complications of typhoid fever is small bowel perforation. Chloramphenicol, in 1948 converted this lethal disease to curable one. Efficacy of this drug reduced within 2 years. These strains of salmonella typhi were also found resistant to sulphonamide, tetracycline and streptomycin and are called as multidrug-resistant strains salmonella typhi (MDRST). Due to this resistance amoxycilin, and trimethprim with sulphamethoxazole replaced these drugs. Emergence of MDRST led to the use of quinolones as the first line drug. With the developing resistance to flouroquinolones, 3rd generation cephalosporins such as ceftriaxone and cefotaxime are now increasingly being used in the treatment of typhoid fever.

Materials and Methods: This prospective, descriptive study was conducted at surgical ward- III of Liaquat university hospital, Hyderabad from Jan 2007 to Dec 2010. All patients of either sex above the age of 02 years having high-grade fever for more than 1 week associated with features of peritonitis secondary to hollow viscus perforation and later on confirmed through various investigations as cases of perforation of hollow viscus due to typhoid were included in the study.

Subject's data was collected for age, sex, mode of presentation, treatment history, & blood culture and sensitivity pattern. Variable studied in this study were age, sex & Sensitivity pattern of Salmonella Typhi in Typhoid small bowel perforation Antibiotics assessed for sensitivity after culture of the organism were: ampicillin, amoxycilin, augmentin, ceftriaxone, cefotaxime, ceftazidime, cefixime, cefipime, cefuroxime, chloramphenicol, amikacin, gentamicin, Ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, imipenem, meropenem, Piperacillin with Cefbactum and sulphonamide derivative.

Results: During the study period of 4 years; a total of 41/187(21.92%) blood culture isolates were identified for salmonella typhi. Mean age of this group of patients was 27.35 years. Amongst them 113(60.42%) were male and 74(39.57%) were female. The antibiotics sensitivity showed that all organisms were sensitive to imipenem and meropenem while sensitivity of the organism to Piperacillin with Sulbactum was 97.56%. 90.24% isolates were sensitive to cefotaxime and ceftazidime while 95.12% & 92.68% to Cefipime & Ceftriaxone respectively. Sensitivity pattern of salmonella typhi to ciprofloxacin, ofloxacin, levofloxacin and moxifloxacin was 80.48%, 73.17%, 82.92% and 85.36% respectively. 41.46% Isolates were resistant to amoxycilin; and 63.41% to Chloramphenicol.

Conclusion: This study concludes that there is an increasing resistant trend of salmonella typhi to 2nd line drugs like ciprofloxacin, and 3rd generation cephalosporins. At the same time there is re-emergence of chloramphenicol sensitivity.

Keywords: Typhoid fever, Perforation of small bowel, Blood culture & sensitivity pattern

INTRODUCTION

Salmonella typhi are gram-negative bacilli, which are transmitted through faeco-oral

route, and is responsible for typhoid fever[1]. One of the notorious and potentially lethal complications of typhoid fever is small bowel perforation[2]. Enteric fever is counted as a major public health problem, especially in underdeveloped countries of tropic region[3]. In one study it has been reported that highest incidence of typhoid fever is found in South East Asia, Africa, and in Latin America[4].In India, Nigeria and in Indonesia mortality rate due to typhoid fever is noted at 12-32% in different studies[5, 6]. The factors responsible for increase in the incidence of typhoid fever in these countries is due to poor sanitary conditions, supply of contaminated water, rapid population growth, and increased urbanization and overburden health care system[1, 4].

In 1948 with the introduction of chloramphenicol this lethal disease was converted to curable disease[7]. Efficacy of this drug reduced within 2 years. However until in 1970 when resistance to it lead to major public health problem through out the world, especially in Latin America[8] and in Asia[9, 10].Although chloramphenicol is still the drug of choice in many countries in the management of typhoid fever but is used to limited extent due to its severe toxicity[11]. These strains of salmonella typhi were also found resistant to sulphonamide, tetracycline and streptomycin[7]. Due to this resistance amoxycilin, and trimethprim with sulphamethoxazole replaced these drugs.

It was until late 1990's when resistance to these all-first line drugs erupted & in one series it was found to be near 68.9% in one area of India[7, 12]. These strains are called as multidrug-resistant strains salmonella typhi (MDRST). In Karachi typhoid fever caused by MDRST has been isolated in 1986. However its frequency has increased to a very large extent for the last 7 years[14].

Emergence of MDRST led to the use of quinolones as the first line drug in the treatment of adult patients with typhoid fever[13]. However sensitivity to ciprofloxacin of salmonella typhi has decreased in endemic areas of Asia, especially in Indian subcontinent as shown by Threlfall and Ward in their study[15]. In 1997 such strains caused typhoid fever in 8000 people and killed 150 of them in Tajikistan[16].

With the developing resistance to flouroquinolones, 3rd generation cephalosporins such as ceftriaxone and cefotaxime are now increasingly being used in the treatment of typhoid fever. In study by Threlfall and Ward they have mentioned that all strains of salmonella typhi were sensitive to these drugs[15]. However in another study by Saha SK et al[17] there has been reports of sporadic resistance to these drugs as well.

Because of this increasing resistance of salmonella typhi to 2nd line drugs and at the same time presentation of many cases of small bowel perforation secondary to typhoid fever compelled us to conduct study to assess sensitivity pattern of this organism in our setup.

MATERIALS AND METHODS

This was a prospective, descriptive study conducted at surgical ward- III of Liaquat university hospital, Hyderabad, Pakistan from Jan 2007 to Dec 2010. All patients of either sex above the age of 02 years having high-grade fever for more than 1 week associated with features of peritonitis secondary to hollow viscus perforation and later on confirmed through various investigations as cases of perforation of hollow viscus due to typhoid were included in the study. All patients below the age of 02 years and with non-typhoid hollow viscus perforation were excluded.

These patients were admitted in ward. Detailed history was taken from these patients especially in data related to age, symptomatology especially symptoms of high grade fever with step-ladder pattern, duration of symptoms of peritonitis, and duration, dose and type of antibiotic used during this illness; and any prior investigation performed to diagnose disease. Thorough examination was performed with special focus on variables like fever, anemia, and abdominal examination. Investigations were performed to establish diagnosis and to assess general fitness. These include complete blood count, blood sugar, blood urea, serum electrolytes; blood culture and sensitivity, typhidot test, x-ray abdomen in erect position, ultrasound abdomen and where required ECG and chest x-ray. Preoperative diagnosis was made. General management of the patients was started which includes I/V fluids, I/V antibiotics like injection ceftriaxone 1 gram and metronidazole 500mg(after getting blood samples for blood culture), nasogastric suction, measurement of urinary volume after passing two ways foley's catheter. Preoperative resuscitation performed and patient's condition was optimized. Patients were briefed about the diagnosis and procedure to be undertaken or performed. Patients were informed and permission was obtained. They were assured that their participation is voluntary with no harms to them in terms of getting due treatment. They were also given right to withdraw from study without putting any reasons. Postoperatively same antibiotics continued until blood culture report came.

Subject's data was collected on preformed proforma for age, sex, mode of presentation, treatment history and blood culture & sensitivity pattern. Variable studied in this study were age, sex, & Antibiotic sensitivity pattern of Salmonella Typhi in these patients.

All the blood samples submitted for culture & sensitivity. Initial identification of salmonella typhi was made with routine culture technique that was later confirmed by slide agglutination method. Antibiotic sensitivities were assessed by stokes or Kirby Bauer disc diffusion method. Antibiotics assessed for sensitivity after culture of the organism were: ampicillin, amoxycilin, augmentin, ceftriaxone, cefotaxime, ceftazidime, cefixime, cefipime, cefuroxime, chloramphenicol, amikacin, gentamicin, Ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, imipenem, meropenem, Piperacillin with Sulbactum and sulphonamide derivative. Results were compiled and compared to national and international literature. Data was analyzed using spss version 10.

RESULTS

During the study period of 4 years a total of 187 patients of small bowel perforations, most probably due to typhoid, were admitted. Blood of all these patients was sent for culture & sensitivity. Out of these 41 patients (21.92%) yielded positive blood culture for salmonella typhi. All these cultured organisms were submitted to different antibiotics for sensitivity.

Mean age of this group of patients was 27.35 years. Amongst them 113(60.42%) were male and 74(39.57%) were female making the male to female ratio of 1.52: 1.00.

The antibiotics sensitivity using disc diffusion method (Table.1) showed that all organisms were sensitive to imipenem and meropenem while sensitivity of the organism to Piperacillin with Sulbactum was found in 40 (97.56%) patients. 39 (95.12%) organisms were sensitive to Cefepime and 37 (90.24%) organisms to cefotaxime and ceftazidime. Sensitivity of Ceftriaxone was present in 38 (92.68%) organisms. Cefixime and Cefuroxime showed sensitivity in 31 (75.60%) and in 32 (78.04%) patients respectively.

TABLE 1.

NUMBER OF SALMONELLA TYPHI ISOLATES FOUND SENSITIVE TO ANTIBIOTICS BY DISC DIFFUSION METHOD (N=41)

Antibiotics screened	No & % of isolates
Ampicillin	07 (17.07%)
Amoxicillin	17 (41.46%)
Augmentin	18 (43.90%)
Ceftriaxone	38 (92.68%)
Cefotaxime	37 (90.24%)
Ceftazidime	37 (90.24%)
Cefixime	31 (75.60%)
Cefipime	39 (95.12%)
Cefuroxime	32 (78.04%)
Chloramphenicol	26 (63.14%)
Amikacin	32 (78.04%)
Gentimycin	27 (65.85%)
Ciprofloxacin	33 (80.48%)
Oflaxacin	30 (73.17%)
Levofloxacin	34 (82.92%)
Moxifloxacin	35 (85.36%)
Imipenem	41 (100%)
Meropenem	41 (100%)
Piperacillin with Sulbactam	40 (97.56%)
Sulphonamide derivatives	06 (14.63%)

Amongst the Quinolones, Moxifloxacin has got the highest sensitivity i-e in 35 (85.36%) patients while sensitivity pattern of salmonella typhi to ciprofloxacin, ofloxacin & levofloxacin was 33(80.48%), 30(73.17%) and 34(82.92%) respectively.

From the penicillin derivatives 17(41.46%), 7 (17.07%) and 18(43.90%) isolates were sensitive to amoxicillin, ampicillin, and augmentin.

Among the aminoglycoside group gentamicin, and amikacin showed positive sensitivity ratio of salmonella typhi in 27(65.85%) and 32(78.04%) patients respectively.

Twenty six (63.14%) & 06(14.63%) isolates were found sensitive to Chloramphenicol and sulphamethoxazole-Trimethoprim.

DISCUSSION

Salmonella typhi, the organism responsible for enteric fever is counted as leading cause of morbidity and mortality through out the world. It is one of the common causes of small bowel perforation in many developing countries especially in south East Asia. However after the introduction of chloramphenicol in 1948 this lethal disease was counted as the completely curable disease. With the passage of time organism got resistance to this and other first line drugs like sulphonamide derivatives, ampicillin and tetracycline. These organisms were called as MDRST organisms. These organisms were now treated with quinolones and 3rd generation cephalosporins. There have been reports that organism is getting increasing resistance to these 2nd line drugs[18]. These patients have also been found in countries like USA and UK after their visits to south east asia[17, 19].

The sensitivity of salmonella typhi has continuously changed. Initially chloramphenicol was used to treat this infection. However emergence of resistant strains to this and other first line drugs like sulphonamide derivatives, ampicillin, amoxicillin, and tetracycline decreased their usage to treat typhoid fever. The can be depicted from the study by Sadarsana et al at Calicut in which they have mentioned that resistance of salmonella typhi to first line drugs was < 15% in 1982 and it increased to 68.9% in 1988-89. However recent studies have clearly mentioned the decreasing trend of resistance of this organism to Chloramphenicol and other first line drugs. One such study varied out by Raveendran R et al[20] mentioned 27% resistance in 2003 which reduced to 14.9% in 2008.

Same trend has also been reported by Ranju C et al and Gautum V et al in their studies. In this study 36.59% organisms were resistant to Chloramphenicol and other first line drugs.

Since the emergence of multidrug-resistant salmonella typhi (MDRST) in early 90's Quinolones are the drug of choice to treat these MDRST infections. In one study by Shaikh RB et al[21] sensitivity of salmonella typhi to quinolones was reported as > 98%. Studies by Munir T et al[22] and Nadeem et al[23] reported 100% sensitivity of salmonella typhi to ciprofloxacin and ceftriaxone. In our study sensitivity of both drugs was 80.48% and 92.68% respectively. However studies by Akhtar R et al [24] at Karachi, and Raveendran R et al at India mentioned increasing resistance of salmonella typhi to ciprofloxacin. In their studies they have mentioned 29/82 organisms and 24/431 isolates were resistant to ciprofloxacin respectively.

Due to this increasing resistance of salmonella typhi to ciprofloxacin case of typhoid perforation has increased to the significant extent. In their studies by Raveendran R et al, Gautum V et al, and Akhtar R et al 100% sensitivity of the organism to 3rd generation cephalosporins especially ceftriaxone has been mentioned. In study by Shaikh RB et al 90 –91% sensitivity of salmonella typhi to ceftriaxone has been reported. Mushtaque MA in his study has reported 17.5% organisms resistant to Ceftriaxone.

Sensitivity of salmonella typhi to meropenem & imipenem was 100% while of Piperacillin with Sulbactum; it was 97.56% in this study. Study by Mushtaque MA has also reported 100% sensitivity of organism to these antibiotics. These drugs are now considered safe choice in patients with typhoid bowel perforation.

CONCLUSION

This study concludes that there is an increasing resistant trend of salmonella typhi to 2nd line drugs like ciprofloxacin, and 3rd generation cephalosporins. At the same time there is re-emergence of chloramphenicol sensitivity. Therefore sensitivity pattern of salmonella typhi must be sought if patient is not responding to conventional antibiotics so that life- threatening complications associated with typhoid fever like typhoid perforation of small bowel may be decreased. In surgical wards patient presenting with typhoid perforation may be started to meropenem or imipenem group until sensitivity pattern is defined through blood or tissue culture.

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REFERENCES

1. Madukosiri CH, Edike T, Ghandi EO. Comparative studies of susceptibility of salmonella typhi to antibiotics and some plant extracts. Nig J of Biochem & Molec Biolog. 2009; 24(1): 16-21.
2. Neil J, Mortensen McC, Jones O. The small & large intestines. In Bailey & Love's short practice of surgery by Russel RCG, Williams NS, Bulstrode CJK. 2004; 68: 1173.
3. Gautum V, Gupta NK, Chaudhary U, Arura DR. Sensitivity pattern of salmonella serotypes in northern India. Braz J Infect Dis 2002; 6: 281-7.
4. Nair L, Sudarsana. Changing sensitivity pattern of salmonella typhi in Calicut; Calicut Med J 2004; 2(1): e 2.
5. Edelman R, Levine MM. Summary of an international workshop on typhoid fever. Rev Infect Dis 1986; 8; 329-49.
6. Anderson ES, Joseph SW, Nasution Q. Febrile illness resulting in hospital admission, A bacteriological & serological studying Jakarta, Indonesia. Am J Trop Med Hyg 1976; 25: 116-121.
7. Mushtaque MA. What after ciprofloxacin and ceftriaxone in the treatment of Salmonella Typhi. Pak J Med Sci 2006; 22(1): 51-54.
8. Olark J, Galindo ES. Salmonella typhi resistant to C, A and other antimicrobial agents: Strains isolated in extensive typhoid fever epidemic in Mexico. Antimicrobial agents Chemother. 1973; 4: 597-601.
9. Panicker CK, Vimala KN. Transferable chloramphenicol resistance in salmonella. Nature 1972; 239: 109-110.
10. Mendel, Douglas and Bennetts. Principles & practice of Infectious diseases, 4th Edi; Year 2005;2: 2017-2020.
11. Dambrot C. Women's History. Month: Typhoid Marry. Google.http:// www.cbwinfo.com/biological/pathogens/ST.html.
12. Sudarsana J, Lathi N, Devi KI. Multidrug-resistant salmonella typhi in Calicut south India. IJMR [A] 95, 1992; 3: 68-70.
13. Ranju C, Pais P, Ravindran GD, Singh G. Changing pattern of antibiotic sensitivity of salmonella typhi. Natl Med J India 1998; 11(6): 266-7.
14. Farooqui BJ. Genetic analysis of multidrug-resistant strains of salmonella typhi isolated in Karachi, Pakistan. Thesis. Dept of genetics/University of Karachi. Year 2002: 1-301?
15. Threlfall EJ, Ward LR. Decreased susceptibility to ciprofloxacin in salmonella enterica serotype typhi, United Kingdom. Emerg Infect Dis 2001; 7: 448-50.
16. Mermin JH, Villar R, Carpenter J et al. A massive epidemic of multidrug-resistant typhoid fever in Tajikistan associated with consumption of municipal water. J Infect Dis 1999; 179: 1416-22.
17. Saha SK, Talukder SY, Islam M, Saha S. A highly ceftriaxone resistant salmonella typhi in Bangladesh. Pediatr Infect Dis J 1999; 18: 387.
18. Ivanoff B. Typhoid fever: global situation and WHO recommendations. South Asian J Trop Med Public Health 1995; 26(suppl 2): 1 – 6.
19. Ackers ML, Puhr ND, Tauxe RV, MintzED. Labortory- based surveillance of salmonella serotype typhi infections in the United states. Antimicrobial resistance on the rise. JAMA 2000; 283: 2668 – 73.
20. Raveendran R, Wattal C, Sharma A, Oberoi JK, Prasad KJ, Datta S. High level ciprofloxacin resistance in salmonella enterica isolates from blood. Indian J Med Microbiol 2008, Jan – March; 26(1): 50-3.
21. Shaikh RB, Khemani AM, Shaikh S, Nizamani MA. Antibiotic sensitivity pattern of salmonella typhi isolates in rural Sindh. Pak Armed Forces Med, Jun 1998; 48(1): 43-5.
22. Munir T, Lodhi M, Butt T, Karamat KA. Incidence and Multidrug resistance in Typhoid Salmonellae in Bahawalpur area. Pak Armed Forces Med J 2001; 51(1): 10-13.
23. Nadeem M, Ali N, Achakzai H, Ahmed I. Profile of enteric fever in adults at Quetta. Pak J Pathol 2002; 13(1): 12-17.
24. Akhtar R, Mehmood A, Hassan F. Drug sensitivity pattern of salmonella typhi. J Surg Pak sep 2006; 11(3): 97 –99.