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REVIEW OF FIFTY CULTURE PROVEN *SALMONELLA* CASES

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ABSTRACT

BACKGROUND: *Enteric fever has huge global burden. Surrogate markers may have a role in early diagnosis. AIM: Unselected retrospective analysis of 50 culture positive Salmonella enterica cases for epidemiology, laboratory markers, antibacterial susceptibility, therapy, and outcome was done. This was a retrospective chart review of electronic medical records for 50 patients with Salmonella in blood cultures for in our hospital during May 2009-April 2010.* ***MATERIALS AND METHODS:*** *Blood culture was by automated Bactec™ system and antimicrobial susceptibility test was performed by disk diffusion method or automated system Phoenix 100™. Sensitivity of Widal, S. typhi IgM, C-reactive protein (CRP), total leukocyte count, erythrocyte sedimentation rate (ESR), differential eosinophil and lymphocyte counts, and liver enzymes, was determined for these cases.* ***RESULTS:*** *Salmonella cases were seen in all ages from 8 months to 59 years; serotype Typhi was the most common (72%). Sensitivity of S. typhi IgM immunochromatographic test was 78.9%, of Widal was 88.8%, and that of CRP, serum aspartate transaminase (AST), and serum alanine transaminase (ALT) ranged from 81.8 to 89.4%. Eosinophil count of zero and ESR were found to be 78.2% and 85.7% sensitive. Nalidixic acid resistance was seen in 96% cases and ciprofloxacin resistance/intermediate sensitivity in 26% cases. Resistance was not seen with ceftriaxone, while ampicillin, chloramphenicol, and co-trimoxazole (ACCo) resistance was 4%. Seven cases relapsed mostly due to improper treatment associated with choice/dose/duration of antibiotics.* ***CONCLUSIONS:*** *Surrogate laboratory markers can be utilized pending culture results. Though antibiotics and vaccines against Salmonella, and good sanitation facilities are available, it causes morbidity in all sections, gender, and ages of society. Strategies of prevention have not been very successful; therefore, early detection and effective treatment can prevent its complications and relapses.*

Key words: *Blood cultures, relapse, Salmonella, therapy*

INTRODUCTION

Typhoid and paratyphoid fever continue to be important causes of illness and death, particularly among children and adolescents in Southeast Asia. Crude typhoid fever incidence in Southeast Asia is 622 per 10^5 per year and in India it is 493.5 per 100,000 patient years.[1] Humans are the only known reservoirs for *Salmonella enterica* serotypes Typhi and Paratyphi A, B, C, the causative agents of enteric fever. Currently fluoroquinolones and third-generation cephalosporins are the drugs of choice for treatment. However, recent reports of decreased susceptibility to these agents, especially fluoroquinolones, have led to the prospect of re-emergence of untreatable typhoid fever and an increased global burden. The present study was done retrospectively to analyze the epidemiology and clinical correlation of blood culture positive *Salmonella* cases with other markers of disease progression.

MATERIALS AND METHODS

Electronic medical records of blood culture positive *Salmonella* cases from May 2009 to April 2010 were retrieved. The epidemiological data, serotypes, and sensitivity patterns of these isolates were recorded and analyzed. All blood cultures were processed in BACTEC 9120 automated blood culture system. Antimicrobial susceptibility test was performed by disk diffusion method and/or automated system (Phoenix™ 100) following CLSI (Clinical and Laboratory Standards Institute) guidelines. Culture being the gold standard was used to determine the sensitivity of other laboratory tests like *S. typhi* IgM immunochromatographic test (CTK Onsite Typhoid IgG and IgM Rapid Test), Widal (TYDAL^R) using tube agglutination technique employing colored antigens, CRP by nephelometry (MININEPH™), liver enzymes like aspartate transaminase (AST) and alanine transaminase (ALT), total leukocyte count (TLC), eosinophil count, lymphocyte count, and erythrocyte sedimentation rate (ESR). Package insert protocol instructions were followed for all these tests. Single Widal titers were noted and those ≥1:120 were considered significant. Relapse cases were traced through electronic records and the implicating factors were analyzed.

RESULTS

In our study, male to female ratio was 3:2 and adult to pediatric (0-19 years) ratio was 2.1:3. Nearly half the cases (21/50) were treated on an OPD basis and others had to be admitted. Of those admitted, 19 (65.5%) were below 19 years of age. The youngest patient was 8 months old

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while the oldest was 59 years old. Majority (26%) of the patients was in the age group >5-14 years and 5 patients were infants [Table 1]. Most of the cases were seen to occur in November and no case was recorded in January [Figure 1].

S. enterica serotype Typhi was the most common isolate (*n* = 36 [72%]) followed by Paratyphi A (*n* = 12) and Choleraesuis (*n* = 2). The earliest time to detection (TTD) for isolates in Bactec cultures was 7.93 h and longest TTD was 63.4 h (median 22.80 h). The volume of blood for culture was adequate in all cases (8-10 ml for adults and 1-3 ml for children). Paired blood cultures, as recommended by CLSI,[2] were not collected in any patient. Findings of few other laboratory tests were compared to positive blood cultures [Table 2]. Urine cultures were done in 14 cases on admission; none grew *Salmonella.* No stool cultures were done. Widal and *S. typhi* immunochromatographic test were done together in seven cases. Both were suggestive of *S. Typhi* in six cases. However, in a case of culture proven Paratyphi A with significant AH titer, *S. typhi* IgM was also positive. CRP ranged from 22 to 195.5 mg/L, ALT from 42 to 217 U/L, AST from 54 to 365 U/L, lymphocyte count from 21% to 66%, TLC from 2400 to 13,600/mm³, and ESR from 7 to 37 mm. Eosinophil count of 0% was seen in 36 cases.

The susceptibility results of all these isolates are presented in Table 3. Ampicillin, chloramphenicol, and co-trimoxazole (ACCo) co-resistance was seen in only two cases.

Defervescence was documented in three cases only. They were at 5, 9, and 10 days of adequate treatment. Treatment of 41 cases could be retrieved electronically. Ceftriaxone was given in 38 (92.6%) cases, 23 as monotherapy, and in 15 with other antibiotics (azithromycin/ofloxacin/co-trimoxazole/gentamicin/metronidazole). Five cases were treated with co-trimoxazole - in four as monotherapy and in one combined with ceftriaxone. All these patients recovered well with no evidence of relapse after 3-month follow-up. In total, there were seven cases of relapses (14%) which were proven by positive blood culture growing the same isolate (based on biochemical and serotypic characterization) after a variable period of 1-3 weeks [Table 4]. Of these, six were

Table 1: Demographic details of the subjects

Age (years)	*Males*	*Females*
0-1	3	2
>1-5	4	3
>5-14	9	2
>14-19	1	3
>19	12	10

Table 2: Comparison of various laboratory tests in culture positive cases

Investigation	*Reference range for normal*	*Specimens tested*	*Positive correlation in culture positive cases*	*Sensitivity (%)*
S. typhi (IgM)	Non-reactive	19	15	78.9
Widal (1st week)	<1:120 TO/TH/AH	18	16	88.8
CRP	<10 mg/L	12	10	83.3
ALT	10-40 U/L	38	34	89.4
AST	10-41 U/L	11	09	81.8
Eosinophil count	1-6%	46	36	78.26
Lymphocyte count	35-61%	46	22: Lymphopenia	47.8
			3: Lymphocytosis	6.5
Total leukocyte count	4000-10,000/mm³	46	2: Leukopenia	6.5
			11: Leukocytosis	23.9
ESR	1-10 mm 1st h	7	6	85.7

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, AST: Aspartate transaminase, AST: Alanine transaminase

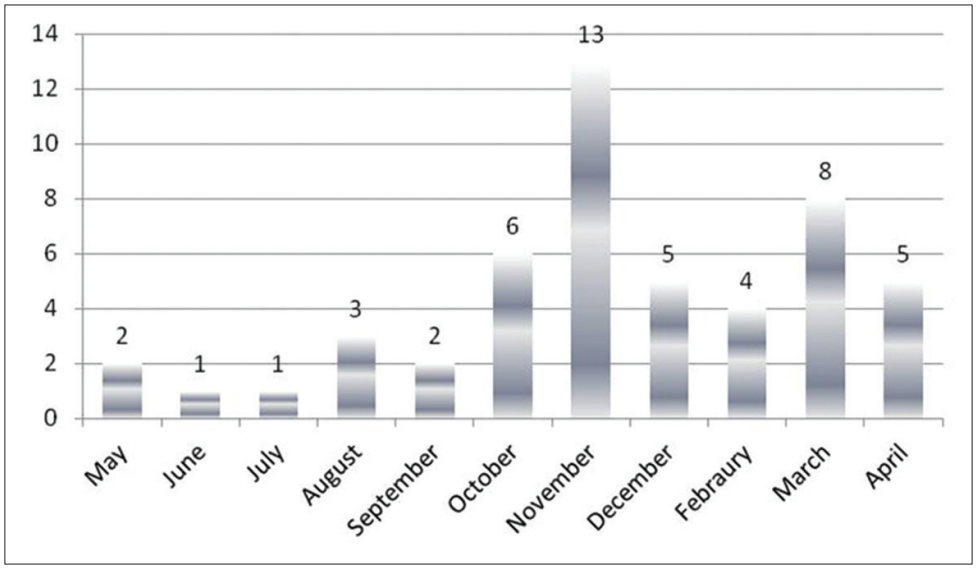

Figure 1: Distribution of *Salmonella* culture positive cases in various months

due to inadequate therapy in terms of dose or duration or both. Their antibiotic susceptibility pattern did not change during relapse.

DISCUSSION

Enteric fever was seen to occur in all ages and both sexes, but was more common in children. Similar observation was made by Misra *et al.* in the United States among predominantly Asian population.[4] The most common isolate was Typhi followed by Paratyphi A, though there was no age or gender bias or changes in antimicrobial resistance pattern observed in different *Salmonella* serotypes for the different antibiotics tested. This was observed by other researchers from Delhi[5] also. According to WHO reports, the ratio of disease caused by *S. Typhi* to that of *S. Paratyphi* A is about 10:1 in most countries.[6] In India, incidence of Paratyphi A serotype as high as 46% has also been noted.[7] Most of the cases were seen to occur in November as against another study from Delhi reporting maximum incidence in the dry months of April to June[8] or from Kolkata urban slums showing monsoon season to be the most vulnerable.[9] A peak of such cases in November in our study could be attributed to the preceding festive season where because of bulk production and purchase of food products, there might have been lapses in food and water hygiene, resulting in disease after a variable incubation period of 5-21 days.[10] Nearly half the cases were managed at home. Indian Academy of Pediatrics[11] also states that with oral antibiotics and good nursing, most of the cases can be managed at home. All cases of typhoid fever were confirmed cases according to WHO definition[6] as they were all culture positive. Volume of blood cultured was adequate in most of the cases. Sensitivity of blood culture varies according to the amount of blood cultured, number of specimens, antibiotic therapy, and timing of specimen collection. The sensitivity of culture is 85-90% for bone marrow, 40-50% for blood, around 60% for rose spots, 40-60% and <10% for stool and urine cultures, respectively.[12,13] Higher sensitivity of bone marrow cultures can be attributed to intracellular niche of these bacilli. However, after introduction of automated blood cultures, sensitivity of blood cultures has reached very close to those of bone marrow cultures.[14] Though blood/bone marrow cultures are considered gold standard,[15] it takes 16-36 h to be positive. Before that, other tests can help to start treatment. Our results showed good correlation between Widal and culture positivity even in the first week of infection. Two targeted serological tests - Widal and *S. typhi* immunochromatographic test - were done in some of our cases and they correlated well when done together. Single Widal titers were noted and titers ≥0:120 were considered significant. Kalhan *et al.* conducted a study at UCMS and GTB hospital, Delhi, where single TO, TH titers ≥0:128 were considered high.[16] In our study, sensitivity of S. *typhi* IgM immunochromatography and Widal were 79% and 89%, respectively. In a study by Ismail *et al.*,[17] significant titers of Widal were found only in 56% of culture positive cases. In another major study conducted in Vietnam,[18] the sensitivity and specificity for various serological tests for *S. Typhi* were 79% and 89%, respectively, for TyphiDot and 64 and 76%, respectively, for Widal. For all assays, sensitivity was the highest in the second week of the illness. In other studies,[19] comparing TyphiDot and Widal, TyphiDot was better with sensitivity, specificity, and positive predictive value of 96%, 89.5%, and 95%, respectively, compared to Widal test with sensitivity, specificity, and positive predictive value of 72%, 87%, and 87%, respectively. Absolute eosinophil

Table 3: Antibiotic resistance profile of tested isolates (*n*=50)

Antibiotic	*Resistance typhi n=36 (%)*	*Resistance Paratyphi A n=12 (%)*	*Resistance all isolates n=50 (%)*
Ceftriaxone (*n*=50)	0	0	0
Cefexime (*n*=50)	0	1 (8.3)	2.0
Azithromycin* (*n*=37)	0	0	2.7
Chloramphenicol (*n*=50)	3 (8.3)	0	6
Co-trimoxazole (*n*=50)	3 (8.3)	0	8
Ampicillin (*n*=50)	3 (8.3)	2 (16.6)	12
Ciprofloxacin (*n*=50)	7 R, 1 I (22.22)	4 I (30)	7 R (14), 6 I (12)
Nalidixic acid (*n*=50)	33 R, 1 I (94.44)	12 (100)	96

R: Resistant, I: Intermediate sensitive *Azithromycin CLSI disk diffusion zone criteria are not defined for *Salmonella* spp.[3] Resistance was observed in an isolate of *S. choleraesuis* based on absence of zone. *S. choleraesuis*: *Salmonella choleraesuis*

Table 4: Relapse cases of *S. enterica*

Age/sex	*Isolate*	*Treatment given*	*2nd episode*	*Probable cause of relapse*
01/M	*S. Typhi*	Cefpodoxime for 4 days, ceftriaxone for 2 days, cefexime for 10 days in adequate doses	2 weeks after completion of treatment	Frequent change in antibiotics in an attempt to defervesce early, parental pressure
07/F	*S. typhi*	Cefexime for 21 days, initially 300 mg/day, increased to 400 mg	8 days after treatment completion	Incorrect dose recommended dose of cefexime: 20 mg/kg/day for 14 days
08/M	*S. Typhi*	Treatment details not available	2 weeks after completion of treatment	Inappropriate treatment
14/M	*S. choleraesuis*	Treatment details not available	13 days after completion of treatment	Inappropriate treatment
15/F	*S. typhi*	Ceftriaxone 1.5 g twice daily for 7 days	3 weeks after completion of treatment	Inadequate treatment
03/F	*S. typhi*	Cefexime 100 mg twice daily for 14 days	5-6 weeks after completion of treatment	Inadequate treatment
18/F	*S. typhi*	Ceftriaxone 2 g twice daily for 7 days, then cefixime for 7 days	4 weeks after completion of treatment	Relapse despite adequate treatment

S. typhi: *Salmonella typhi*, *S. choleraesuis*: *Salmonella choleraesuis*, *S. enterica*: *Salmonella enterica*

count of 0% could be an important marker of typhoid. TLC did not show a positive correlation though lymphocytopenia was present in nearly half the cases and ESR was raised in most of the cases. Measurement of biochemical and hematological parameters like CRP, AST, ALT, TLC, eosinophil, lymphocyte counts, and ESR are non-specific in cases of typhoid fever, but given their positive correlation, they can be utilized before culture results are available to initiate appropriate therapy in time. Generally, TLC, platelet count, and hemoglobin levels are normal or reduced, but liver enzymes (AST/ALT) are usually twice to thrice of normal values.[20]

Antibiotic susceptibility of *Salmonella* to ceftriaxone was 100%. Resistance to azithromycin, chloramphenicol, cotrimoxazole, and ampicillin was minimal, therefore these can be used as oral alternatives to ceftriaxone. Most isolates were nalidixic acid resistant (NARST). It has been suggested that strains resistant to NA but sensitive to fluoroquinolones should be considered resistant.[20] Therefore, it is used as a surrogate marker to predict fluoroquinolone failure. In India, nalidixic acid resistance increased from 57% in 2003-2004[21] to >90% in 2005-2006.[22] Fluoroquinolones are the most effective drug for treatment of typhoid fever. They have the advantages of lower rates of stool carriage and are rapidly effective.[23] For life-threatening infections resistant to all other recommended antibiotics, fluoroquinolones may be used in patients less than 18 years. For nalidixic acid sensitive *S. Typhi* (NASST) a 7-day course and for nalidixic acid resistant *S. Typhi* (NARST) a 10-14 day course with maximal permitted dosage is recommended.[11]

Chloramphenicol inhibits growth and reproduction of bacteria by inhibiting protein synthesis; it may cure the active disease but the possibility of carrier state may remain.[24] Ampicillin, amoxicillin, and co-trimoxazole reduce the risk of the carrier states.[20] Multidrug resistant typhoid cases, resistant to first-line drugs, namely chloramphenicol, cotrimoxazole, and ampicillin have been reported since 1990. They need to be treated with second-line drugs like third-generation cephalosporins. First, second-generation cephalosporins and aminoglycosides have no action against *Salmonella.* Of the third-generation cephalosporins, oral cefixime has been widely used in children in higher doses. Ceftriaxone, cefotaxime, and cefoperazone are injectable drugs, of which ceftriaxone is the most convenient.[11] One study even showed that taking ceftriaxone for 5 days was as effective as taking chloramphenicol for 14 days; blood cultures became negative earlier and bone marrow suppression was reduced; however, prolonged fever persisted in some patients.[25] Drug of choice for empiric therapy in uncomplicated typhoid should be oral third-generation cephalosporin, e.g. cefixime, and for complicated typhoid, the choice should be parenteral third-generation cephalosporin, e.g. ceftriaxone. If by 5 days there is no clinical improvement and culture report is inconclusive, addition of a second-line drug, e.g. azithromycin, or any other drug known to be sensitive to *S. Typhi* in that endemic area can be used.[11] During acute infections, *S. Typhi* multiplies in mononuclear phagocytic cells and azithromycin has high intracellular concentration (almost 100-fold) and long elimination half-life (72 h).[26] However, use of azithromycin should be restricted to children with confirmed diagnosis of enteric fever and inadequate response to first-line drugs to prevent emergence of resistant strains.[11] A study on 31 ciprofloxacin-resistant S. *enterica* showed increased azithromycin minimum inhibitory concentration (MIC) in one case only (3.2%).[27] Resistance to ceftriaxone has been reported from Bangladesh, Pakistan, and Philippines.[28-30] Rarely, carbapenem resistance has been noted.[31] Aztreonam and imipenem are potential third-line drugs which have been used recently.[20] Most common combinations used in the study were ceftriaxone with azithromycin, ofloxacin, gentamicin/amikacin even in uncomplicated cases where there is no role of combination therapy. IAP[11] has provided guidelines for antibiotic management of pediatric enteric fever cases, which should be followed. It was observed that many uncomplicated cases were on parenteral therapy which increases the cost of therapy, hospitalization, and need for an intravenous access. This was, in most cases, insisted by parents. Most typhoid cases (60-90%) can be managed at home with oral antibiotics and good nursing care with close follow-up. General supportive measures like antipyretics, maintenance of hydration, appropriate nutrition, and prompt recognition and treatment of complications are extremely important for a favorable outcome.[11,20] In our study, the relapse rate was 14%. They generally occur in 5-10% cases, usually within 2-3 weeks of defervescence.[20] Relapses in typhoid fever can result from recrudescence or reinfection. If the same strain of *S. Typhi* causes the second attack, it would be termed recrudescence, but if these are two different strains, then the second attack would be classified as reinfection.[32] In the present study, they occurred at intervals ranging from 8 days to 6 weeks, and wherever treatment history was available, it showed that the subjects had taken third-generation cephalosporins. Incidence of relapse varies with treatment - following fluoroquinolones it is 1.5%, for cephalosporins it is 5%, and for chloramphenicol, ampicillin, co-trimoxazole, it is approximately 10%.[24]

Vaccines have a limited role in curbing the spread and morbidity of this disease. In various randomized control trials, the cumulative efficacy for 3 years was 48% for Ty21a and 55% for Vi polysaccharide vaccines.[33]

This study has certain limitations as it was a retrospective study and hence there are gaps since tests under comparison were not done in all subjects. Also, complete

follow-up of patients and period to defervescence was not recorded.

To conclude, enteric fever was and still remains a major health problem despite our continued efforts toward its early diagnosis and adequate treatment. Proper antibiotic (guided by susceptibility results), dose, duration, and appropriate follow-up can go a long way in reducing relapses and complications in cases of enteric fever.

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