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CLINICAL AND MICROBIOLOGICAL PROFILE OF BLOOD CULTURE POSITIVE SALMONELLA SP IN DELHI: A HOSPITAL BASED STUDY.

Microbiology

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ABSTRACT

To improve the selection of an appropriate antimicrobial agent and to understand the clinical and microbiological characteristics of bacteremic Salmonella sp, a laboratory-based surveillance of blood culture positive Salmonella sp was conducted during two year period in a tertiary care hospital. The clinical profile and antibiotic usage were obtained from Hospital Information system and medical record department. 16649 patient's blood samples received for blood culture and sensitivity test. Of these 501 (3.01%) patients' blood yielded Salmonella sp (S.Typhi 385; S.Paratyphi A 116, a ratio of 3.32). It was isolated throughout the year but peaked in April-May. Paediatric age group constitutes quarter of the burden of enteric fever. All patients presented with fever (100%), followed by pain abdomen (33%), vomiting (27%), diarrhoea (18%), constipation (4%), splenomegaly (30%) and hepatomegaly (20%). Complications were seen in 5% cases. No mortality was observed. The antimicrobial sensitivity of Ampicillin was 92%, Ceftriaxone 94%, Ciprofloxacin 39%, Levofloxacin 33%, Cotrimoxazole 88.2%, Chloramphenicol 87% and MDR observed in 4%. The most commonly used antibiotics were 3rd generation Cephalosporin. Enteric fever is a significant public health problem in Delhi. It is important to be aware of local antibiotic sensitivity pattern as limited options are available to commence the treatment empirically.

KEYWORDS

Salmonella, blood culture, antimicrobial susceptibility

Introduction

Enteric fever or typhoid fever remains till date a leading infectious disease in India (1). Poor hygiene in particular hand hygiene, unregulated street food, contaminated drinking water and lack of sanitation facilities are probable drivers of the problem in India (2). Untreated enteric fever carries the risk of severe complication and high mortality (3). Enteric fever may also present as fever of unknown origin and found to be the leading etiology in certain Indian cities (4). Masking of symptoms and laboratory parameters due to the propensity of taking inappropriate and inadequate over the counter antimicrobials makes the diagnosis even more difficult. Added to this is the rising trend of antimicrobial resistance in Salmonella sp (1,5).

Blood culture is the mainstay for diagnosis of this infection (3). Bone marrow culture though more sensitive especially if the patient has taken prior antimicrobials, is an invasive procedure (3,6). Blood culture, however, approaches the sensitivity of bone marrow culture if the volume of blood cultured is increased (more than 15 ml in an adult) (6). Culture isolation in addition to making a correct diagnosis also helps in selecting an appropriate antimicrobial agent for treatment.

At our 600 bedded hospital in North Delhi, enteric fever along with malaria, dengue, chikungunya, pneumonia, urinary tract infections, tuberculosis, varicella, and measles represent the major share of community-onset febrile illnesses of infective etiology. Though a provisional diagnosis of typhoid fever is possible in many patients, appropriate antimicrobial selection remains a problem in view of the emerging resistance of the bacterium and its propensity for relapse. To understand the clinical and microbiological characteristics of bacteremic Salmonella sp, a laboratory based surveillance of blood culture positive Salmonella sp was conducted during two year period in a tertiary care hospital.

Material and Methods

A retrospective study was conducted from January 2012 to December 2013 in St Stephen's Hospital, Delhi. The hospital is 600 bedded multispecialty tertiary care hospital situated in North Delhi and caters low and middle-income population of Delhi and surrounding states. The hospital has a clinical diagnostic laboratory that is accredited by National Accreditation Board for Testing and Calibration Laboratories (NABL).

All patients with positive blood culture for Salmonella sp were included in the study. BACTEC® blood cultures bottles (5-10 ml blood for adult and 2-5 ml blood for pediatrics) were used to collect and transport blood to the microbiology laboratory. These bottles were incubated in BACTEC 9120 machine at the ambient temperature of 35±2oC for a maximum of five days. Upon signal emitted by machine, the blood was subcultured on sheep blood agar and MacConkey Agar and any growth was processed as per and standard microbiological procedure (7). The identification of isolate was done by automated identification and sensitivity system using MicroScan® WalkAway System (Siemens healthcare diagnostics Inc, USA).

For all patients with positive blood culture for Salmonella sp, their clinical profile and antibiotic usage were obtained from Hospital Information system and medical record department. Data analysis was done in Microsoft Excel® software. Student's t-test (two-tailed) was done to find the significance of the difference of means of proportions.

Results

During the study period, 16649 patient's blood samples received for blood culture and sensitivity test. Of these 501 (3.01%) patients' blood yielded Salmonella sp (S.Typhi 385; S.Paratyphi A 116, a ratio of 3.32) as shown in Table-1. S.Paratyphi B was not isolated during the study period. Although the organism was isolated throughout the year the peak was observed in April and May (Table 1).

Table 1: Month wise distribution of Salmonella sp. isolated from blood culture

	Salmonella Typhi N=385 n (%)	Salmonella Paratyphi A N=116 n (%)	Salmonella sp N=501 n (%)
January	17 (4.4)	13 (11.2)	30 (6.0)
February	20 (5.2)	8 (6.9)	28 (5.6)
March	36 (9.4)	13 (11.2)	49 (9.8)
April	54 (14.0)	14 (12.1)	68 (13.6)

May	66 (17.1)	17 (14.7)	83 (16.6)
June	41 (10.6)	5 (4.3)	46 (9.2)
July	26 (6.8)	10 (8.6)	36 (7.2)
August	35 (9.1)	7 (6.0)	42 (8.4)
September	27 (7.0)	5 (4.3)	32 (6.4)
October	24 (6.2)	10 (8.6)	34 (6.8)
November	19 (4.9)	7 (6.0)	26 (5.2)
December	20 (5.2)	7 (6.0)	27 (5.4)
Total	385 (76.8)	116 (23.1)	

Table 2 shows the antimicrobial susceptibility pattern of Salmonella sp. Maximum susceptibility was observed to Cefotaxime/ Ceftriaxone (n=473, 94.4%) and minimum to fluoroquinolones (FQ-S NA-R; n=16, 3.1%). Resistance to Fluoroquinolones was significantly higher in S. Paratyphi A than in S. Typhi (P=.001). Multidrug resistance was seen in 19 (3.8%) Salmonella isolates.

Table 2: Antimicrobial susceptibility of Salmonella sp isolated from blood

Antimicrobial Agent	Salmonella sp N=501 n (%)	S. Typhi N=385 n (%)	S. Paratyphi A N=116 n (%)	P value
Ampicillin	460 (91.8)	349 (90.6)	111 (95.7)	> 0.05
Cefotaxime /Ceftriaxone	473 (94.4)	359 (93.2)	114 (98.3)	> 0.05
Trimethoprim-Sulfamethoxazole	428 (85.4)	328 (85.2)	100 (86.2)	> 0.05
Chloramphenicol	436 (87.0)	333 (86.4)	103 (88.7)	> 0.05
Ciprofloxacin*	193 (38.5)	178 (46.2)	15 (12.9)	< 0.001
Levofloxacin*	165 (32.9)	161 (41.8)	4 (3.45)	< 0.001
FQ-S, NA-S*	16 (3.1)	7 (1.8)	9 (7.7)	0.002
MDR	19 (3.8)	16 (4.1)	3 (2.5)	> 0.05

FQ- Fluoroquinolone, NA-Nalidixic acid, S-Susceptible, R-Resistant, MDR- Multi drug resistant (Resistance to all three agents – Ampicillin, Chloramphenicol, Trimethoprim-Sulfamethoxazole Table 3 shows the age and gender distribution of patients who tested positive for Salmonella sp on blood culture. Majority of the infection occurred in the age group of 19-30 years (n=189, 37.72%). However pediatric age group (less than 14 yr.) constitutes the quarter of Salmonella infection (n=126, 25.1%).

Table 3: Age and gender distribution of patients with blood culture positive for Salmonella sp

Age group (years)	Male N=307 n (%)	Female (%) N=194 n (%)	Total (%) N=501 n (%)
<1*	2 (0.65)	5 (2.58)	7 (1.4)
1 to 2	18 (5.86)	8 (4.12)	26 (5.19)
3 to 13	64 (20.85)	29 (14.95)	93 (18.56)
14 to 18	70 (22.80)	35 (18.04)	105 (20.96)
19 to 30	112 (36.48)	77 (39.69)	189 (37.72)
31 to 40	19 (6.19)	17 (8.76)	36 (7.19)
41 to 50	12 (3.91)	14 (7.22)	26 (5.19)
51 to 60	5 (1.63)	5 (2.58)	10 (2.0)
≥ 60	5 (1.63)	4 (2.06)	9 (1.80)

The medical record of all patients showing blood culture positive for Salmonella sp (n=501) was analyzed. It was found that ninety-six patients (96/501, 19.1%) were diagnosed with enteric fever and treated on outpatient basis while 405 patients (405/501, 80.8%) were admitted to the hospital. The most common clinical presentation of patients with salmonella infection was fever (n=501, 100%), followed by abdominal pain (n=164, 32.7%). Mean duration of fever in hospitalized patients was 9.53 ± 0.6 days (9.8 ± 1.7 days for typhoid fever and 8.6 ± 2.3 days for paratyphoid fever) and mean duration of hospitalization was 6.5 ± 1.4 days (6.6 ± 0.6 days for typhoid fever and 6.1 ± 1.1 days for paratyphoid fever). Abdominal pain, constipation, and hepatomegaly were significantly more common in S. Typhi than S. Paratyphi A infection (Table 4). Complications of enteric fever were noted in 16 patients (11 adults, 7 children; 15 S. Typhi infections and 3 S. Paratyphi A infections). Most common complications were encephalitis (n= 6) and intestinal obstruction (n=3). However, no mortality was observed in our study population

Table 4: Clinical profile of patients with blood culture positive for Salmonella sp

Clinical features	Total patients N=501 n (%)	S. Typhi N=385 n (%)	S. Paratyphi A N=116 n (%)	P value
Fever	501 (100)	385 (100)	116 (100)	> 0.05
Abdominal pain	164 (32.7)	136 (35.3)	25 (21.6)	0.02
Vomiting	134 (26.7)	103 (26.7)	29 (25)	> 0.05
Diarrhoea	90 (17.9)	68 (17.7)	15 (12.9)	> 0.05
Constipation	19 (3.7)	17 (4.4)	0	0.02
Splenomegaly	148 (29.5)	117 (30.4)	29 (25)	> 0.05
Hepatomegaly	110 (21.9)	94 (24.4)	15 (12.9)	0.009
Complication	54 (10.8)	44 (11.4)	11 (9.5)	> 0.05
Mortality	0	0	0	> 0.05

*P value < 0.05 significant difference of means of proportion

The details of prescription of antibiotics were obtained from medical record section. The most common antimicrobial agent prescribed for the treatment of salmonella infection was 3rd generation cephalosporin (3GC) as monotherapy (n=400, 80%). Ceftriaxone injection was the commonly used 3GC in admitted patients while Cefixime/ Cefpodoxime tablets in out-patients as well as patients who switched from injectable 3GC to oral 3GC. Other regimes included the combination of a 3GC with a fluoroquinolone (63, 12.6%) or Azithromycin (38, 7.9%). The reason for the combination therapy was lack of defervescence with 3GC as monotherapy and most commonly observed in pediatric age group (74/101, 73.2%).

Discussion

The burden of bloodstream salmonellosis in India is considerable (1). Typhoid and Paratyphoid fever accounted for 3.01% of suspected bacteremias in our study. This is of significant public health importance since these infections represent community-acquired septicemic illness that often occurs as a result of poor hygienic conditions and is preventable. A study from Orissa has documented even higher rates (5.58%) of blood culture positivity for Salmonella species amongst suspected patients (1). These findings suggest that enteric fever is rampant in India, where the rate of the disease is only lower than sub-Saharan Africa (10). Though India has advanced to a lower- middle-income country, our findings indirectly suggest that hygiene and food and water safety standards need to be strengthened.

In our study the proportion of cases due to S.Paratyphi A to S.Typhi is low as compared to other studies (2,11). The proportion of paratyphoid fever has steadily increased especially in the Indian subcontinent more due to the decline of typhoid fever than an increase in Paratyphi A infection (2). Most often the increasing use of typhoid vaccines has been referred to be the cause of this effect (2). Others, yet undetermined factors may be responsible for high Paratyphi A prevalence. In our study population, there was no report of S. Paratyphi B infection. Similar findings observed in most of the Indian and South Asian studies (5).

Among the antimicrobial groups Ceftriaxone had the best in-vitro activity (94.4%). A recent multicentric study in India, did not document cephalosporin resistance (1). However, the same study found evidence of 'a creeping increase of MIC values of ceftriaxone from 0.032 to 0.94 in S. Typhi over the years'. Majority of the isolates were non-susceptible to Ciprofloxacin and Levofloxacin. Concurrently, nalidixic acid resistance was very high (97%). Similar reports of high prevalence of were found in Indian literature (1). This suggests that the role of fluoroquinolones in enteric fever therapy is getting marginalized.

Multi-drug resistance (MDR) in Salmonella, defined as resistance to three class of antibiotics viz ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol. MDR-Salmonella has been reported in India for over forty years now. The peak incidence greater than 90% was reported from centers in South India in late 1980s. Ever

since, their incidence has progressively been declined (12); in our study, it stands at 3.8%. The overall decline in the incidence of MDR-Salmonella is noteworthy. Reasons for this decline are not precisely deciphered. One among many factors may be the decreased usage of chloramphenicol over a period of time across India (12).

Real life clinical practices at our hospital too reflect the changes in susceptibility of Salmonella over the years. 3rd generation cephalosporin therapy was overwhelmingly preferred for treatment. Combination therapy, though not recommended was seen in quite a few cases. Successful combination therapy against Salmonella Typhi and Paratyphi A has been reported previously (13-15) especially if the isolate is multi-drug resistant (14) or the infection is deep seated like spondylodiscitis (15). However, combination therapy was not found to be superior to single susceptible agent therapy by Jog S et al. 2008 (13). Failure of empirical therapy highlights the importance of blood/bone marrow culture to determine the susceptibility of the infecting isolate (16).

Conclusion: Enteric fever is still a major public health concern in urban centres of India. The need for culture isolation of the causative organism is of paramount importance in view of the increase of antimicrobial resistance. Fluoroquinolones are no longer the recommended therapy for patients in Delhi where 3rd generation cephalosporins are now the drug of choice.

Limitations of our study: There are few limitations of the study. Firstly, it was retrospective study and secondly, azithromycin susceptibility was not tested.

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