Enteric fever and changing trends in antimicrobial susceptibility pattern: Case series from a tertiary care hospital in Kerala

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ABSTRACT

Enteric fever remains a major source of morbidity and mortality worldwide. Despite advances in therapy, the emergence of drug-resistant strains and their persistence confound this. The clinical profile of *Salmonella* infections and its drug susceptibility varies between geographical regions and countries, attributable to inadequate hygiene, and sanitation as a common factor. In this article, we describe a series of seven cases of enteric fever due to *Salmonella* Typhi *and Salmonella* Paratyphi A, which were diagnosed at a tertiary care hospital in Kerala with the purpose of identifying their antibiotic sensitivity pattern. Ceftriaxone is presently considered as the drug of choice due to increasing fluoroquinolone resistance. Oral Azithromycin remains a good substitute. Decreasing multidrug-resistant strains and increase in susceptibility to Ampicillin, Chloramphenicol, and Cotrimoxazole were noted. These changing trends highlight the need for better preventive measures, including proper sanitation and judicious use of antibiotics, adhering to correct dosage and duration, rather than searching for novel treatment options. Vaccination should be ideally promoted in endemic areas.

Key words: Antibiotic susceptibility pattern, enteric fever, *Salmonella*

INTRODUCTION

The bacterium Salmonella was named after Daniel Elmer Salmon, a veterinary pathologist working with the United States Department of Agriculture, although the actual discovery can be credited to Theobald Smith, a research assistant at the same institute.[1] The organism was discovered in 1885, while investigating an outbreak of hog cholera and thus named *Salmonella* Choleraesuis.[2] More than a century later, the classification of Salmonella has evolved into a complex group of organisms. The pioneering classification was done by Kauffman and White during the early part of the 20th century. Their antigenic classification of Salmonella forms the backbone of serotyping Salmonella species and stands true to date. Currently, Salmonella is responsible for approximately 3 billion infections annually. WHO estimates reveal that about 22 million of these are due to typhoidal strains and among these around 200, 000 are fatal.[3] The disease is most common in South and South East Asia and is endemic in India. In fact, the incidence of Salmonella infection is an indirect indicator of overall sanitation in the population and personal hygiene levels. The emergence of drug resistant Salmonella is partly due to indiscriminate antibiotic use, but predominantly due to spread of pre-existing resistant organisms and the simultaneous appearance of new resistance mechanisms. This ultimately has an important global impact on public health. The appearance of Extended Spectrum Beta lactamases, novel methods of fluoroquinolone resistance, and spread of the Salmonella genomic island 1, a complex class 1 integron that contains genes mediating antibiotic resistance are important developments that may have a significant impact on the outcome of infection.[4] In this article, we describe a series of cases diagnosed with enteric fever caused by the typhoidal strains with established microbiology and antibiotic sensitivity patterns. Non-typhoidal strains and typhoidal strains isolated from sources other than blood are excluded from the series.

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CASE SERIES

All cases described (n = 7, male-5, female-2) were diagnosed during a 6-month period (January to June 2014) in Government Medical College, Thiruvananthapuram — a premier tertiary level teaching hospital in Kerala, India.

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All patients presented with gastrointestinal symptoms (vomiting, loose stools, non-specific abdominal pain) and fever. The organism was isolated by conventional blood culture methods [Table 1]. All samples were cultured on blood agar and MacConkey agar. Growth was analysed by Gram staining and microscopy. This was followed by biochemical testing and agglutination for serovar identification. Antibiotic sensitivity testing was done on Mueller-Hinton agar using Kirby-Bauer disc diffusion method and E strips and susceptibility patterns identified.

The clinical profiles of the patients were varied. One of the cases was admitted in the Division of Medical Gastroenterology with high-grade fever and a provisional diagnosis of acute pancreatitis. Blood culture yielded *Salmonella* Typhi. Another patient presented with low-grade fever, loose stools, and abdominal pain of 1-month duration. A colonoscopic evaluation revealed transverse ulcers in the ascending and descending colon, and he later developed peritonitis. A biopsy was done suspecting a diagnosis of tuberculosis. A concurrent blood culture, however, yielded S. Typhi and so antimicrobial therapy was administered. One case presented with features of metabolic encephalopathy. A blood culture was done during the work up and this yielded Salmonella Paratyphi A. All patients had a fever and abdominal discomfort of at least 2 weeks duration.

RESULTS AND DISCUSSION

Salmonellae are Gram-negative, non-spore forming, facultatively anaerobic bacilli that are actively motile (the only exception being *Salmonellae* Gallinarum — Pullorum). Excluding around 1% of organisms, the remainder uniformly do not ferment lactose. In our series, all isolates were obtained from blood. In cases of Salmonella bacteraemia, blood samples are usually positive in the 1st week, but the setting of our cases is somewhat different. Being a tertiary referral centre, all our cases were initially managed outside with probably inappropriate antibiotics and suboptimal diagnostic tests. It is pertinent to assume that this has a significant impact on treatment outcome, as in our series, one case proved fatal, and one patient developed a small bowel ulcer that perforated and subsequently produced peritonitis.

Isolates with typical biochemical profiles for *Salmonella* should be serogrouped with commercially available polyvalent antisera. Salmonellae are sero grouped according to their polysaccharide O (somatic) antigens, Vi (capsular) antigens, and H (flagellar) antigens according to the Kauffman-White scheme.

Salmonella (genus — *Enterobacteriaceae*) are broadly classified into two species, *Salmonella enterica* and *Salmonella bongori*. Of these, *S. enterica* is grouped into six subspecies (I, II, IIIa, IIIb, IV, and VI). Subspecies V is currently designated as *S. bongori*. The seven subspecies of Salmonella together contain more than 2500 serovars, based on 3 major surface structures: The flagellar (H) antigen, somatic (O) antigen, and the Vi antigen. Newer techniques like ribotyping, pulsed-field gel electrophoresis, insertion sequences analysis, polymerase chain reaction-based fingerprinting, multilocus sequence typing, and genomic DNA analysis using microarrays have been used in epidemiologic studies to differentiate strains within a given serotype. The strains S. Typhi and S. Paratyphi A, B, and C are commonly referred to as typhoidal Salmonella (TS) and the remaining as NTS. The typhoidal strains of Salmonella have no known hosts other than humans and the NTS strains usually do not cause bacteraemia.

The most common route of spread for salmonellosis remains faeco — oral, through contaminated food or water. In recent years, an increase in the incidence of S. Paratyphi A has been reported, especially from India, due to vaccination against S. Typhi.[6] In our series, two out of the seven cases (28.5%) were due to S. Paratyphi A.

Table 1: Clinical details of cases

Case	Age	Sex	Admitting department	Clinical features-duration	Organism and drug sensitivity	Treatment given	Outcome
1	27	Male	Internal medicine	Loose stools: 2 weeks	*S. Typhi*	Ciprofloxacin	Cured
2	33	Male	Internal medicine	Fever, vomiting: 3 weeks	*S. Paratyphi* A	Ciprofloxacin	Cured
3	62	Female	Internal medicine	Loss stools, fever: 2 weeks Metabolic encephalopathy	*S. Paratyphi* A	Ceftriaxone	Expired before report issued
4	50	Male	Medical gastroenterology	Loose stools, fever: 2 weeks	*S. Typhi*	Ceftriaxone	Cured
5	50	Female	Medical gastroenterology	Loose stools, fever, abdominal pain 1-month, transverse ulcers in colon, peritonitis	*S. Typhi*	Ceftriaxone	Cured
6	31	Male	Medical gastroenterology	Low grade fever, acute abdomen: 2 days, features of acute pancreatitis	*S. Typhi*	Ceftriaxone	Cured
7	33	Male	Internal medicine	Fever, loose stools: 2 weeks	*S. Typhi*	Ciprofloxacin	Cured

S. Typhi: Salmonella typhi; S. Paratyphi: Salmonella paratyphi

Table 2: Antibiotic sensitivity pattern (percentage sensitivity)

Isolate	Ampicillin (%)	Cotrimoxazole (%)	Chloramphenicol (%)	Nalidixic acid (%)	Ciprofloxacin (%)	Ceftriaxone (%)	Azithromycin (MIC) (%)
Salmonella typhi (*n*=5)	5 (100)	5 (100)	5 (100)	0	2 (40)	5 (100)	5 (100)
Salmonella paratyphi A (*n*=2)	2 (100)	2 (100)	2 (100)	1 (50)	1 (50)	2 (100)	2 (100)

MIC: Minimum inhibitory concentration

Between 1970 and 1989, many strains of S. Typhi developed plasmid-mediated multidrug-resistance (MDR) to the common first-line antimicrobials Chloramphenicol, Ampicillin, and Trimethoprim in many regions of the world, especially in the Indian subcontinent and south Asia.[7] In the 1990s, with the increased use fluoroquinolones for treatment of MDR typhoid fever, chromosomal and plasmid-encoded resistance to Ciprofloxacin emerged among S. Typhi and S. Paratyphi A isolates from the Indian subcontinent and south Asia.[8] In 2005, a study from New Delhi, India showed that 22% of S. Typhi strains were resistant to Ciprofloxacin and 16% were resistant to Ceftriaxone. In our series [Table 2], all strains were sensitive to Ceftriaxone, Chloramphenicol, Ampicillin, Azithromycin, and Cotrimoxazole. Resistance to Ciprofloxacin and Nalidixic acid were 57% and 84%, respectively. As per Clinical and Laboratory Standards Institute 2014 guidelines, when fecal isolates of Salmonella spp. are tested, only Ampicillin, a fluoroquinolone, and Cotrimoxazole should be reported routinely. In addition, for extraintestinal isolates of Salmonella spp., a 3rd-generation cephalosporin should be tested and reported, and Chloramphenicol may be tested and reported if requested. Susceptibility testing is indicated for typhoidal Salmonella (S. Typhi and S. Paratyphi A-C) isolated from extraintestinal and intestinal sources. For strains sensitive to Ciprofloxacin, zone size of ≥31 mm is taken as sensitive, 21-30 mm as intermediate and ≤20 as resistant. The MIC criteria for interpretation are taken as ≤0.06 as sensitive, 0.12-0.5 as intermediate, and ≤1 as resistant. For intermediate sensitive strains, double dose antibiotic therapy can be given.

Prompt administration of antibiotic therapy can prevent complications and result in case fatality rates of <1% with near complete cure rates. Only one fatality was seen in our series. One patient, as mentioned earlier, developed peritonitis secondary to bowel ulcer perforation. In fact at the time of developing peritonitis, the patient was not considered to have salmonellosis in view of first negative subculture. The physicians attending to him were on the verge of treating him empirically for tuberculosis of the bowel, when his second subculture yielded S. Typhi. Subsequent treatment with parenteral Ceftriaxone resulted in a complete cure. This only highlights the need for early diagnosis with blood cultures.[5]

When susceptible, current guidelines still recommend fluoroquniolones. However, this may not be appropriate in India. In our series, resistance to Nalidixic acid and Ciprofloxacin were more than 50%, thus prompting us to consider parenteral Ceftriaxone or oral Azithromycin as the drug of choice.

Around 1-4% of patients develop into chronic carriers and remain a source of disease spread. This is highlighted in history by the case of "typhoid Mary" a housemaid who was responsible for several deaths at the various homes where she worked. At her death, her gall bladder was found to be teeming with bacilli. Chronic carriage is more common among women, infants, and persons who have biliary abnormalities or concurrent bladder infection with *Schistosoma haematobium*. These patients can be treated with a 4-6 weeks course of Amoxicillin, Cotrimoxazole or Ciprofloxacin.[6]

In developing nations and where Salmonella is endemic and access to healthcare suboptimal, physicians must be trained and updated with the optimum treatment guidelines. This is because the increase in the incidence of fluoroquinolone-resistant Salmonella is on the rise and these are often the drugs that are prescribed empirically. This can have potentially adverse outcomes.

CONCLUSION

Salmonella infections remain a major public health problem. This case series highlights the shift among patterns of drug-resistance of Salmonella with a concomitant increase in resistance to fluoroquinolone. One-hundred percent sensitivity was observed with Cotrimoxazole, Chloramphenicol, and Ampicillin predicting a decline in MDR strains. In view of emerging drug-resistance and continued morbidity due to disease, the need for emphasis on prevention cannot be understated. Adequate sanitation and hygenic food habits are important preventive measures in infection control. In addition, the role of prophylactic vaccination also needs to be emphasised and increasingly promoted. From our observations, it can be concluded that, 3rd-generation cephalosporins are the best available treatment option in the current setting, in view of increasing resistance to fluoroquinolones. Azithromycin is an excellent standby drug. Owing to decline in MDR strains, older drugs like Ampicillin, Chloramphenicol, and Cotrimoxazole may

still have an important role in management. In our opinion, the need for antibiotic protocols based on region dependant susceptibility patterns is important.

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