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Paratyphoid fever– Emerging problem in South India

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ABSTRACT

Objective: To review the clinical profile and drug susceptibilities of *Salmonella paratyphi* A in a tertiary care hospital. **Methods:** Retrospective analyses of 113 patients with paratyphoid fever and 101 culture proven *Salmonella paratyphi* A infection were included in the study. The study extended over a period of 3 years (2006–2008). Diagnosis of patients were based on clinical features, serology and blood culture. The drug susceptibility testing of the isolates were performed by the disc diffusion method. Clinical presentation, laboratory parameters, susceptibility patterns of isolates, treatment and clinical response were studied. **Results:** Of the 113 cases, 77 (68.4 %) were males and 36 were females (32.8%), which included 2 pediatric patients. Fever was the most common symptom (100.0%) followed by loose stools (37.2%), headache (35.4%), myalgia (31.9%), pain abdomen (29.2%), dry cough (19.5%) and vomiting (13.3%). All patients were clinically cured. Majority of the isolates (46%) were resistant to cotrimoxazole in 2006, however they became 100% sensitive in 2007 and 2008. whereas the strains became 100% sensitive to ampicillin and chloramphenicol only in 2008. In 2006 the sensitivity of organisms to ciprofloxacin was 89% but in 2007 and 2008 there has been an increasing resistance to ciprofloxacin (46% and 86%) respectively . Surprisingly 3 isolates (8.1%) were resistant to ceftriaxone in 2006 , showed 100% sensitivity in 2008. Common drugs used were ceftriaxone in 100 cases (88.4%) and ciprofloxacin in 13 cases (11.6%).One patient had relapse of paratyphoid fever after treatment with ciprofloxacin which responded to ceftriaxone. **Conclusions:** Paratyphoid fever A is one of the emerging infections and a significant problem in India. An increasing resistance to fluoroquinolones is noted. Continuous monitoring of drug susceptibilities is mandatory in instituting appropriate therapy.

1. Introduction

Salmonella enterica serovar Paratyphi A is the second most common cause of enteric fever after *Salmonella typhi* with infection rate between *Salmonella typhi* to paratyphi being approximately 4:1. Population based studies have estimated the global burden of enteric fever, to be >21 million cases of typhoid fever in the year 2000 and >5 million cases of paratyphoid fever with regions of high incidence of typhoid fever(>100/100000cases/yr) at South Central Asia and South East Asia[1]. Typhoid and paratyphoid fever have only humans as reservoir, but recently the bacilli has been isolated from domestic animals and fish. Enteric fever is endemic in India and other Asian countries and is classically caused by *Salmonella enterica* serovar Typhi. *Salmonella enterica Paratyphi* A, which causes milder form of the disease and had been reported less frequently, hence very few reports on the pattern of disease by this pathogen are available. Since 1996, an increasing trend in isolation of *Salmonella paratyphi* A (*S. paratyphi* A)causing enteric fever has been noticed in India[2]. A rise in proportion of *S. paratyphi* A was noticed from Calicut[3], Nagpur (46.15%)[4], Sevagram (53.33%)[5], Rourkela[6], and Chandigarh[7]. Improved standards of public health have resulted in a marked decline in the incidence of enteric fever in developed countries[1], but is still a major public health problem in developing countries including India. The disease burden is compounded by the emerging multidrug resistant isolates of Salmonella[8,9]. Present study was undertaken to evaluate the clinical profile and changing susceptibility pattern to antimicrobials of *S. paratyphi* A isolates over the period of 3 years in a tertiary care hospital in southern India.

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2. Materials and methods

The study was carried out at Kasturba Hospital Manipal, Karnataka, a tertiary care hospital over a period of 3 years, from 2006 to 2008.

We retrospectively analysed the records of 113 patients suffering from paratyphoid fever due to *S. paratyphi* A. Of the 113 patients, 77 (68%) were males and 36(32%) were females, which included 2 female children. The mean age of presentation was 29.27 years with age ranging from 6-74 years. More number of *S. paratyphi* were isolated compared to *Salmonella typhi* in the year 2006 and 2007.

Cases were diagnosed based on clinical features, isolation of *S. paratyphi* A from blood using BactT/Alert automated blood culture system and widal tube agglutination test. Widal titres O & AH > 1:160 with four fold rise were considered positive for paratyphi A infection. Antimicrobial susceptibility testing was done using Kirbey-Bauer disc diffusion method, according to standard guidelines for ampicillin, cotrimoxazole, chloramphenicol, ciprofloxacin and ceftriaxone. The clinical presentation, antimicrobial susceptibility, antimicrobial therapy, laboratory parameters, response to treatment and complications were recorded. Analysis of data was done using SPSS (11.0 for Windows) Defervescence was defined as the number of days required for abatement of fever after starting the antibiotics. Relapse was defined as the recurrence of fever or other clinical signs of infection within 2 months of completion of treatment with positive blood culture, after an appropriate initial clinical and bacteriological response.

3. Results

Fever was the most common symptom present in all cases (100.0%) followed by loose stool (37.2%), headache (35.4%), myalgia(31.9%), pain abdomen (29.2%), dry cough (19.5%), and vomiting(13.3%). Hepatomegaly was found in 14(12.4%) cases and splenomegaly in 29(25.7%), liver function test abnormality was noted in 30(26.6%) cases. Thrombocytopenia was noticed in 19 (16.8%) patients. Of these 5 patients had dengue co-infection proved by IgM ELISA and had significantly low platelet count.

Blood cultures grew *S. paratyphi* A in 101 patients, in the remaining 12 cases the diagnosis was made by widal test which showed significant titres(>1:160 for O& AH antigen) with four fold rise. Among the culture positive cases ,Widal test showed significant titres ($\geqslant$1:160 for O and AH antigen) in 22 patients(19.5%) and Widal test was negative in 79 patients(70%), majority of them presented with fever less than one week duration.

In our study there was evidence of other co-infection. Of the 12 culture positive cases with paratyphoid A cases 5 patients were tested positive in dengue IgM ELISA. Three had associated urinary tract infections due to *Escherich coli* and one each were positive for HIV, hepatitis, malaria and leptospirosis.

In our study 100 patients received ceftrioxone and 13 patients received ciprofloxacin. The mean time of defervescence in patients who received ciprofloxacin was 7 days as compared to ceftriaxone group which took only 5.1 days. One patient treated with ciprofloxacin had a relapse after 2 months and *S. paratyphi* A grown in blood culture which responded to ceftriaxone and declared clinically cured.

The antimicrobial sensitivity of *S. paratyphi* A has changed over the period of 3 years.This has been depicted in Table 1.There was a drastic upsurge of ciprofloxacin resistance from 2006-2008. The resistant isolates have almost increased by 10 fold. It is interesting to note that susceptibility of *S. paratyphi* A to ampicillin, chloramphenicol and cotrimoxazole (first line drugs) increased with decreasing resistance in 2007 and 2008. The widely used drug ciftriaxone, 3rd generation cephalosporin has been shown to be effective over years. There was no reported resistance to this drug in 2008 which made it the drug of choice for *S. paratyphi* A.

Table 1
Drug susceptibility pattern of *S. paratyphi* A [*n*(%)].

Year	Total No. of isolates	Ampicillin	Chloramphenicol	Cotrimoxazole	Ciprofloxacin	Ceftriaxone
2006	37	34 (92)	36 (97.3)	20 (54)	33 (89)	34 (92)
2007	35	34 (97)	34 (97)	35 (100)	19 (54)	34 (97)
2008	29	29 (100)	29 (100)	29 (100)	4 (14)	29(100)

4. Discussion

Salmonella enterica serovar Paratyphi A was the less frequent cause of enteric fever in earlier days, with isolation rates being 3-17% from India. The incidence of enteric fever due to *S. paratyphi* A is increasing since 1996[2]. An increase in isolation of *S. paratyphi* A was reported with 11.1%(2001) to 59%(2003) from Calicut[3]. Between 2001 to 2003 an unusually high occurrence of *S. paratyphi* A infection was reported from Nagpur[4]. A recent study from Chandigarh also showed an increasing trend of isolation of *S. paratyphi* from January 2003 to April 2007[7]. Regarding the differential risk factors for typhoid and paratyphoid, the infections have distinct routes of transmission. Paratyphoid fever was associated with sources outside the household such as food from street vendors and flooding in contrast to typhoid fever which is mostly due to household contacts as reported by Vollard AM *et al*[10]. It is also noticed increased cases of paratyphoid fever among students, young population and males related to the eating behaviour of these people. Drug resistance in typhoid fever is considered as one of the most important factors in the morbidity and mortality of the disease. The quinolone group of drugs emerged as useful drugs for the treatment of multiple drug resistant cases of Salmonella typhi but unfortunately ciprofloxacin resistance in the *S. paratyphi* A isolates has been reported from various

parts of India[11-13] . Adverse impact of nalidixic acid resistant *S. typhi* (NARST) strains, with longer duration of fever, higher frequency of hepatomegaly and elevated liver enzymes with increased MIC of ciprofloxacillin have been reported[14]. The global emergence of multidrug resiatant strain with decreased susceptibility to fluoroquinolones with poor clinical response despite disk sensitivity was reported by Bhan MK *et al* in 2005[15]. Multi drug resistant *Salmonella enterica* serotype *Typhimurium* associated with pet rodents was reported[16]. The resistance to quinolone is due to an altered DNA gyrase subunit. Indiscriminate use of drugs is one of the important factors leading to drug resistance and in case of ciprofloxacin, moderate cost, advantage of oral route, convenient dosage schedule, tolerability have contributed towards its indiscriminate use. Improved standards of public health have resulted in a marked decrease in the incidence of typhoid fever in developed countries[1], whereas in developing countries with poor water and sanitation system, practices treatment of enteric fever is a great challenge to modern medicine. Azhithromycin and third generation cephalosporins are the drugs of choice for enteric fever, but reports by Slinger *et al*. showed an incomplete response to cephalosporins[17]. Emergence of ciprofloxacin resistant isolates have allowed the extensive use of cephalosporins in the treatment of enteric fever in recent years. We have noted an increase in cases of paratyphoid fever in recent years in our hospital which might be due to increased laboratory confirmation of cases. The antimicrobial susceptibility has changed over the period of 3 years with increasing resistance to ciprofloxacin from 2006 to 2008, and sensitivity to first line drugs have shown an avenue for therapy with these drugs in uncomplicated cases, under the guidance of appropriate susceptibility results. However in rural India, where general population do not have an access to tertiary care hospital with laboratory facilities, most of the cases of suspected enteric fever are treated with empirical antibiotics. Recently we are seeing many cases of fever with features of enteric fever responding to cephalosporins, sometimes requiring addition of azithromycin but culture being repeatedly sterile due to the prior use of antibiotics by the general practitioners before referring the patients. Poor patient compliance, improper and inadequate dosages of antibiotics have contributed to emergence and spread of resistant isolates in the community. It is not a surprise in future if we see more cephalosporin resistant isolates.

In conclusion, though paratyphoid fever is relatively milder compared to typhoid fever, our findings highlight the importance of changing trends in susceptibility pattern of isolates. Since there is no effective vaccination against *S. paratyphi* A, we also reiterate the fact that public health interventions are constantly needed in educating general population about safe drinking water, food and personal sanitation measures. Antibiotics should be used cautiously according to susceptibility pattern and indiscriminate use should be discouraged.

Conflict of interest statement

We declare that we have no conflict of interest.

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