

SALMONELLA MENINGITIS AND ANTIMICROBIAL SUSCEPTIBILITIES

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Abstract. Meningitis caused by *Salmonella* species is not uncommon in many developing countries. Patients suspected of bacterial meningitis who were admitted to Siriraj Hospital were enrolled in this study during 1986-2001. There were only 19 cases of *Salmonella* meningitis. *Salmonella* serogroup D ranked first, followed by serogroup C, serogroup B and then serogroup H. Most patients were children under 1 year of age. The antimicrobial susceptibility pattern for *Salmonella* meningitis may provide a guideline for the selection of appropriate drug treatment.

INTRODUCTION

Salmonella is an important public health problem throughout the world. Although most *Salmonella* infections are self-limited, systemic infections and death can occur. *Salmonella* infection may occur in 5 different clinical forms, including gastroenteritis, enteric fever, bacteremia, meningitis, and a chronic carrier state. Finally, *Salmonella* may localize to one site in the body, often producing a characteristic clinical syndrome. Acute meningitis due to *Salmonella* spp is an unusual clinical problem occurring primarily in newborns and young infants in whom it is associated with significant mortality. In 1999, three fourths of the reported cases of *Salmonella* meningitis occurred among children under two years of age and the peak incidence occurred under the age of three months. The case fatality rate for *Salmonella* meningitis was high in all age groups; 73.5% overall and 92.5% in the neonatal patients (Hendersen, 1999). In general, antimicrobial agents are not essential for the treatment of most *Salmonella* infections, but they can be life-saving in the case of severe infection. Fluoroquinolones, such as ciprofloxacin, are commonly used for adult patients with *Salmonella* infection and for the treatment of acute gastroenteritis. The use of ampicillin, chloram-

phenicol and co-trimoxazole is limited because of increasing antimicrobial resistance to these agents (Cohen and Tauxe, 1986). While *Salmonella* spp are initially detected by their biochemical characteristics, groups and species are identified by antigenic analysis. Like other Enterobacteriaceae, they possess several O antigens (from a total of more than 60) and different H antigens in one or both of two phases. Some *Salmonella* have capsular (K) antigens, referred to as Vi, which may interfere with agglutination by O antisera and are associated with invasiveness. Agglutination tests with absorbed antisera for different O and H antigens form the basis for serologic classification (Brooks *et al*, 2001). In this study, we analyzed data of bacterial meningitis caused by various serogroups of *Salmonella* and their antimicrobial susceptibility patterns.

MATERIALS AND METHODS

Cerebrospinal fluid (CSF) was obtained from patients suspected of having bacterial meningitis who were admitted to Siriraj Hospital during a 15-year period (1986-2001).

Bacterial identification procedure

CSF was cultured on 5% sheep blood agar and chocolate agar at 35°C in a 5% CO₂ incubator. *Salmonella* was identified by standard microbiological techniques and serogrouping by slide agglutination by specific antisera purchased from Biotechnical (Thailand), *ie*, polyvalent A-67, polyvalent A-I, *Salmonella* Vi, antiserum specifi-

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cally to *Salmonella* for serogroup A (O:2), serogroup B (O:4, 5, 27), serogroup C (O:6, 7, 8, 14, 20), serogroup D (O:9, 46), serogroups E, F, G, H, and I.

Antimicrobial susceptibility test

The test was performed by the Kirby-Bauer disk diffusion method as described by the National Committee for Clinical Laboratory Standards (NCCLS, 2003). The testing conditions were Mueller Hinton (MH) agar, growth method or direct colony suspension for inoculum preparation; an ambient air temperature of 35°C; and 16-18 hours for incubation of the MH plates. *Escherichia coli* ATCC 25922 was used as the standard quality control in each batch of antimicrobial susceptibility tests.

All serogroups of *Salmonella* were tested for resistance to 9 antimicrobial agents: ampicillin, co-trimoxazole, chloramphenicol, norfloxacin, ciprofloxacin, ofloxacin, pefloxacin, ceftriaxone, and cefotaxime. Since there were few *Salmonella* strains isolated from the CSF, the susceptibility tests were performed using 739 *Salmonella* strains isolated from blood, CSF, and stool. Redundant isolates from the same infection were discarded. They were *Salmonella* serogroup A (62 strains), serogroup B (187 strains), serogroup C (187 strains), serogroup D (269 strains), and serogroup E (34 strains).

RESULTS

The number of patients suspected of having bacterial meningitis who were admitted to Siriraj Hospital during 1986-2001, and the percentage of positive CSF cultures for the patho-

genic bacteria are shown in Table 1. *Salmonella* meningitis is uncommon at Siriraj Hospital. For 15 years, there were only 19 cases of *Salmonella* meningitis (Table 2). *Salmonella* serogroup D ranked first (9 cases=47%), followed by *Salmonella* serogroup C (6 cases=32%), *Salmonella* serogroup B (3 cases=16%), and *Salmonella* serogroup H (1 case=5%) (Fig 1). Most patients were children (16/19=84%) especially under 1 year of age. A few patients were adults (3/19=16%) (Fig 1). The distribution of various serogroups in each age group is shown in Table 3.



Fig 1—Percentage of *Salmonella* in different serogroups during 1986-2001.

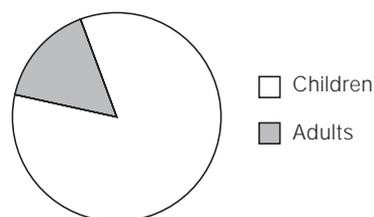


Fig 2—Percentage of children and adults with *Salmonella* meningitis.

Table 1
The number of patients suspected of bacterial meningitis and percentage of positive CSF cultures during 1994-2001.

No. of patients	1994	1995	1996	1997	1998	1999	2000	2001	Total
All patients	2,253	2,520	2,721	2,919	2,763	2,974	2,982	3,834	22,966
Patients with positive CSF cultures	126	123	189	220	200	160	163	163	1,344
Percentage (%)	5.59	4.88	6.95	7.54	7.24	5.38	5.47	4.3	5.86

Table 2
Number of children with *Salmonella* meningitis in different age groups.

Age	Number of patients	<i>Salmonella</i> serogroup
1 month	3	serogroup B, D, H
3 months	1	serogroup D
4 months	4	serogroup C (1), serogroup D (3)
5 months	1	serogroup D
6 months	3	serogroup C (2), serogroup D (1)
8 months	1	serogroup C
< 14 years	3	serogroup B (2), serogroup C (1)
Adults	3	serogroup C (1), serogroup D (2)
Total	19	

Table 3
Salmonella strains used in antimicrobial sensitivity tests.

<i>Samonella</i> serogroup	Number of strains
<i>Samonella</i> serogroup A	62
<i>Salmonella</i> serogroup B	187
<i>Salmonella</i> serogroup C	187
<i>Salmonella</i> serogroup D	269
<i>Salmonella</i> serogroup E	34
Total	739

Table 4
Susceptibility patterns of various *Salmonella* serogroups to 9 antimicrobial agents.

Antimicrobial agents	% Sensitive				
	<i>Sal. A</i>	<i>Sal. B</i>	<i>Sal. C</i>	<i>Sal. D</i>	<i>Sal. E</i>
Ampicillin	95	22	46	92	67
Co-trimoxazole	99	17	73	92	67
Chloramphenicol	97	46	27	94	100
Norfloxacin	100	93	100	100	100
Ciprofloxacin	100	92	96	100	100
Ofloxacin	100	94	96	100	100
Pefloxacin	100	75	100	100	-
Ceftriaxone	100	100	97	100	78
Cefotaxime	99	100	100	100	82

Antimicrobial susceptibility tests

Table 3 shows the 739 *Salmonella* strains of various serogroups which were included in the antimicrobial sensitivity tests. Table 4 shows that *Salmonella* serogroups A and D, including *Salmonella typhi*, were sensitive to all drugs tested (range 92-100%). *Salmonella* serogroup B was sensitive to norfloxacin, ciprofloxacin, ofloxacin, pefloxacin (range 92-100%) but resistant to ampicillin, co-trimoxazole, and chloramphenicol. *Salmonella* serogroup C was similar to *Salmonella* serogroup B, except that it was still sensitive to co-trimoxazole (73%). *Salmonella* serogroup E was sensitive to chloramphenicol, norfloxacin, ciprofloxacin, and ofloxacin (100%) but less sensitive to ampicillin, co-trimoxazole, ceftriaxone, and cefotaxime (range 67-82%).

DISCUSSION

Although *Salmonella* is not a frequent cause of meningitis and less than 1% of cases of *Salmonella* infection were associated with this disease, numerous cases of *Salmonella* meningitis were reported in children. From this study, it was found that the percentage of positive CSF cultures for any pathogenic bacteria was 2%. *Salmonella* meningitis is rare. Most patients were children, especially under 1 year of age. These data are in concordance with a previous field study in Nigeria, which showed that *Salmonella* meningitis is predominantly a disease of neonates and young infants. Only 2 out of 38 pa-

tients developed the disease after the age of 1 year, at 18 months and 3 years, respectively (Barclay, 1971). Previous studies from 1976 to 1984 (Cohen *et al*, 1987) in the United States found that the incidence of *Salmonella* meningitis is relatively low. Of 158 cases of gram-negative meningitis in adults, 14 cases (8%) were due to *Salmonella*; it was more common in children (95% of cases) than adults; 74% of all cases occurred in infants less than 4 months old. Infants are generally less resistant to meningeal infection than older children and adults. The predominance of neonates with *Salmonella* meningitis may be due to increased permeability of the blood brain barrier, birth trauma, immaturity of cellular immunity or transmission of infection from an infected mother or nursery mate (Geiseler, 1980). A possible mechanism for susceptibility to meningitis in infants was suggested by Black *et al* (1960) who demonstrated in premature infants an increased permeability of the meninges to a dye. Organism that gains access to the circulation may localize to the central nervous system to a greater degree in infants than in older age groups.

Our study showed that the most commonly isolated serotypes in the CSF were serogroups D, C, B and H. Currently, there are well over 2,000 different antigenic types of *Salmonella* reported. The nomenclature and classification of these bacteria have been changed many times and are still not established. It is now generally accepted that these represent serotypes of a single species *ie*, *Salmonella enterica*. The full correct name is, for example, *Salmonella enterica* subspecies *enterica* serotype Enteritidis, but this is usually abbreviated to *Salmonella* Enteritidis. Earlier studies indicated that among the various serogroups of *Salmonella*, most cases of meningitis were due to *Salmonella typhimurium* (serogroup B), *Salmonella enteritidis* (serogroup D), *Salmonella paratyphi* B (serogroup B) and *Salmonella panama* (serogroup D) (Denis *et al*, 1977). These data are in contrast to a study in the United States from 1976 to 1984 which found that *Salmonella havana* and *Salmonella typhimurium* were the most commonly isolated serotypes in children. *Salmonella bredeney* and *Salmonella panama* were frequently isolated,

usually in association with epidemic gastroenteritis and meningitis (Cohen *et al*, 1987).

During the antimicrobial sensitivity tests, we found that *Salmonella* serogroups A and D, including *Salmonella typhi*, were sensitive to all 9 drugs tested, whereas serogroup C was sensitive to most drugs except ampicillin and chloramphenicol. *Salmonella* serogroup E was sensitive to chloramphenicol and norfloxacin, but was less sensitive to ampicillin, co-trimoxazole, ceftriaxone and cefotaxime. Most patients with *Salmonella* meningitis received multiple antimicrobial agents, although some were cured with a single drug. Investigation in 1981 reported that adults with *Salmonella* meningitis who were treated with chloramphenicol had persistently positive CSF cultures. *Salmonella* spp are facultative intracellular organisms. The ability to survive intracellularly protects *Salmonellae* from the actions of extracellular antimicrobial agents. Ceftriaxone has intracellular penetration and enters the intracellular host compartment, which contains engulfed bacteria (Maurin and Raoult, 1997). In such cases, the intracellular activity of the antimicrobial agent is dependent on the extracellular concentration achieved. This information suggests that for the successful treatment of *Salmonella* meningitis, the dose of the third generation cephalosporin used should be high. Recently, quinolone resistance in the most common *Salmonella* serotype worldwide has become a serious public health concern. Resistance to fluoroquinolones, such as ciprofloxacin, has been reported (Helms *et al*, 2002). The prevalence of resistance is high in some serovars, such as *Salmonella enterica* serovar Hadar or in some clone, such as the epidemic *Salmonella typhimurium* DT104 in the UK (Ribot *et al*, 2002). Various studies carried out to determine the penetration of ciprofloxacin into CSF (Cohen *et al*, 1987) suggested that a therapeutic concentration could be achieved with adequate dosages, in patients with inflamed meninges.

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