

# *Salmonella enterica* serotype Choleraesuis infection in a medical center in northern Taiwan

Shun Chiu, Cheng-Hsun Chiu, Tzou-Yien Lin

Division of Pediatric Infectious Diseases, Department of Pediatrics, Chang Gung Children's Hospital, Taoyuan, Taiwan, ROC

Received: April 11, 2003 Revised: May 14, 2003 Accepted: June 9, 2003

This retrospective study was conducted in order to determine the clinical and microbiologic features of infection with *Salmonella enterica* serotype Choleraesuis. Between March 1999 and December 2002, 55 patients with 66 isolates were enrolled for analysis. The ratio of males to females was 2.2:1. Most patients were older than 60 years (56%) and had underlying diseases (78%), such as diabetes mellitus, malignancy, and peptic ulcer. Fever (85%) was the most common clinical manifestation, followed by abdominal pain/fullness (31%). The gastrointestinal manifestations, including nausea/vomiting or diarrhea, accounted for only 13% and 11% of patients, respectively. *S. enterica* serotype Choleraesuis was extremely invasive, with a high predilection to cause bacteremia (78% of the isolates were from blood). Various types of metastatic focal infections were found, including infected arterial aneurysm, osteomyelitis, septic arthritis, urinary tract infection and wound infection. The crude mortality rate was 18% (10 deaths in 55 cases). Nearly all isolates were susceptible to the third-generation cephalosporins. A higher resistance rate to commonly used antimicrobial agents was found with ampicillin (85%, 56/66), trimethoprim-sulfamethoxazole (81%, 40/49), chloramphenicol (96%, 47/49), and ciprofloxacin (49%, 30/61). In view of the emergence of fluoroquinolone resistance, the third-generation cephalosporins appear to be the best choice for treatment of invasive infections caused by this organism.

**Key words:** Bacteremia, infected aneurysm, *Salmonella enterica*, Taiwan

*Salmonella* infection can cause 3 distinct clinical syndromes, including acute gastroenteritis, enteric fever, and bacteremia with or without focal extraintestinal infection [1]. The most common manifestation of non-typhoid *Salmonella* infection is self-limited enterocolitis [1]. Despite being host-adapted to domestic animals, among the more than 2000 non-typhoid *Salmonella* serotypes, *Salmonella enterica* serotype Choleraesuis is extremely invasive and is usually associated with bacteremia in humans. *S. enterica* serotype Choleraesuis has a high ratio of blood isolates to total *S. enterica* serotype Choleraesuis isolates. Between 1981 and 1990 in England and Wales, the ratio of bloodstream isolates to total isolates of *S. enterica* serotype Choleraesuis was 74.1% [2]. A similar result was also obtained in a study of multidrug-resistant non-typhoid *Salmonella* infections in northern Taiwan [3], in which the ratio was 50% between 1998 and 2000. Drug resistance of *S. enterica* serotype Choleraesuis infection is another difficult issue to handle. The first recognized outbreak

of fluoroquinolone-resistant *Salmonella* infection in the United States occurred in 1997 [4].

Information regarding the infection of *S. enterica* serotype Choleraesuis is limited in Taiwan, although such infection is rampant. We therefore carried out this study to delineate the clinical and microbiologic features of *S. enterica* serotype Choleraesuis infection in Taiwan.

## Patients and Methods

Patients enrolled in this study were those who were treated in Chang Gung Memorial Hospital from March 1999 to December 2002 because they had a positive culture for *S. enterica* serotype Choleraesuis. The case definition was a patient who developed a positive culture of *S. enterica* serotype Choleraesuis during hospitalization, isolated from blood, urine, stool, a wound or tissue. We identified 55 adult patients from whom 66 isolates were recovered. The medical charts of these 55 cases were retrospectively reviewed for demographic data, laboratory data, underlying disease, clinical manifestation, prior use of antibiotics and antibiotic susceptibility. Mortality due to *S. enterica*

---

Corresponding author: Dr. Cheng-Hsun Chiu, Division of Pediatric Infectious Diseases, Department of Pediatrics, Chang Gung Children's Hospital, 5 Fu-Hsin Street, Kweishan, Taoyuan, Taiwan 333, ROC. E-mail: chchiu@adm.cgmh.org.tw

serotype Choleraesuis infection was defined as death occurring within 7 days of the onset of the infection.

*Salmonella* was first identified by standard biochemical procedures [5]. The serogroup was checked with O antisera by the slide agglutination method (Difco Laboratories, Detroit, MI, USA). The antimicrobial susceptibility of these isolates was investigated by using a standard disk-diffusion method [6]. The antibiotics tested included ampicillin, ciprofloxacin, ceftriaxone, trimethoprim-sulfamethoxazole, and chloramphenicol. The interpretive standard for these susceptibility categories was as recommended by the National Committee for Clinical Laboratory Standards [6]. Isolates in the “intermediate” category were considered resistant in this study.

### Results

Thirty eight patients (69%) were male, and 17 female. Their ages ranged from 26 to 85 years with a mean of 57 years, and 31 (56%) were ≥60 years of age. Most cases in this series (78%) had significant underlying medical conditions, including immunosuppressive and chronic debilitating diseases. Only 12 patients had no underlying diseases. The major underlying conditions are summarized in Table 1. The history of patients’ prior use

**Table 1.** Underlying diseases in patients with *Salmonella enterica* serotype Choleraesuis infection

Underlying disease	No. of cases
Immunosuppressive disease	
Systemic lupus erythematosus	3
Malignancy	11
Diabetes mellitus	11
Chronic debilitating disease	
Rheumatic heart disease/heart failure	4
Liver cirrhosis	5
Cerebrovascular accident	1
Myocardial infarction	2
Chronic obstructive pulmonary disease	4
Peptic ulcer	7
Subtotal gastrectomy	2
Cholecystectomy	2
Total hip joint replacement	2
Hypertension	3
Renal insufficiency	3
Pulmonary tuberculosis	2
Others <sup>a</sup>	10

<sup>a</sup>One case each of gout, hyperthyroidism, chronic osteomyelitis, amphetamine abuse, AIDS, autoimmune hemolytic anemia, Parkinsonism, lumbar spine stenosis, ankylosing spondylitis, and idiopathic myelofibrosis.

**Table 2.** Sites of isolation of *Salmonella enterica* serotype Choleraesuis

Specimen	No. of isolates (%)
Blood	52 (78)
Tissue <sup>a</sup>	7 (10)
Wound	3 (6)
Urine	2 (3)
Joint	1 (1)
Abscess	1 (1)
Stool	0
Total	66 (100)

<sup>a</sup>Four specimens from aortic wall, 3 from bone debridement.

of antibiotics was available only for some of the patients. As mentioned above, from the 55 patients we recovered 66 isolates. All of the isolates were derived from non-fecal specimens. On the whole, we found that *S. enterica* serotype Choleraesuis had a high predilection for causing bacteremia and extraintestinal infections (Table 2).

Cultures of aneurysmal wall tissue and blood yielded *S. enterica* serotype Choleraesuis in 4 patients. Three patients experienced 2 episodes of bacteremia. Seven cases had bacteremia and concurrent focal infection. It is apparent that *S. enterica* serotype Choleraesuis infections were characterized by primary bacteremia and metastatic focal infection.

The detailed clinical symptoms of each patient and other signs of infection on admission are shown in Table 3. Fever (≥38°C) [85%] was the most common, followed by abdominal pain/distention (31%). Although the gastrointestinal tract was the main portal of entry for *Salmonella*, gastrointestinal manifestations, including nausea/vomiting (13%) or diarrhea (11%), were not that frequently seen. Five patients initially had ruptures of abdominal aortic aneurysms or aortic dissection presented with severe abdominal pain. A shock/hypotension status was present in 5 patients.

**Table 3.** Clinical manifestations of patients with *Salmonella enterica* serotype Choleraesuis infection

Symptom/sign	No. of cases (%)
Fever (≥38°C)	47 (85)
Abdominal pain/fullness	17 (31)
Nausea/vomiting	7 (13)
Lower back pain/hip joint pain	7 (13)
Cough/tachypnea	6 (11)
Diarrhea	6 (11)
Wound discharge	5 (9)
Conscious disturbance	5 (9)
Hypotension/shock	5 (9)
Generalized pain/malaise	4 (7)
Chest pain	3 (5)

**Table 4.** Diagnosis in patients with *Salmonella enterica* serotype Choleraesuis infection (n = 55)

Diagnosis	No. of cases (%) <sup>a</sup>
Bacteremia	49 (89)
Ruptured aorta/iliac artery/ superficial artery aneurysm	6 (11)
Type A aortic dissection	1 (1)
Enterocolitis	6 (11)
Pyogenic spondylitis	3 (5)
Lumbar spondylolithesis	1 (1)
Pneumonia	4 (7)
Wound infection	3 (5)
Osteomyelitis (femoral head, proximal femoral bone)	2 (3)
Septic arthritis (hip joint)	2 (3)
Urinary tract infection	2 (3)
Splenic fossa abscess	1 (1)

<sup>a</sup>Some patients had more than one diagnosis.

Table 4 shows the different types of infection that patients suffered from. They were more likely to experience extraintestinal infections and only 6 (11%) patients had enterocolitis. The localized infections other than enterocolitis included pneumonia (patch infiltration with or without pleural effusion) in 4 cases, culture-proved pyogenic spondylitis in 3, culture-proved urinary tract infection in 2, culture-proved splenic fossa abscess in 1, and septic hip in 1 case. There were 4 cases with ruptured abdominal aorta aneurysms and 1 case each of ruptured right iliac artery aneurysm, type A aortic dissection and rupture of left superficial femoral artery pseudoaneurysm. The excised arterial specimens revealed atherosclerosis with calcification in 5 patients (71%).

Table 5 lists the antimicrobial susceptibilities of the 66 isolates identified during this period. Nearly 100% of the isolates were sensitive to ceftriaxone. Resistance to ciprofloxacin and ampicillin was found in 49% and 85% of isolates, respectively. Eighty one percent of isolates were resistant to trimethoprim-sulfamethoxazole. Ten deaths among these patients occurred during this period. There were 4 cases (7%)

**Table 5.** Susceptibility of *Salmonella enterica* serotype Choleraesuis to antimicrobial agents by standard disk-diffusion method

Antimicrobial agent	Resistance rate (%)
Ampicillin	56/66 (85)
Chloramphenicol	47/49 (96)
Trimethoprim-sulfamethoxazole	40/49 (81)
Ciprofloxacin	30/61 (49)
Ceftriaxone	1/50 (2)

whose mortality was considered related to *S. enterica* serotype Choleraesuis infection (all were sepsis). Three patients died of terminal stage of malignancy. The other 3 patients died because of organ failure.

## Discussion

*S. enterica* serotype Choleraesuis, the swine-adapted serotype, has commonly caused enteritis in pigs [7], but may be isolated from other animals, including humans. Although *S. enterica* serotype Choleraesuis infrequently causes human infections, this highly invasive serotype is of particular concern in Taiwan. It represented the third most common serotype causing non-typhoid salmonellosis in Taiwan [8]. In this study, we found bacteremia (78%) was the main mode of disease caused by *S. enterica* serotype Choleraesuis. Furthermore, various types of extraintestinal localized infections were common. Our data showed that most patients (78%) had pre-existing underlying diseases. The most common 3 were malignancy, diabetes mellitus, and peptic ulcer/gastrointestinal surgery. These underlying diseases, which impaired cellular immune mechanisms or caused rapid gastric emptying, have been regarded as predisposing factors for *Salmonella* infections [1].

This study also demonstrated that most patients (56%) were older than 60 years old. These findings are consistent with an earlier report [9], showing that pre-existing underlying disease, particularly immunosuppressive disease, and old age were frequently associated with extraintestinal infection of non-typhoid *Salmonella* in adult patients. On the other hand, *S. enterica* serotype Choleraesuis is one of a small number of non-typhoid *Salmonella* species that have virulence plasmids. The virulence plasmids are highly associated with bacteremia and disseminated infection in humans [8,10]. Several studies indicate that the plasmid-containing organisms outgrow plasmidless strains in the liver and spleen, leading to an overwhelming infection [11,12].

In the present study, we identified 6 cases of mycotic aneurysm. Four (66%) of the 6 were caused by *S. enterica* serotype Choleraesuis and had underlying atherosclerosis. Early in 1962, Sower and Whelan demonstrated that *Salmonella* was a common cause of mycotic aneurysms in patients with pre-existing atherosclerosis [13]. Wang et al [14], and more recently Hsu et al [15], reported that the majority of the mycotic aneurysms in Taiwan were caused by *S. enterica* serotype Choleraesuis. It is reasoned that *Salmonella* organisms, *S. enterica* serotype Choleraesuis in

particular, can seed in atheroma and subsequently induce the formation of mycotic aneurysm [13-16]. In a patient with a pre-existing arteriosclerotic change and concomitant *S. enterica* serotype Choleraesuis bacteremia, it should be kept in mind that an infected aortic aneurysm is highly possible.

The majority of the isolates were resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole and only half of them were susceptible to ciprofloxacin in our study. The third-generation cephalosporins are active against this serotype. This finding could be the result of the increased use of these drugs in the treatment of salmonellosis or other bacterial infection in Taiwan.

The emergence of fluoroquinolone resistance in *S. enterica* serotype Choleraesuis was first reported in Taiwan by Chiu et al [17]. It was demonstrated that most of the *S. enterica* serotype Choleraesuis isolates from humans and swine exhibited the same or similar DNA fingerprints, indicating that human infections were acquired from pigs [17]. We postulated that the habit of eating pig offal by the local population might be one cause for the spread of *S. enterica* serotype Choleraesuis infection in the locality. Since the use of antibiotics can reasonably be expected to select for resistance, inappropriate use of antibiotics in humans as well as domestic animals should be avoided.

In conclusion, *S. enterica* serotype Choleraesuis causes mainly primary bacteremia and various types of metastatic focal infections, of which infected arterial aneurysm is of particular importance. Old age and underlying medical comorbidities are strongly associated with *S. enterica* serotype Choleraesuis infection. Most of the *S. enterica* serotype Choleraesuis isolates were highly resistant to conventional antibiotics. In view of the emergence of fluoroquinolone resistance, the third-generation cephalosporins appear to be the best choice for treatment of invasive infections caused by this organism.

## Acknowledgments

The authors would like to thank Dr. Luan-Yin Chang, Dr. Yhu-Chering Huang, and Dr. Chien-Yu Lee for their advice and help in the conduct of this study.

## References

1. Cohen JI, Bartlett JA, Corey GR. Extraintestinal manifestations of *Salmonella* infection. *Medicine* 1987;66:349-88.
2. Threlfall EJ, Hall MLM, Rowe B. *Salmonella* bacteremia in England and Wales, 1981-1990. *J Clin Pathol* 1992;45:34-6.
3. Lee CY, Chiu CH, Chuang YY, Su LH, Wu TL, Chang LY, et al. Multidrug-resistant non-typhoid *Salmonella* infections in a medical center. *J Microbiol Immunol Infect* 2002;35:78-84.
4. Olsen SJ, DeBess EE, McGivern TE, Marano N, Eby T, Mauvais S, et al. A nosocomial outbreak of fluoroquinolone-resistant salmonella infection. *N Engl J Med* 2001;344:1572-9.
5. Farmer JJ, III. *Enterobacteriaceae*: introduction and identification. In: Murray PR, Baron EJ, Pfaller MA, Tenoer FC, Tenover RH, eds. *Manual of clinical microbiology*. 6th ed. Washington, DC: American Society for Microbiology; 1995:438-49.
6. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests. 7th ed; approved standard. Villanova, PA: National Committee for Clinical Laboratory Standards; 2000. NCCLS document M2-A7.
7. Field HI. Salmonellosis in animals. *Vet Rec* 1958;70:1050-2.
8. Chiu CH, Lin TY, Ou JT. Prevalence of the virulence plasmids of nontyphoid *Salmonella* in the serovars isolated from humans and their association with bacteremia. *Microbiol Immunol* 1999;43:899-903.
9. Chiu CH, Lin TY, Ou JT. Predictors for extraintestinal infection of non-typhoidal *Salmonella* in patients without AIDS. *Int J Clin Pract* 1999;53:161-4.
10. Guiney DG, Fang FC, Krause M, Libby S, Buchmeier NA, Fierer J. Biology and clinical significance of virulence plasmids in *Salmonella* serovars. *Clin Infect Dis* 1995;21(Suppl 2):S146-51.
11. Gulig PA. Virulence plasmids of *Salmonella typhimurium* and other *Salmonellae*. *Microb Pathog* 1990;8:3-11.
12. Gulig PA, Danbara H, Guiney DG, Lax AJ, Norel F, Rhen M. Molecular analysis of *spv* virulence genes of the salmonella virulence plasmids. *Mol Microbiol* 1993;7:825-30.
13. Sower ND, Whelan TJ Jr. Suppurative arteritis due to *Salmonella*. *Surgery* 1962;52:851-9.
14. Wang JH, Liu YC, Yen MY, Wang JH, Chen YS, Wann SR, et al. Mycotic aneurysm due to non-typhi *Salmonella*: report of 16 cases. *Clin Infect Dis* 1996;23:743-7.
15. Hsu RB, Tsay YG, Chen RJ, Chu SH. Risk factors for primary bacteremia and endovascular infection in patients without acquired immunodeficiency syndrome who have nontyphoid salmonellosis. *Clin Infect Dis* 2003;36:829-34.
16. Chiu CH, Ou JT. Risk factors for endovascular infection due to nontyphoid salmonellae. *Clin Infect Dis* 2003;36:835-6.
17. Chiu CH, Wu TL, Su LH, Chu C, Chia JH, Kuo AJ, et al. The emergence in Taiwan of fluoroquinolone resistance in *Salmonella enterica* serotype choleraesuis. *N Engl J Med* 2002;346:413-9.