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Multidrug-resistant non-typhoid *Salmonella* infections in a medical center

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Due to the high incidence of antimicrobial-resistant *Salmonella* in Taiwan, the emergence of multidrug-resistant *Salmonella* has become of particular concern. This retrospective study assessed the clinical features of patients with multidrug-resistant *Salmonella* treated from January 1998 through June 2000. A total of 201 children and 33 adults with multidrug-resistant *Salmonella* infections treated during a 2.5-year period were included. Sixty-percent of these patients had used antibiotics before multidrug-resistant *Salmonella* infection developed. The incidence of extra-intestinal infections was higher in adults (51.4%) than in children (4.9%). Infection with an invasive serotype of *Salmonella*, such as *Salmonella choleraesuis*, and host factors appeared to be predisposing factors for bacteremia or extra-intestinal infections. None of the patients had mortality attributable to multidrug-resistant salmonellosis. The increasing rate of resistance to third-generation cephalosporins and fluoroquinolones and the high multidrug-resistant rate of *S. choleraesuis* found in this study indicate the importance of judicious use of antimicrobial agents in both humans and animals to reduce the selection and spread of resistant strains.

Key words: Extra-intestinal infection, multidrug-resistant *Salmonella*

Despite improved sanitation, non-typhoid salmonellosis remains an important public health problem worldwide [1]. Most non-typhoid salmonellosis is usually self-limiting and does not require antimicrobial treatment [2,3]. Studies have indicated that antimicrobial treatment for uncomplicated gastroenteritis does not shorten the duration and severity of symptoms; in contrast, it may prolong fecal excretion, increase the risk of relapse, and result in the emergence of antibiotic resistance [2,3]. Nevertheless, if extra-intestinal complications occur, effective antimicrobial treatment is essential.

In 2 university hospitals in northern Taiwan—Chang Gung Memorial Hospital and Chang Gung Children's Hospital—the total number of *Salmonella* isolates was 7986 from 1983 through 1999. The annual number of isolates increased from 94 in 1983 to 774 in 1999 [4]. Among these non-typhoid isolates, antimicrobial resistance to ampicillin (62%), chloramphenicol (67%), and trimethoprim/sulfamethoxazole (37%) was high [4]. The antimicrobial resistance rate to the newer generation cephalosporins and ciprofloxacin was generally under 2.5%, while all of the resistant strains were isolated in 1999 [4]. Similar situations have been observed in other countries [5-13]. The emergence of multidrug-resistant (MDR) *Salmonella* is also of serious concern. In this study, we retrospectively analyzed the clinical data of patients with MDR *Salmonella* infections treated at the Chang Gung Memorial Hospital and the Chang Gung Children's Hospital during a 2.5-year period to determine the possible predisposing factors, clinical features, and complications associated with MDR *Salmonella* infections.

Materials and Methods

Patient enrollment

All patients with MDR *Salmonella* infections between January 1998 and June 2000 were included in the study, regardless of whether the infection was community- or hospital-acquired. Multidrug resistance was defined as resistance to 3 or more antimicrobial agents tested. The patients were divided into 2 groups—the pediatric group including patients aged below 18 years; and the adult group including patients aged 18 years or above. We reviewed medical charts of these patients and collected the following data: demographic characteristics,

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underlying diseases, prior use of antimicrobial agents and steroids, clinical symptoms and signs, laboratory data, origin of disease (community-acquired or nosocomial), management, and outcome. Prior antimicrobial or steroid use was defined as the consumption of these agents 6 months before the onset of salmonellosis. Hospital-acquired salmonellosis was defined as fever or other symptoms in a patient with a positive culture over 72 h after admission if the patient had no signs of other infection until then. Episodes of salmonellosis were considered to be distinct if occurrences were at least 2 weeks apart, and *Salmonella* serogroups in each episode were different.

Microbiological studies

All isolates were cultured and identified according to standard methods [14]. No major changes in the policy concerning identification of *Salmonella* were made during the study period. The serogroup of *Salmonella* isolates was checked with O antisera (Difco Laboratories, Detroit, MI, US) by the slide agglutination method. The antimicrobial susceptibility of these isolates was investigated by using a standard disk-diffusion method [15] for all isolates and further confirmed by the microbroth dilution method [16] for blood isolates. The antibiotic disks tested included ampicillin 10 μg, cefepime 30 μg, cefixime 5 μg, ceftazidime 30 μg, ceftizoxime 30 μg, ceftriaxone 30 μg, chloramphenicol 30 μg, ciprofloxacin 5 μg, and trimethoprim-sulfamethoxazole 1.25/23.75 μg. Susceptible or resistant isolates were defined according to the criteria suggested by the National Committee for Clinical Laboratory Standards [15,16]. Isolates in the "intermediate" category were considered as resistant in this study.

Statistical analysis

Continuous variables were analyzed with unpaired *t* test. Chi-square and Fisher's exact 2-tailed tests were used to examine nominal data. Univariate analysis was used to identify the risk factors associated with extra-intestinal salmonellosis. A p value of less than 0.05 was considered significant.

Results

Demographic data

A total of 234 cases (240 episodes) with culture-documented MDR *Salmonella* infections treated during the study period were identified. Two hundred and one (85.9%) patients were children (age <18 years) and 33 (14.1%) were adults (age ≥18 years). There was no sex difference between the 2 groups. Eighty-percent of patients were under 5 years old, and 10% were older than 45 years. The demographic data of these patients are summarized in Table 1. The duration of hospital stay in pediatric patients was shorter than that in adults ($p<0.05$). Antibiotic use history was available only in a part of the patients. Fifty (55.6%) of 90 children and 15 (65.2%) of 23 adults with valuable data had a history of antibiotic use 6 months before the onset of infections ($p=0.403$). No difference in steroid use before the infection was found between the 2 groups ($p=0.222$).

Clinical manifestations

The clinical features of the patients are summarized in Table 2. Pediatric patients were more likely to have fever ($p<0.05$), diarrhea ($p<0.05$), mucoid stool ($p<0.05$), and bloody stool ($p<0.05$). Only one child and 2 adults experienced hypotension, which necessitated therapy with an inotropic agent.

Major underlying diseases

Eleven (5.5%) children and 23 (69.7%) adults had one or more major underlying diseases, including immunosuppressive and chronic debilitating diseases

Table 1. Demographic and clinical data of patients with multidrug-resistant *Salmonella* infections

Characteristic	Children n = 201, 203 episodes	Adults n = 33, 37 episodes	*p*
Sex (M/F)	110/91	17/16	0.731
Age (year)			
Mean ± SD	1.7 ± 1.7	51.4 ± 1.7	
Range	14 days-12 years	19-80 years	
Inpatient (%)	167 (82.3)	33 (89.2)	
Outpatient (%)	36 (17.7)	4 (10.8)	
Duration of hospital stay (days)			0.001
Mean ± SD	8.4 ± 18.3	21.1 ± 22.9	
Range	2-191	1-96	
Antimicrobial exposure (%)	50/90 (55.6)	15/23 (65.2)	0.403
Steroids used (%)	5/65 (7.7)	4/22 (18.2)	0.222

Table 2. Clinical manifestations in patients with multidrug-resistant *Salmonella* infections

Symptom/sign	Children n = 203 (%)	Adults n = 37 (%)	*p*
Fever (≥38°C)	177 (87.2)	27 (73.0)	0.026
Duration of fever (days)			0.933
Mean ± SD	4.7 ± 3.0	4.7 ± 3.0	
Range	1-22	0-11	
Diarrhea	194 (95.6)	22 (59.5)	<0.001
Watery	117/194 (60.3)	18/21 (85.7)	0.022
Mucoid	91/194 (46.9)	2/21 (9.5)	0.001
Blood-tinged	120/194 (61.9)	4/21 (19.0)	<0.001
Duration of diarrhea (days)			0.081
Mean ± SD	7.0 ± 4.1	9.1 ± 8.3	
Range	1-29	1-30	
Frequency of diarrhea (times/day)			0.278
Mean ± SD	8.6 ± 4.9	7.0 ± 2.8	
Range	2-31	1-30	
Seizure	4 (2)	0	1.000
Shock	1 (0.5)	2 (5.4)	0.063

($p<0.05$). The major underlying conditions are summarized in Table 3.

Diagnoses

Table 4 shows the diagnoses of these patients. One hundred and ninety-five (96.1%) children had enterocolitis, compared with only 21 (56.8%) adults ($p<0.05$). Adult patients (51.4%) were more likely to experience extra-intestinal infections than children (4.9%), including urinary tract infection, bacteremia, intra-abdominal abscess, aortic mycotic aneurysm, and osteomyelitis. Six children have complication of toxic megacolon, whereas no adults experienced this complication. Two patients each with volvulus and rectal prolapse had stool cultures positive for *Salmonella*. One child had catheter-associated bacteremia caused by *Salmonella*. One adult presented with chronic sore throat and neck masses. The diagnosis of *Salmonella* lymphadenitis was confirmed with the culture of aspirate from the neck mass. No difference

Table 3. Major underlying diseases in patients with non-typhoid *Salmonella* infection

Underlying disease	Children n = 201 (%)	Adults n = 33 (%)
Immunosuppressive disease		
Diabetes mellitus	0	9 (27.3)
Malignancy	2 (1)	5 (15.2)
End-stage renal disease	0	2 (6.1)
Systemic lupus erythematosus	0	1 (3)
Severe combined immunodeficiency	1 (0.5)	0
Debilitating disease		
Cerebral vascular accident	0	9 (27.3)
Chronic liver disease	0	2 (6.1)
Peptic ulcer	0	4 (12.1)
Gastrectomy	0	2 (6.1)
Congenital heart disease/heart failure	4 (2)	1 (3)
Failure to thrive	2 (1)	0
Others	3 (1.5)[a]	4 (12.1)[b]
Total	11 (5.5)[c]	23 (69.7)[c]

[a]One case each of Edward's syndrome, vesicoureteral reflux, and scald burn status post skin graft transplantation.
[b]One case each of blunt abdominal trauma status post splenectomy, urolithiasis, bladder hemangioma status post excision, and liver cysts.
[c]$p<0.001$.

Table 4. Diagnosis in children and adults with episodes of culture-confirmed multidrug-resistant *Salmonella* infections

Diagnosis	Children n = 203 (%)	Adults n = 37 (%)	*p*
Enterocolitis	197 (96.1)	21 (56.8)	<0.001
Septic joint	1 (0.5)	1 (2.7)	0.285
Urinary tract infection	5 (2.5)	8 (21.6)	<0.001
Bacteremia	12 (5.9)	12 (32.4)	<0.001
Wound infection	2 (1.0)	1 (2.7)	0.396
Bowel perforation	1 (0.5)	1 (2.7)	0.285
Intraabdominal abscess	0	3 (10.1)	0.003
Perianal abscess	1 (0.5)	1 (2.7)	0.285
Aortic aneurysm	0	2 (5.4)	0.023
Osteomyelitis	0	3 (8.1)	0.003
Toxic megacolon	6 (3.0)	0	0.591
Appendicitis	0	1 (2.7)	0.154
Volvulus	1 (0.5)	0	1.000
Rectal prolapse	1 (0.5)	0	1.000
Neck lymphadenitis	0	1 (2.7)	0.154
Nosocomial infection	4 (2.0)	3 (8.1)	0.076
Catheter-related infection	1 (0.5)	0	1.000

was found in the rate of nosocomial infections between pediatric and adult patients. The mean rate of nosocomial infections due to *Salmonella* was 2.9%.

Culture sites and serogroup distribution

A total of 260 (14.6%) among 1784 strains of *Salmonella* isolated from January 1998 through June 2000 were resistant to 3 or more of the antimicrobial agents tested. These strains were isolated from 10 different sites. The culture sites and serogroup distribution are summarized in Table 5. Stool and blood were the 2 most common sites for positive culture of *Salmonella*. The MDR rate of *S. choleraesuis* (21.4%) was highest among these serogroups, followed by serogroup B *Salmonella* and non-*choleraesuis* serogroup C *Salmonella*. The MDR rates of serogroup D and E were very low. Most MDR *Salmonella* strains were isolated from stool (210; 80.8%), blood (22; 8.5%), and urine (12; 4.6%). Other sites included the tip of the central venous catheter, synovial fluid, wounds, ascites, abscess, aortic aneurysm, and lymph nodes. More than 85% of MDR *Salmonella* isolates from children were serogroup B and no *S. choleraesuis* infection was found; whereas in adults, only 51% of MDR isolates were serogroup B and about one quarter were *S. choleraesuis* ($p<0.001$).

Multidrug resistance patterns

Four different MDR patterns were identified among the 260 isolates. Multidrug resistant patterns by year

Table 5. Culture site and serogroup distribution of multidrug resistant *Salmonella*

Culture site	Serogroup					Total
	B	C[a]	D	E	*S. choleraesuis*	
Stool	183	23	2	2	0	210[b]
Blood	10	5	1	0	6	22
Urine	9	0	1	1	2	12
CVC tip	1	0	0	0	0	1
Synovial fluid	1	0	0	0	0	1
Wound	2	0	0	0	1	3
Ascites	3	0	0	0	0	3
Abscess	2	0	1	0	1	4
Tissue	0	0	0	0	2	2
Lymph node	0	1	0	0	0	2
MDR rate (%)[c]	211/1229 (17.2)	29/226 (12.8)	5/222 (2.3)	3/51 (5.9)	12/56 (21.4)	260

Abbreviations: CVC = central venous catheter; MDR = multidrug resistant

[a]Excluding *S. choleraesuis*.

[b]2 isolates could not be serogrouped by the slide agglutination method.

[c]No. of MDR isolates/No. of total isolates in each serogroup during the study period.

Table 6. Multidrug resistant patterns of *Salmonella* isolates by year

MDR pattern	Year			Total
	1998 n = 121 (%)	1999 n = 106 (%)	2000[a] n = 33 (%)	n = 260 (%)
C-AM-SXT	118 (97.5)	97 (91.5)	24 (70.6)	239 (91.9)
C-AM-SXT-CRO	3 (2.5)	4 (3.8)	0 (0)	7 (3.0)
C-AM-SXT-CIP	0	4 (3.8)	7 (20.5)	11 (4.1)
C-AM-SXT-CRO-CIP	0	1 (0.9)	2 (5.9)	3 (1.2)

Abbreviations: MDR = multidrug resistant; C = chloramphenicol; AM = ampicillin; SXT = sulfamethoxazole-trimethoprim; CRO = ceftriaxone; CIP = ciprofloxacin

[a]Isolates were collected from January through June 2000.

distribution are shown in Table 6. Ninety-percent of them grouped in a major pattern—chloramphenicol-ampicillin-trimethoprim/sulfamethoxazole (C-AM-SXT), which was the predominant pattern throughout the study period. Eighteen (6.9%) isolates were resistant to 4 antibiotics. Only 3 (1.2%) isolates showed 5-drug resistance (C-AM-SXT- ceftriaxone [CRO]- ciprofloxacin [CIP]). Among the 18 isolates, the most common pattern was C-AM-SXT-CIP (11), followed by C-AM-SXT-CRO (7). Although the total number of MDR *Salmonella* isolates did not increase during the study period (121 in 1998, 106 in 1999, and 33 in January- June 2000), the rate of resistance to 4 or 5 antibiotics increased gradually from 2.5% in 1998, 8.5% in 1999, to 26.4% in January through June 2000.

Management and outcome

Ninety-seven percent (32/37) of adults and 61.1% (124/203) of pediatric patients received antimicrobial therapy (p=0.003). Eight (3.9%) children needed nasogastric tube or anal tube decompression for severe distension of the abdomen or toxic megacolon. Two adults received pig-tail drainage for intraabdominal abscess. Four (2%) children and 7 (18.9%) adults received surgical intervention for complications associated with *Salmonella* infections (p<0.001). None of these patients had mortality attributable to salmonellosis. Two previously healthy children had recurrent MDR *Salmonella* infections that were caused by different serogroups. One man with a history of diabetes mellitus and gastric ulcer after subtotal gastrectomy had 4 episodes of salmonellosis within 2 years.

Risk factors associated with extra-intestinal salmonellosis

Results in this study indicate that adult patients had a higher incidence of underlying diseases, extra-intestinal salmonellosis, and infection with *S. choleraesuis*. Univariate analysis showed underlying disease to be a significant risk factor for extra-intestinal infection (p=0.013), and infection with invasive serotype (*S. choleraesuis*) was a possible risk factor of developing extra-intestinal salmonellosis although the p value revealed borderline significance (p=0.062).

Discussion

Salmonella are important enteric pathogens and generally infect people of extreme ages. In this series, most patients (80%) were under 5 years old. Many aspects of the clinical manifestations of MDR *Salmonella* infections were different between the pediatric and adult groups. First, symptoms and signs such as gross bloody or mucoid stool, and fever were more common in the pediatric group, indicating that enterocolitis is a more common mode of salmonellosis in children. About 40 % of adult patients had no intestinal manifestations and were afebrile. Most patients with diarrhea had watery diarrhea (85.7%). Second, the incidence of bacteremia was lower in children (5.9%) than in adults (32.4%). The rate of extra-intestinal infections was also higher in adults. Third, the serogroup distributions were different between pediatric and adult groups. Most of the strains isolated from children were serogroup B (86.9%). Although serogroup B remained the most common strain isolated in adults (51%), *S. choleraesuis* accounted for 26.7% of the isolates in adults. Almost all *S. choleraesuis* isolates were from blood and vascular tissues and not from stool. Nearly 70% of adult patients had immunocompromised or debilitating disorders. This may explain why bacteremia or extra-intestinal infections occurred with greater frequency in adult patients. The reported frequency of bacteremia or extra-intestinal infections ranged from 2% to 45% [17], depending on the presence of underlying diseases, extremes of age, serotypes of the isolates, and geographic differences [18-23]. Data in this study are in accordance with these reports since we found that host factors and virulence of certain serotypes, such as *S. choleraesuis*, are the major factors facilitating the

development of bacteremia or extra-intestinal infections in adult patients, although the *p* value for the correlation of infections with *S. choleraesuis* was only of borderline significance, perhaps due to the small case number of adult patients.

Salmonella resistant to multiple antimicrobial agents is an emerging problem worldwide [7,24]. Infections with antimicrobial-resistant *Salmonella* are associated with extremes of age, exposure to antimicrobial agents, exposure to animals, prior hospitalization, underlying diseases, or specific serotypes [25-27]. In this study, prior medication history is traced in only 47% of patients; however, 55.6% of pediatric patients and 65.2% of adult patients had been exposed to one or more antibiotics in the past 6 months before infections occurred. The high rate of prior exposure to antimicrobial agents could have resulted in the development of MDR infections in these patients. A previous study [28] has shown that patients infected with antibiotic-resistant *Salmonella* had a higher mortality rate than those without. Reports from England and Wales [29], however, indicated that the incidence of bacteremia caused by MDR *S. typhimurium* DT 104 was not significantly higher than that by other phage types. In this study, there was no mortality due to infections with MDR *Salmonella*, suggesting that patients with MDR *Salmonella* infection were not at increased risk of unfavorable outcome.

Although the number of MDR *Salmonella* isolates decreased during the study period, the rate of resistance of *Salmonella* isolates to third-generation cephalosporins and ciprofloxacin gradually increased. The MDR rate of *S. choleraesuis* was higher than that of other serogroups. These findings could be the result of the increased use of fluoroquinolones and third-generation cephalosporins in the treatment of salmonellosis or other bacterial infections in Taiwan. Fortunately, *Salmonella* with concomitant resistance to these 2 antimicrobials remains uncommon [30]. Nevertheless, the development of increased resistance of *Salmonella* is expected if no further strategy is taken to avoid unnecessary and inappropriate antibiotic use.

In conclusion, the clinical features of children and adults infected with MDR *Salmonella* are different due to different serogroup distribution and patients' underlying diseases. The emergence of *Salmonella* infections resistant to third-generation cephalosporins and fluoroquinolones is an issue of concern and needs more attention. Salmonellosis is a zoonosis. The use of antimicrobial agents in humans and animals should be restricted to reduce the selection and spread of resistant *Salmonella*.

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