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Original Article

Extraintestinal focal infections in adults with *Salmonella enterica* serotype Choleraesuis bacteremia

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Background and Purpose: *Salmonella enterica* serotype Choleraesuis, which is associated with severe human infections and multidrug resistance, poses a serious problem in Taiwan. The aim of the study was to investigate the epidemiology and clinical features of *S.* Choleraesuis bacteremia.

Methods: Medical records and antimicrobial susceptibility of blood isolates were investigated for 43 adults (≥18 years old) with *S.* Choleraesuis bacteremia from 1999 to 2005.

Results: The proportion of *S.* Choleraesuis in non-typhoidal *Salmonella* bacteremia increased in the latter three years (2003-2005). The elderly with aged-related disorders, and younger patients receiving immunosuppressive therapy for their underlying diseases were two high-risk groups. Twenty cases (47%) had extraintestinal focal infections, including 10 cases of mycotic aneurysm, six of osteomyelitis, and 4 pleuropulmonary infections. Univariate analysis revealed that age ≥50 years was associated with occurrence of endovascular infection (p=0.008), while immunosuppressive therapy was negatively associated with endovascular infection (p=0.043). Significant resistance to first-line antimicrobial agents (i.e., ampicillin, trimethoprim-sulfamethoxazole or chloramphenicol) was noted. All strains were resistant to nalidixic acid, and 56% were resistant to ciprofloxacin. Few (<5%) isolates were resistant to ceftriaxone, and all were susceptible to cefepime, aztreonam, imipenem, meropenem and ertapenem. Multivariate analysis showed that shock (odds ratio [OR], 20.6; 95% confidence interval [CI], 1.8-239.4; p=0.016) and apyrexia (OR, 36.2; 95% CI, 3.7-358.2; p=0.002) were independent risk factors for mortality.

Conclusion: *S.* Choleraesuis bacteremia was usually complicated with extraintestinal focal infections in the elderly. With a high level of resistance among *S.* Choleraesuis, fluoroquinolones should be avoided for critically ill patients with suspected *Salmonella* bacteremia.

Key words: Bacteremia; Drug resistance, bacterial; Microbial sensitivity tests; Mortality, *Salmonella enterica*

Introduction

Non-typhoidal *Salmonella* (NTS) species are important foodborne pathogens, which can result in self-limited gastroenteritis, bacteremia, or subsequent metastatic focal infections. Of the more than 2000 NTS serotypes, *Salmonella enterica* serotype Choleraesuis is usually associated with bacteremia and invasive extraintestinal infections in humans. Approximately 5% of individuals with gastrointestinal illness caused by NTS will develop bacteremia [1]. On the contrary, *S.* Choleraesuis rarely resulted in gastrointestinal diseases, but was associated with bacteremia in over 70% of infected persons [2-4]. In Taiwan, *S.* Choleraesuis is the second most common NTS isolate found in humans, but is an infrequent serotype in western countries [2,3,5-8].

S. Choleraesuis bacteremia develops in patients with old age, and immunodeficiency. It is also identified as an important risk factor for endovascular infection among patients with NTS bacteremia [3,9]. Notably,

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antimicrobial resistance to broad-spectrum cephalosporins or fluoroquinolones in *S.* Choleraesuis is becoming a global concern [10]. In Taiwan, increasing fluoroquinolone resistance for this organism is reported [11], and concomitant ceftriaxone-resistant strains have become therapeutic challenges [10,12,13].

In recent years in our hospital, the proportion of *S.* Choleraesuis in NTS bacteremia among adult patients has increased, and *S.* Choleraesuis bacteremia often occurred with feared extraintestinal focal infections (EFIs). This study was undertaken to evaluate the secular trends of *S.* Choleraesuis bacteremia in adult patients and antimicrobial resistance of isolates in a medical center in southern Taiwan. Also, clinical features and risk factors of mortality for those patients were investigated.

Methods

The blood culture records at the clinical microbiology laboratory of National Cheng Kung University Hospital were reviewed to identify cases of *S.* Choleraesuis bacteremia between January 1999 and December 2005. Medical records of adult patients (aged 18 years or older) were reviewed and demographic data, underlying diseases, clinical manifestations, and laboratory data on admission were retrieved. For patients with recurrent *S.* Choleraesuis bacteremia, only the first episode was included.

Microbiology and antimicrobial susceptibility

All blood isolates were cultured and identified according to standard methods [14]. The serogroup of *Salmonella* isolates was determined by O antisera (Difco Laboratories, Detroit, MI, USA) first by the slide agglutination test. For serogroup C or D isolates, the presence of Vi antigen in *S.* Typhi or *S.* Paratyphi was screened by Vi antisera (BBL, Cockeysville, MD, USA). *S.* Choleraesuis was identified if the citrate test was negative in isolates of serogroup C1 [15].

Antimicrobial susceptibilities were determined by the disk-diffusion method or Etest strips (AB Biodisk, Solna, Sweden) for all *S.* Choleraesuis isolates. The interpretations of susceptibility data followed the criteria proposed by the National Committee for Clinical Laboratory Standards [16]. First-line antimicrobial agents were determined by the disk-diffusion method for susceptibility, including ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole. The antimicrobial agents tested by Etest strips included nalidixic acid, ciprofloxacin, ceftriaxone, cefepime, meropenem and ertapenem.

Definitions

Patients were considered to have EFIs following bacteremia if there was a clinical evidence of infectious focus or identical organisms isolated from a clinical specimen other than blood or feces. Patients were assumed to have diabetes mellitus if the fasting serum glucose level was >126 mg/dL. Renal insufficiency was defined as a serum creatinine >1.5 mg/dL. Liver cirrhosis was defined by abdominal ultrasonography and clinical follow-up findings. Immunosuppressive therapy was defined as the receipt of corticosteroid (at least 10 mg prednisolone per day or equivalent dosage for at least two weeks), chemotherapy for malignancy, or immunosuppressive agents for organ transplantation within one month prior to the admission.

Fever was defined as an axillary body temperature ≥38°C. Shock was defined as a systolic blood pressure ≤90 mm Hg or an unstable hemodynamic status requiring inotropic agents to maintain blood pressure. Empirical antibiotic therapy was considered to be appropriate if the etiological pathogen was susceptible in vitro to at least one drug administered within 72 h after the onset of bacteremia. An episode of bacteremia was considered to be "persistent" when blood cultures yielded the identical organism in patients with adequate antimicrobial therapy for at least 72 h.

Statistical analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 12.0; SPSS, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation and were compared with Student's *t* test. Categorical variables, expressed as numbers and percentages, were compared using chi-squared test or Fisher's exact test. Odds ratio (OR) for mortality with corresponding 95% confidence interval (CI) was calculated in unadjusted and multivariable-adjusted models. Multivariate analysis was performed with the stepwise logistic regression model on the variables with a p value ≤0.1 as the limit for entering or removing terms.

Results

During the 7-year period, there was a total of 47 episodes of *S.* Choleraesuis bacteremia in 43 patients. The incidence rate and proportion of *S.* Choleraesuis

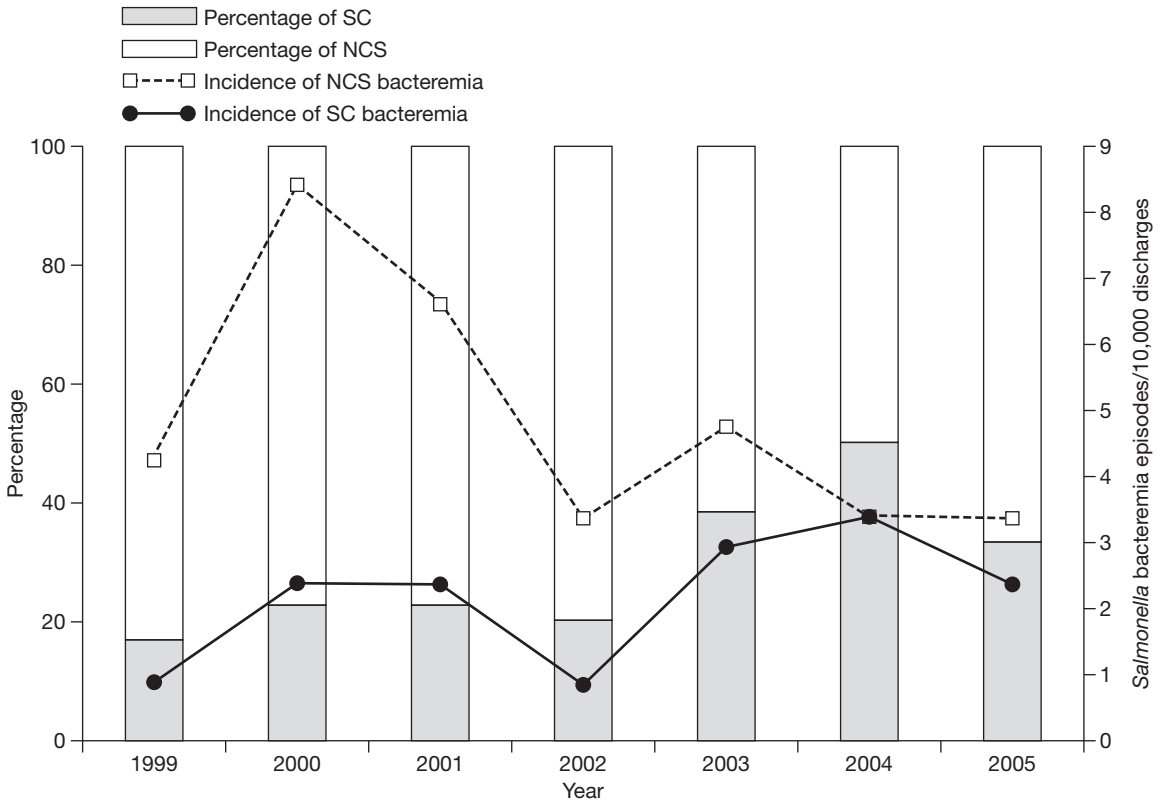

Fig. 1. Proportion and incidence of *S.* Choleraesuis (SC) bacteremia and non-Choleraesuis *Salmonella* (NCS) bacteremia at a medical center in southern Taiwan, from 1999 to 2005.

bacteremia increased during the study period (Fig. 1). The proportion of *S.* Choleraesuis among NTS blood isolates increased significantly from 22% in the first four years (1999-2002) to 41% in the latter three years (2003-2005) [p=0.018].

Clinical characteristics and laboratory data

The clinical characteristics of 43 patients with *S.* Choleraesuis bacteremia are summarized in Table 1. Their mean (± standard deviation) age was 56.5 (± 20.8) years, with a range of 19 to 98 years, and males predominated (28 cases, 65%). Thirty nine patients (91%) had at least one systemic medical disease, mainly diabetes mellitus (35%), renal insufficiency (30%), hypertension (28%), or receipt of immunosuppressive therapy (26%). Among seven patients with connective tissue disorders, six had systemic lupus erythematosus, and one had dermatomyositis. Of 23 patients tested for human immunodeficiency virus (HIV) antibodies, three were infected by HIV-1. Their CD4 counts at presentation were ≤40 cells/mm^3, and therefore all three patients were regarded as cases of acquired immunodeficiency syndrome (AIDS).

In the present study, most patients (34, 79.1%) had been empirically treated by appropriate antimicrobial agents, i.e., third-generation cephalosporins (21 patients; cefotaxime or ceftriaxone), fourth-generation cephalosporin (6 patients; cefepime) and fluoroquinolones (5 patients; ciprofloxacin or levofloxacin). However, the appropriateness of empirical antimicrobial use did not affect the clinical outcome nor the development of EFIs. Of 13 fatal patients, 84.6% (11 patients) received appropriate empirical therapy, as did 23 (76.6%) of the 30 survivors (p=0.69) [Table 2]. Moreover, twenty patients (47%) with EFIs all received appropriate empirical antibiotics, in contrast to eight (34.9%) of 23 patients without obvious EFIs (p=0.004). Among six patients with persistent bacteremia, four of them had EFIs (3 with vascular infection; 1 with cervical spine osteomyelitis); one had HIV infection; and one had underlying diseases of diabetes mellitus and alcoholic liver cirrhosis. Mycotic aneurysm was the most common EFI, followed by osteomyelitis, and pleuropulmonary infections. A total of ten cases (23%) developed mycotic aneurysm (4 with thoracic aorta involvement and 6 with abdominal aorta involvement), and six cases were fatal. Six of them underwent surgical vascular interventions

Table 1. Clinical characteristics of 43 adults with *Salmonella enterica* serotype Choleraesuis bacteremia

Characteristics	No. of patients (%)
Age (years) [mean (standard deviation; range)]	56.5 (20.8; 19-98)
Male gender	28 (65.1)
Underlying diseases	
Diabetes mellitus	15 (34.9)
Renal insufficiency	13 (30.2)
Hypertension	12 (27.9)
Immunosuppressive therapy	11 (25.6)
Malignancy	7 (16.3)
Connective tissue disorders	7 (16.3)
HIV infection[a]	3 (13.0)
Coronary heart disease	5 (11.6)
Chronic lung disease	5 (11.6)
Liver cirrhosis	4 (9.3)
Congestive heart failure	3 (7.0)
Extraintestinal infections	
Absence (only bacteremia)	23 (53.5)
Presence	20 (46.5)
Mycotic aneurysm	10 (23.2)
Osteomyelitis	6 (14.0)
Pleuropulmonary infections	4 (9.3)

Abbreviation: HIV = human immunodeficiency virus
[a]Only 23 patients were tested for HIV-1 antibodies.

and three died. Of four cases not treated with vascular surgery, only one patient survived with antimicrobial therapy for 12 months, and was still alive three months after discontinuing treatment.

Of note, six cases of acute osteomyelitis were spinal infections, and their mean age was 69 years. The most common infection site was lumbar spine, which was involved in four patients. One patient had cervical spine infection, and evolved into severe sequelae of respiratory failure and quadriplegia. Five patients were complicated with paraspinal abscess, and three patients had epidural abscess. All patients had received surgical interventions, and one died 45 days after surgical and medical therapy.

There were four patients diagnosed as having *Salmonella* pneumonia, on the basis of concurrent *S.* Choleraesuis bacteremia and pulmonary infiltrations in chest films. Two patients had positive sputum culture result. One was complicated with pleural empyema, and received chest tube drainage. All four patients survived.

Among 23 patients with primary *S.* Choleraesuis bacteremia, twenty (90.9%) denied symptoms of gastroenteritis before admission. About one-half (12, 52.2%) of 23 patients received immunosuppressive therapy for their underlying diseases: connective tissue diseases (6 patients), malignancy (3 patients), renal transplantation (2 patients), psoriasis (1 patient), chronic obstructive pulmonary disease (1 patient) and adrenal insufficiency (1 patient). All three HIV-infected patients had primary bacteremia, and recovered uneventfully with antimicrobial treatment.

Risk factors for mortality

To access the risk factors of mortality in patients with *S.* Choleraesuis bacteremia, several host factors were analyzed (Table 2). Univariate analysis showed that risk factors associated with unfavorable outcomes included age ≥50 years, diabetes mellitus, vascular infection, shock, persistent bacteremia, and absence of fever. However, logistic regression analysis revealed that only shock (OR, 20.6; 95% CI, 1.8-239.4; p=0.016) and apyrexia at initial presentation (OR, 36.2; 95% CI, 3.7-358.2; p=0.002) were independent risk factors for mortality.

Risk factors for endovascular infection

The potential factors for endovascular infection among patients with *S.* Choleraesuis bacteremia are listed in Table 3. Univariate analysis showed that age ≥50 years increased the risk of endovascular infections, and in contrast, the receipt of immunosuppressive therapy was negatively associated with endovascular infections.

Microbiology and susceptibility data

Of 43 *S.* Choleraesuis bacteremic isolates, the susceptibility rates to trimethoprim-sulfamethoxazole, ampicillin, and chloramphenicol were 21%, 14%, and 9%, respectively. All strains were resistant to nalidixic acid (minimal inhibitory concentration at which 90% of isolates were inhibited [MIC_{90}] ≥256 μg/mL) [Table 4]. More than one-half (56%) of these isolates were non-susceptible to ciprofloxacin. There were few isolates resistant to ceftriaxone, accounting for <5% of all isolates tested. All isolates were susceptible to cefepime, meropenem and ertapenem. The in vitro activity of cefepime against *S.* Choleraesuis (MIC_{90}, 0.38 μg /mL) was superior to that of ceftriaxone (MIC_{90}, 2 μg/mL). Among six drugs tested for MIC values, meropenem and ertapenem were the most active drugs in vitro, and their MICs were comparable.

Discussion

In Taiwan, *S.* Choleraesuis is the second most common serotype isolated from humans [3,5], but it is an infrequent

Table 2. Risk factors of mortality for patients with *Salmonella enterica* serotype Choleraesuis bacteremia

Variables	No. of patients (%)		Odds ratio	95% confidence interval	*p*
	Fatal group (n = 13)	Non-fatal group (n = 30)			
Age ≥50 years	10 (76.9)	18 (60.0)	10.5	1.21-91.27	0.033
Male gender	7 (53.8)	21 (70.0)	1.25	0.32-4.83	0.746
Extraintestinal focal infections	7 (53.8)	13 (43.3)	1.53	0.41-5.64	0.527
Vascular infections	6 (46.2)	4 (13.3)	5.57	1.22-25.36	0.026
Comorbidity					
Diabetes mellitus	6 (46.2)	9 (30.0)	5.26	1.29-21.35	0.020
Hypertension	5 (38.5)	7 (23.3)	2.05	0.51-8.43	0.314
Congestive heart failure	2 (15.4)	1 (3.3)	5.27	0.43-64.16	0.192
Renal insufficiency	8 (61.5)	5 (16.7)	1.72	0.43-6.83	0.442
Liver cirrhosis	2 (15.4)	2 (6.7)	2.55	0.32-20.38	0.379
Immunosuppressive therapy	2 (15.4)	9 (30.0)	0.42	0.08-2.32	0.322
Malignancy	3 (23.1)	4 (13.3)	0.513	0.10-2.71	0.432
Clinical presentations					
Absence of fever	7 (53.8)	3 (10.0)	10.11	2.01-50.98	0.005
Altered consciousness	4 (30.8)	3 (10.0)	4.00	0.75-21.38	0.105
Persistent bacteremia	5 (38.5)	1 (3.3)	18.13	1.84-178.14	0.013
Presence of shock	10 (76.9)	4 (13.3)	21.67	4.10-114.54	<0.0001
Appropriateness of empirical antibiotic therapy	11 (84.6)	23 (76.7)	0.697	0.121-4.028	0.687

serotype in western countries [1,7,17]. The reason for the difference is unclear. In our study, the ratio of *S.* Choleraesuis to total NTS isolated from blood increased gradually in recent years. During the same period, the annual isolate number of *S.* Choleraesuis also increased in a large-scale survey in northern Taiwan [18].

The increasing rate of resistance to multiple antimicrobial agents, including third-generation cephalosporins and fluoroquinolones has also been noted in this serotype since 2000 [11,13]. Because most *S.* Choleraesuis isolates in humans are derived from swine [11,19], increasing infection and resistance of this serotype in humans may be ascribed to antimicrobial selective pressure in livestock and spreading of clones [19,20]. Further surveillance of antibiotic use in food animals is an important public health issue.

Most patients with NTS bacteremia have extremes of age and severe immunosuppression, such as malignancies, HIV infection, or connective tissue disorders [21-23]. In our study, two high risk groups, the elderly with aged-related disorders, and those who received immunosuppressive therapy for their underlying diseases were affected. Of note, those who had immunosuppressive therapy or AIDS were much younger than those who did not (42.1 vs 62.5 years, p=0.006).

Table 3. Risk factors for endovascular infections in 43 patients with *Salmonella enterica* serotype Choleraesuis bacteremia

Variables	No. of patients (%)		*p*
	Endovascular infection (n = 10)	Non-endovascular infection (n = 33)	
Age ≥50 years	10 (100)	18 (54.5)	0.008
Male gender	7 (70.0)	21 (63.6)	1.000
Comorbidity			
Diabetes mellitus	6 (60.0)	9 (27.3)	0.073
Hypertension	4 (40.0)	8 (24.2)	0.427
Congestive heart failure	1 (10.0)	2 (6.1)	0.558
Renal insufficiency	2 (20.0)	11 (33.3)	0.696
Liver cirrhosis	0 (0)	4 (12.1)	0.558
Immunosuppressive therapy	0 (0)	11 (33.3)	0.043
Malignancy	0 (0)	7 (21.2)	0.172
Ciprofloxacin-resistant strain	7 (70.0)	17 (51.5)	0.470
Appropriate antibiotic treatment	10 (100)	24 (72.7)	0.089

Table 4. Minimal inhibitory concentrations (MICs) of six antimicrobial agents in 43 clinical isolates of *Salmonella enterica* serotype Choleraesuis, 1999-2005

Antibiotics	MIC (μg/mL)			Susceptibility (%)
	50%	90%	Range	
Nalidixic acid	≥256	≥256	≥256	0
Ciprofloxacin	12	≥32	0.125-≥32	44.2
Ceftriaxone	0.064	2	0.047-12	95.3
Cefepime	0.125	0.38	0.064-0.38	100
Meropenem	0.023	0.032	0.008-0.047	100
Ertapenem	0.008	0.032	0.008-0.047	100

The most common EFI in our survey was mycotic aneurysm (10/43, 23%). Most affected patients were ≥50 years old, and had a high mortality rate (60%). Moreover, 36% of adults aged ≥50 years with *S.* Choleraesuis bacteremia had endovascular infections. The risk factors for vascular infection in adult patients with NTS bacteremia described previously included age ≥50 years, underlying atherosclerosis, and infections caused by *S.* Choleraesuis [9,24,25]. Several publications from Taiwan revealed that the incidence of mycotic aneurysm in aged patients with NTS bacteremia is 35-40.6% [3,26]. In contrast, the incidence of endovascular infections in the aged with *Salmonella* bacteremia in western countries is about 10% [24,25,27]. Such a difference could be ascribed to the higher prevalence of *S.* Choleraesuis infections in Taiwan [3,5]. Our study revealed that immunosuppressive therapy was negatively associated with endovascular infections. In a study with 28 patients with endovascular infections among 121 NTS bacteremic adults from northern Taiwan [9], logistic regression analysis showed that solid organ malignancy and immunodeficiency were negative predictors for endovascular infections. The reason for this phenomenon is still unclear. However, early diagnosis of mycotic aneurysm in high-risk populations with *S.* Choleraesuis bacteremia is crucial, since only early surgical intervention in conjunction with antibiotic therapy can improve clinical outcome for these patients [28].

Osteomyelitis was the second-common EFI of *S.* Choleraesuis bacteremia in our hospital. None of our affected patients had underlying hemoglobinopathy, which has been described as a risk factor for *Salmonella* osteomyelitis in young people, among whom the frequently affected sites were ribs, spine and long bones [29,30]. To the contrary, our study highlighted another clinical pattern of *Salmonella* osteomyelitis, spinal osteomyelitis in the elderly without hemoglobinopathy. However, due to the limited cases in our series, more clinical observations are required.

The overall mortality rate of patients with *S.* Choleraesuis bacteremia in the present study was 30%, within the reported range of mortality rates of 12.2-40.6% in adults with NTS bacteremia in several previous studies [7,21,22,27]. Unfavorable outcomes for adults with *Salmonella* bacteremia include septic shock, coma, immunosuppression, and neoplasm [7]. In the present study, shock and absence of fever, which were suggestive of the presence of critical illness and impaired host immunity, respectively, were significant prognostic factors for mortality. Thus, patients with critical presentations deserve aggressive medical treatment and detailed examinations to rule out severe EFIs.

The majority of *S.* Choleraesuis isolates in our hospital were resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, the so-called first-line antimicrobial agents for salmonellosis. Moreover, resistance rates to nalidixic acid and ciprofloxacin were 100% and 55.8%, respectively. In Taiwan, ciprofloxacin resistance among clinical isolates of *S.* Choleraesuis has been observed since 2000, usually with resistance rates >50% [15,19]. Quinolone resistance was demonstrated to be associated with genetic mutations in the 120-bp quinolone resistance-determining region of *gyrA* and *parC* [19,31-33]. Moreover, such antimicrobial-resistant strains had been noted to spread from pigs to humans [31], and there was probably wide spread of a resistant clone in Taiwan [20].

Though resistance to ceftriaxone is rare in NTS isolates, it has been reported in Taiwan [30,33] as well as other areas of the world [34,35]. Moreover, concurrent ceftriaxone and ciprofloxacin resistance in this serotype has emerged recently, resulting in substantial morbidity and mortality [10,12,36]. In view of the increasing antimicrobial resistance, the antimicrobial choice for severe *S.* Choleraesuis infections should avoid fluoroquinolones, unless this a class of antimicrobial agents can be proven to be active in vitro.

In conclusion, *S.* Choleraesuis bacteremia should be considered as severe and potentially life-threatening in aged patients. Early identification of extraintestinal complications in patients with specific risk factors will prompt appropriate surgical and medical treatment. Continuing surveillance of antimicrobial resistance in *Salmonella* pathogens from human and food animals is critical for public health.

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