

Streptococcus suis infection

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A recent outbreak of *Streptococcus suis* infection associated with the slaughter, preparation or consumption of pigs in Sichuan, China has led to concerns that similar outbreaks could occur in other Asian countries. Although the pig farming industry is flourishing in Taiwan, reports of *S. suis* infection remain rare. We report 2 cases of *S. suis* meningitis successfully treated with ceftriaxone and penicillin. Previous reports of *S. suis* infection from the English literature are reviewed and the clinical data of cases reported in Asian and European countries are summarized. In Europe, there was good correlation between clinical disease and porcine contact, while few cases in Asia reported this association. Meningitis remained the most common presentation of infection in both areas (84.6% and 75.2%, respectively), followed by sepsis (15.4% and 18.6%, respectively), which had a higher mortality rate, particularly for splenectomized patients. Other clinical presentations included enteritis, arthritis, endocarditis, pneumonia, spondylodiscitis, endophthalmitis, uveitis and peritonitis. Deafness was a distinct sequelae (50.5% in Europe and 51.9% in Asia) after recovery from *S. suis* infection, especially in patients with meningitis. Not all commercial identification systems for streptococci could offer adequate speciation for *S. suis*. When viridans group streptococci are isolated from patients with meningitis and sepsis, prompt and correct identification of isolates to the species level should be performed, especially in areas with a high prevalence of *S. suis* diseases.

Key words: Disease outbreaks, review, risk factors, *Streptococcus suis*

Since the first human case of *Streptococcus suis* infection was reported in Denmark in 1968 [1], diseases caused by this organism have been considered zoonotic and to affect those with occupational exposure to pigs or unprocessed pork [2,3]. Reported clinical presentations in humans include acute bacterial meningitis, sepsis, arthritis, endocarditis and endophthalmitis [2,4]. Permanent hearing loss or vestibular dysfunction are commonly noted sequelae [2,4,5]. From July 2005 to August 2005, an outbreak of *S. suis* infection occurred in Sichuan, China, involving more than 200 cases with 38 deaths [6]. The clinical course of patients in this recent outbreak was more fulminant than in previous reports. Although the pig farming industry is flourishing in Taiwan, *S. suis* infection has rarely been reported [7]. Here, we describe 2 cases of *S. suis* meningitis treated at National Taiwan University Hospital, and also review the English language literature on the microbiology of the pathogen, epidemiology and clinical features of

diseases in humans and swine, and antimicrobial treatment for *S. suis* infection.

Case Report

Patient 1

A 38-year-old previously healthy woman suffered from fever with chills and headache for 1 week. Examination at a local hospital revealed hearing impairment and acute otitis media. She then visited our emergency department for the treatment of headache and persistent fever. At admission, her body temperature was 36.2°C, pulse rate 75 beats/min, and blood pressure 99/56 mm Hg. Physical examination revealed neck stiffness and borderline Kernig's sign. Lumbar puncture 5 h after admission revealed clear cerebrospinal fluid (CSF), with opening pressure of 120 mm H₂O. CSF analysis showed neutrophilic pleocytosis and low glucose level. Ceftriaxone 2.0 g every 12 h was given initially and then shifted to penicillin G 3 MU every 3 h after blood and CSF culture yielded *S. suis*. Audiometry 14 days after admission revealed bilateral moderate to severe sensorineural hearing loss. After completion of a 14-day course of antibiotic therapy, she was discharged

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under a stable condition. One month later, she was re-admitted due to frequent right upper extremity twitching and focal seizure. Follow-up lumbar puncture was sterile without evidence of infection. Valproic acid was used for epilepsy control and no further attack occurred during the following 4 years. She is a bank clerk and denied contact with pigs.

Patient 2

A 52-year-old previously healthy woman had an episode of fever and nausea 1 week prior to admission. She was admitted for recurrence of headache, fever, chills and vomiting. At admission, temperature was 36.2°C, pulse rate 107 beats/min, and blood pressure 164/101 mm Hg. Physical examination revealed neck stiffness and photophobia. Ampicillin (2 g every 4 h) and ceftriaxone (2 g every 12 h) were given intravenously under the impression of bacterial meningitis. Lumbar puncture performed 2 h later revealed elevated opening pressure of 350 mm H₂O. CSF analysis revealed neutrophil-predominant pleocytosis with elevated CSF protein level and low glucose level. Two sets of blood culture on admission yielded *S. suis*, whereas the CSF culture was sterile. Ceftriaxone monotherapy was then given, due to the patient's allergy to penicillin which presented as skin itching. Her symptoms gradually recovered without sequelae and she was discharged after the completion of 14 days of antibiotics treatment. The patient was a poultry seller at local

market and a pig farm was located in the vicinity of her home.

Detailed clinical data for these 2 cases and the only previously reported case of *S. suis* infection in Taiwan are shown in Table 1.

Laboratory Identification of *S. suis*

The isolates from both patients grew well in culture showing gray-whitish colonies of α -hemolysis on Trypticase soy agar supplemented with 5% sheep blood (BBL Microbiology Systems, Cockeysville, MD, USA) in 5% CO₂ and ambient air at 35°C. The isolates were catalase-negative and Gram-positive cocci. The phenotypic reaction profiles obtained with the API Rapid ID 20 Strep system (bioMerieux, Marcy l'Etoile, France) [biotype profile, 0641473; identity, 99.8%] were in accordance with the identification of *S. suis*. The phenotypic reaction profiles obtained with the Vitek GPI Card (bioMerieux Vitek, Inc., Hazelwood, MO, USA) identified *S. anginosus* (biotype profile, 5166333400; identity, 95%) and with the Phoenix System PID (Beckon Dickinson, Sparks, MD, USA) [biotype profile, 420080163621; confidence value, 97%] identified *S. vestibularis*.

Species identification was further confirmed by sequence analysis of the 16S rRNA gene. Polymerase chain reaction amplification of the nearly complete 16S rRNA gene (1475 bp) with 2 primers (primers

Table 1. Clinical characteristics of 3 patients with *Streptococcus suis* infection in Taiwan

Characteristic	Previously reported case [7]	Patient 1	Patient 2
Age	61	38	52
Gender	Male	Female	Female
Time of onset	April 1994	March 2000	September 2002
Place of onset	Southern Taiwan	Northern Taiwan	Northern Taiwan
Occupation	Swine farmer	Bank clerk	Butcher (poultry)
Trauma history	No	No	No
Underlying disease	No	No	No
Clinical presentation	Diarrhea; abdominal pain; consciousness change	Fever and chills followed by hearing impairment	Vomiting, fever
Time of onset prior to admission	2 days	7 days	7 days
Bacteremia	-	+	+
Meningitis	+	+	+
CSF analysis			
WBC count (/mm ³)	160	51	4374
Glucose (mg/dL)	14	<30	<30
CSF protein (g/dL)	84	NA	490.2
CSF Gram stain	Positive	Negative	Not done
Sequelae	Profound bilateral sensory-neural hearing loss	Profound bilateral sensory-neural hearing loss; epilepsy	None

Abbreviations: WBC = white blood cell; CSF = cerebrospinal fluid

8FPL and 1492) was performed as described previously [8]. The amplification products were purified and sequenced. The BLAST (Basic Local Alignment Search Tool) program was used to compare the sequence of our isolates with those in the GenBank and Ribosomal Database Project databases. Analysis of the 16S rRNA gene of both isolates showed a high degree of sequence similarity with both *S. suis* isolates (GenBank accession number AF009476; 99%).

Literature Review and Discussion

Microbiology

S. suis is a Gram-positive, facultatively anaerobic coccus that has been implicated as the cause of a wide range of clinical diseases in swine and can be found in other animals, including wild boars, horses, dogs, cats and birds [9-12]. The pig can be a healthy carrier or afflicted. In pigs, the natural habitat of *S. suis* is the upper respiratory tract, particularly the tonsils and nasal cavities, and the genital and alimentary tract. The tonsil carriage rate in pigs aged 4-6 months was 32-50% [13]. Among the capsular serotypes, serotype 2 is the most pathogenic to pigs. Serotype 2 was isolated in up to 50.6% of all *S. suis* isolates from healthy swine tonsil [13,14].

Diseases in swine

S. suis can affect pigs at different ages, but related disease manifestations are principally noted between 6 and 10 weeks of life. In Denmark, a necropsy study of 21 pigs with *S. suis* infection revealed diffuse exudative meningitis (81%), exudative otitis interna (63%), generalized lung edema (43%), bronchopneumonia (33%), arthritis (24%), exudative pericarditis (10%), and endocarditis (5%) [15]. Septicemic forms of infection with sudden death in younger piglets have been also described [16]. In pigs, transmission is likely caused via close contact or exposure to the pathogen in aerosol form. The latter mode of transmission has been proven experimentally [17].

The pathogenic mechanism of *S. suis* remains unclear. Several virulence factors have been identified, but their roles in pathogenesis and disease have not been well elucidated [18]. *S. suis* vaccines for pigs have not yet been licensed in western Europe. Inactivated autogenous vaccines are used in the field. They are prepared from the virulent strain isolated on the farm. Vaccine safety and efficacy data are lacking [19]. Because of the non-availability of suitable

immunoprophylaxis, control of *S. suis* infection has depended mainly on the use of antimicrobials [20]. However, in the United States, attempts to eradicate tonsillar piglet carriers by administration of short courses of intramuscular penicillin, intramuscular ampicillin, oral ampicillin, intranasal ampicillin or intramuscular ceftiofur failed to eliminate the tonsillar carrier state of *S. suis* [21]. Optimization of management and environment of pigs coupled with strategic medication in clinically ill animals should be used for control and prevention of mortality from *S. suis*.

Human diseases

The first human cases of *S. suis* infection were reported in 1968 in Denmark [1]. Since then, increasing numbers of cases have been reported worldwide in countries including the Netherlands [2,11,22-28], Belgium [29-31], Denmark [1,32-34], the UK [35-48], France [3,12,49-52], Germany [9,12,16,53-55], Sweden [56], Croatia [57], Spain [14], Italy [58], Greece [59], Canada [60], New Zealand [61], Hong Kong [4,62-67], Taiwan [7], China [6,68], Thailand [69-75], Singapore [5,76] and Japan [77,78]. The association between human infection and contact with pigs has been noted since the discovery of the disease [33]. *S. suis* infection has been recognized as an occupational disease since April 1987 in the United Kingdom. In the Netherlands, the estimated annual risk of developing *S. suis* meningitis among abattoir workers and pig breeders of approximately 3.0/100,000 was 1500 times higher than that among persons not working in the pork industry. Butchers had an annual rate of 1.2/100,000 [2]. In Germany, the nasopharyngeal carriage rate of *S. suis* in the high-risk group; e.g. butchers, abattoir workers and meat processing employees, was 5.3%, while none of those without contact with pigs or pork had a positive finding [53]. A study in New Zealand in late 1980 revealed 9% of dairy farmers, 10% of meat inspectors and 21% of pig farmers were seropositive to *S. suis* type 2, indicating the presence of some human subclinical infections [79].

The clinical presentation and outcome of cases from European and Asian countries are compared in Table 2. In patients with meningitis, early hearing impairment and vestibular dysfunction were the characteristic features. Permanent hearing loss may occur, especially high pitch tone. Cochlear sepsis rather than the eighth cranial nerve involvement has been suggested to be the cause [15,41,80]. In a study from Hong Kong, *S. suis* was identified as the

Table 2. Summary of clinical characteristics of patients with *Streptococcus suis* infection reported in the English literature, 1968-2005

Characteristic	Cases from European countries ^a (n = 91)	Cases from Asian countries ^b (n = 129)
	No. (%)	No. (%)
Age range	22 years-76 years	1 month ^e -84 years
Male/female	80/11	94/35
Exposure history		
Porcine exposure	81 (89.0)	51 (39.5)
Skin injury	32 (35.2)	8 (6.2)
Type of infection		
Meningitis	77 (84.6)	97 (75.2)
Bacteremia or septic shock	14 (15.4)	24 (18.6)
Enteritis (diarrhea)	10 (11.0)	22 (17.1)
Arthritis ^c	9 (9.9)	14 (10.9)
Pneumonia	4 (4.4)	2 (1.6)
Endocarditis	2 (2.2)	10 (7.8)
Endophthalmitis ^d	2 (2.2)	1 (0.8)
Peritonitis	0 (0.0)	1 (0.8)
Complication		
Deafness	46 (50.5)	67 (51.9)
Death	12 (13.2)	26 (20.2)

^aData are adapted from references [4,9,11,14,22,28,36-38,43,49-53,57-59].

^bData are adapted from references [4,5,63,69-76].

^cIncludes 3 patients with spondylodiscitis [28,59].

^dIncludes 1 patient with both uveitis and endophthalmitis [30].

^eOne patient with meningitis was 1 month old and the ages of the other patients ranged from 19 years to 84 years.

third leading cause of community-acquired meningitis, causing 9% of all cases [62]. Other clinical presentations included sepsis, endocarditis, arthritis, spondylodiscitis, endophthalmitis and uveitis. *S. suis* among adults usually occurs through occupational exposure via a cutaneous lesion, e.g., cuts or abrasions while handling infected pig carcasses. The oral route was suggested as the portal of entry in Asia in cases where there was no obvious contact history with pigs [4]. This is probably due to the inability to adequately clarify patient history regarding contact with raw pork prior to disease onset, since pork consumption is very common in Asia. Patients with asplenia, diabetes mellitus, alcoholism and malignancy were at greater risk of infection [2,4,36,50,57,71,72]. Patients with structural heart disease (rheumatic heart disease, valvular heart disease or ventricular septal defect) were more likely to have infective endocarditis [50,70,71]. Alcoholism was noted as an underlying condition in several reports from Asia [6,69,71,72]. All 5 previously reported cases in splenectomized patients in the literature were fatal [2,36,38,50,57]. Serotype other than type 2 was noted in splenectomized patients [36,57]. In 1 case of reinfection 15 years after the first episode, occupational exposure of the patient was documented [50]. Hence, asplenic

individuals should take additional precautions when dealing with unprocessed pork and should avoid working in the pig farming or slaughtering industry.

S. suis infection in humans has generally occurred sporadically without obvious seasonal change. In Hong Kong and China, however, a seasonal distribution of cases was evident with several outbreaks occurring in the summer months [4,68]. This is also true for the recent outbreak in Sichuan province [6]. A parallel investigation by animal health authorities into illness and deaths in pigs occurring in the same region of China revealed evidence of *S. suis* infection [6]. Similar cases in humans were also noted in Jiangsu from late July to early August in 1998 and all of these patients had a contact history with sick pigs [68]. The clinical presentations of patients in Sichuan and Jiangsu included high fever, petechiae and ecchymosis, diarrhea and myalgia [6,68]. A case series of patients from northern Thailand reported a similar clinical presentation with fatal outcome in all cases [72]. As shown in Fig. 1, patients with sepsis had a higher mortality rate. Unlike the high mortality in these series, the mortality rate of *S. suis* meningitis in previous reports was around 7-12% or even lower in the recent 10 years (Fig. 1) [2,4]. The mortality rate of *S. suis*

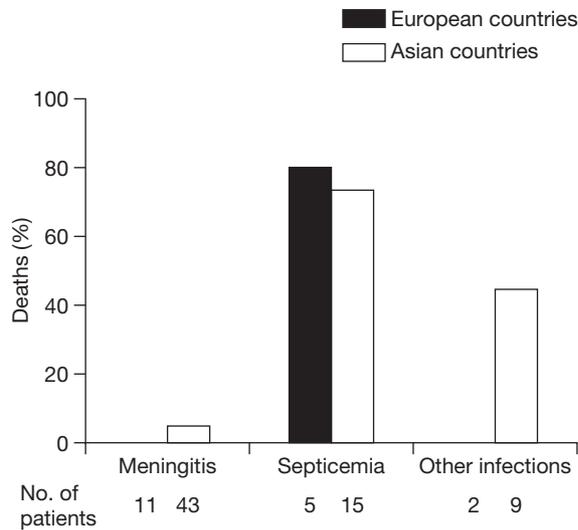


Fig. 1. Summary of mortality in patients with *Streptococcus suis* infection based on the type of infection as reported in the English literature from 1995 to 2005 from European countries [9,11,14,22,28,36-38,49-53,57-59] and Asian countries [5,62,63,69-76], including the 2 patients reported in this study. One case of infective endocarditis was reported in France [51], while 7 patients with infective endocarditis were reported from Hong Kong and Thailand [63,71,72]. Of the 5 fatal cases in “other infections” in Asia, 3 patients died of infective endocarditis, 1 died of fatal pneumonia, and 1 died of fatal peritonitis [71-73].

meningitis was lower compared to meningitis caused by other microorganisms in the same age group [2,4]. This may be due to less comorbidity in infected patients. Our review of the literature revealed the overall case fatality rate from *S. suis* infection was 13% in Europe and 20% in Asia (Table 2). Because of the high mortality rate in the recent outbreak in Sichuan, further survey is needed to determine if there is a new virulent factor or whether these deaths were caused by toxic shock syndrome.

Antibiotic treatment in human diseases

Penicillin-resistant strains have been isolated from 6-28% of nursery swine [81]. However, resistance to penicillin in human strains has rarely been noted [46,73]. Resistance to ofloxacin has been reported in isolates from humans [51]. A study in swine isolates demonstrated that resistance to macrolides, lincosamides and streptogramin B was widespread in *S. suis*, and was mediated by ribosome methylation and encoded by the *ermB* gene [82]. Clinical relapse of *S. suis* infection has been reported in Hong Kong and Thailand and required prolonged treatment [4,69].

***S. suis* in Taiwan**

There have been few reports of *S. suis* infection in Taiwan despite a thriving pig farming industry which relies on production methods which are similar to other regions of Asia (Table 1). An annual microbiology survey involving 1650 swine carcasses in 2003 did not find any isolates of *S. suis* [83]. However, local data on the *S. suis* carrier rate and seroprevalence of pigs are lacking. It is not known whether the low prevalence rate of *S. suis* infection in Taiwan is due to a low carrier rate — as in Japan where only 2 cases in humans have been reported [77,78,84], or a local tendency not to perform further investigation when viridans group streptococci are isolated.

All 3 reported cases of *S. suis* infection in Taiwan have presented as meningitis and 2 of them developed hearing impairment as sequelae. All 3 cases occurred sporadically without seasonal or regional connection. The previously reported case in 1994 occurred in a swine farmer and the third case is a poultry butcher who lived near a pig farm. No underlying disease was noted, although the previously reported case died of B-cell lymphoma 19 months later. All 3 reported cases showed good response to antibiotics without relapse after discontinuation. In the 2 cases of this report, both isolated strains were resistant to tetracycline, clindamycin and erythromycin and were sensitive to ceftriaxone and penicillin. Penicillin thus remains the drug of choice for the treatment of patients with meningitis or sepsis due to *S. suis* in Taiwan.

Conclusion

S. suis infection has been considered a zoonotic occupational disease since its discovery. However, it also occurs sporadically in many cases in Asia. Meningitis and septicemia remain the most common presentations in Europe and Asia. In northern Thailand and China, cases with septicemia usually occurred in patients with a history of contact with pigs. The high mortality rate of this infection in splenectomized patients should raise awareness of the need for extra precautions in handling pork and to avoid work in pork production or processing industries. Outbreaks of *S. suis* infection in pigs paralleled those in humans in China, thus epidemiologic monitoring systems need to be in place to alert pig farmers, the slaughtering industry and the general population when an outbreak in pigs is detected. Monitoring of *S. suis* infection in pigs needs

to be established in Taiwan as part of this process. In the clinical setting, when viridans group streptococci are isolated from patients with meningitis, especially in those presenting with hearing impairment, prompt and appropriate identification of the organism to species level is mandatory.

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