Streptococcus suis: An Emerging Human Pathogen

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Streptococcus suis infection is acquired through exposure to contaminated pigs or pig meat. Over the past few years, the number of reported S. suis infections in humans has increased significantly, with most cases originating in Southeast Asia, where there is a high density of pigs. Increased awareness, improved diagnostics, and the occurrence of outbreaks have contributed to this increase. Meningitis and sepsis are the most common clinical manifestations of S. suis infection; hearing loss is a frequent complication. In this article, we provide an overview of the emergence and clinical manifestations of S. suis infection.

Streptococcus suis is a pathogen in pigs that can cause severe systemic infection in humans [1]. S. suis was first reported by veterinarians in 1954, after outbreaks of meningitis, septicaemia, and purulent arthritis occurred among piglets [2]. Fourteen years later, the first human S. suis cases were diagnosed in Denmark, and subsequently, other cases were reported in other northern European countries and Hong Kong [3–5].

The number of human S. suis cases reported in the literature has increased significantly over the past few years. In a review article published in 2007, 409 human S. suis cases were reported. At the time of writing of this article, this figure has increased to >700 cases, with most cases originating in Southeast Asia (figure 1) [1]. In this review, we discuss whether this increase in reported human S. suis cases is attributable to the emergence and spread of clones with increased capacity to infect humans in certain geographical areas and/or attributable to increased awareness and improved diagnostics of S. suis infection.

EPIDEMIOLOGY

S. suis infection in pigs is reported worldwide, from North America (United States and Canada) to South America (Brazil), Europe (United Kingdom, The Netherlands, France, Denmark, Norway, Spain, and Germany), Asia (China, Thailand, Vietnam, and Japan), Australia, and New Zealand [7]. In addition to pigs, S. suis can be isolated from other animals, such as ruminants, cats, dogs, deer, and horses, and is believed to be a commensal in the intestinal flora [7]. Healthy pigs can carry multiple serotypes of S. suis in their nasal cavities, tonsils, and upper respiratory, genital, and alimentary tracts [7–9]. Of the 35 known serotypes, only a limited number are responsible for infections in pigs, including serotypes 1–9 and 14 [10]. Serotype 2 is considered to be the most pathogenic for both humans and pigs [1]. S. suis is usually transmitted nasally or orally and colonizes the palatine tonsils of both clinically ill and healthy pigs. The infant piglets become infected after contact with colonized sows [11]. Rates of asymptomatic carriage may be as high as 80%, and the morbidity ranges from <1% to >50%, although it rarely exceeds 5% [7, 12].

Since the first human case in Denmark was reported, increasing numbers of human cases have been reported in many countries (figure 1) [1, 4, 13–16]. Recently, a large series of 151 S. suis meningitis cases was described in southern Vietnam over a 10-year period [16]. Although most reports concern sporadic cases of infection, an outbreak of S. suis infection occurred in Sichuan Province, China, during July and August 2005, that involved 215 cases and 38 deaths, emphasizing the importance of S. suis as an emerging zoonosis [17]. In contrast to the serotypes infecting pigs, S. suis serotype 2 is the most common cause of this disease in humans [1]. Serotypes 1, 4, 14, and 16 have caused severe disease in a limited number of persons [18].

Human S. suis infections are most often reported from coun-
tries where pig-rearing is common (figure 1). The relative high mean patient age (47–55 years) and almost complete absence of children in case series, as well as the high male-to-female patient ratio (3.5:1.0 to 6.5:1.0) (table 1), support the notion that infection with *S. suis* is generally an occupational disease [4, 12, 13, 16, 17, 19]. The annual risk of developing *S. suis* meningitis among abattoir workers and pig breeders has been estimated to be 3.0 cases per 100,000 population; the risk is lower for butchers, at 1.2 cases per 100,000 population in developed countries [4]. Such an estimate has not been made for Southeast Asia, where the pig density is high (figure 1).

In a matched case-control study of risk factors for human *S. suis* infection in Sichuan Province, slaughtering (OR, 11.9; 95% CI, 3.4–42.8) and cutting carcasses and processing sick or dead pigs (OR, 3.0; 95% CI, 1.0–8.8) were important risk factors for human infection [20]. Farmers often share accommodations with pigs, and it is common practice for diseased animals to be slaughtered at home and consumed [11]. However, occupational or household exposure to pigs or pork is not present in all cases of *S. suis* infection. Case series from Hong Kong and Vietnam included not only a significant number of housewives, presumably infected as a result of contact with (contaminated) pork [12, 16, 21], but also other individuals who were unaware of any exposure to pork. In Vietnam, pork is the most important meat source, with >98% of households consuming pork [22]. Vietnamese consumers prefer to buy fresh pork from wet markets [22]. Because *S. suis* was isolated from 6.1% of raw pork meat from 3 of the 6 wet markets in Hong Kong, it is likely that, besides occupational exposure, processing or consuming uncooked or partially

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**Figure 1.** World map of human *Streptococcus suis* cases with background pig density data. Published with permission from the Infectious Diseases Research Foundation (World Atlas of Infectious Diseases Project) [6].
cooked pork products is also a risk factor for infection. Local delicacies, such as undercooked pig tonsils, intestines, or uterus and fresh pig blood, may also represent important sources of infection.

The incubation period of *S. suis* infection in 1 Chinese outbreak ranged from 3 h to 14 days (median, 2.2 days) [17]. A very short incubation time is consistent with direct entry of *S. suis* into the blood through skin wounds [17]. Other researchers have reported incubation periods varying from 60 h to 1 week [4, 16]. Patients have generally been healthy prior to infection with *S. suis*, although predisposing factors, such as splenectomy, diabetes mellitus, alcoholism, malignancy, and structural heart diseases have been reported [9, 12]. Whether *S. suis* infection has a seasonal variation remains unclear. In China and Thailand, more patients were admitted during the rainy season, from June through September, than during the rest of the year [9, 12, 13]. In northern Vietnam, more cases were reported during the warmer months, from April through October, than during the rest of the year (unpublished data). In southern Vietnam, where there are fewer climatological differences throughout the year than in northern Vietnam, this distribution of cases was not as clear [16].

Although asymptomatic carriage is common in healthy pigs, it is unknown whether human carriage of *S. suis* is common. A seroprevalence study in The Netherlands revealed that 6% of the veterinarians and 1% of the pig farmers had antibody titers against *S. suis* serotype 2 antigen [23]. Nasopharyngeal carriage of *S. suis* was studied in a group at high risk of infection (butchers, abattoir workers, and meat-processing employees) in Germany. The authors reported a carriage rate of 7 (5.3%) of 132 persons, although none of the 130 control subjects, who had no contact with pigs or pork, were carriers [24]; these findings indicate that *S. suis* carriage does occur in individuals with prolonged and recurrent exposure to pigs and pork. The prevalence, duration, and importance of *S. suis* carriage in humans are unknown.

### CLINICAL FEATURES

*S. suis* causes a systemic infection in humans that affects several organ systems; meningitis is the most common clinical manifestation [4, 13, 17]. The presenting features of *S. suis* meningitis are generally similar to those of other bacterial pyogenic meningitis and include headache, fever, vomiting, and menin-

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**Table 1. Features of *Streptococcus suis* infection reported from published clinical case series.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vietnam (n = 151)</th>
<th>China (n = 204)</th>
<th>Thailand (n = 32)</th>
<th>The Netherlands (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>117 (77.5)</td>
<td>171 (83.8)</td>
<td>23 (71.9)</td>
<td>26 (88.7)</td>
</tr>
<tr>
<td>Age</td>
<td>46.5 years (19–84 years)</td>
<td>54 years (NA)</td>
<td>49 years (1 month to 75 years)</td>
<td>49 years (26–76 years)</td>
</tr>
<tr>
<td><strong>Clinical signs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness, days</td>
<td>4 (1–21)</td>
<td>NA</td>
<td>4.5 (1–14)</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td>Fever</td>
<td>151 (100)</td>
<td>204 (100)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Headache</td>
<td>142 (94.0)</td>
<td>164 (80.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vomiting</td>
<td>NA</td>
<td>117 (57.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>12 (5–15)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Stiff neck</td>
<td>142 (94.0)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Skin findings</td>
<td>9 (6.0)</td>
<td>56 (27.5)</td>
<td>8 (25.0)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td><strong>CSF findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total WBC count, cells/μL</td>
<td>2100 (1–64,000)</td>
<td>NA</td>
<td>925 (0–21,800)</td>
<td>1500 (50–110,000)</td>
</tr>
<tr>
<td>Percentage of neutrophils</td>
<td>84 (1–99)</td>
<td>NA</td>
<td>65 (0–99)</td>
<td>NA</td>
</tr>
<tr>
<td>Total protein level, g/dL</td>
<td>2.06 (0.2–10.19)</td>
<td>NA</td>
<td>1.76 (0.75–4.56)</td>
<td>3 (0.8–9.8)</td>
</tr>
<tr>
<td>Lactate level, mM/L</td>
<td>11.2 (2–17)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CSF: blood glucose level, %</td>
<td>13.76 (0.7–71)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Blood findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total WBC count, cells/μL</td>
<td>16.8 (3.8–57.0)</td>
<td>14.3 (9.4–31.1)</td>
<td>16.4 (5.6–47.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Platelet count, cells/μL</td>
<td>159 (18–933)</td>
<td>NA</td>
<td>224 (22.9–615)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of hospital admission, days</td>
<td>14 (1–43)</td>
<td>15.1*</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Died in hospital</td>
<td>4 (2.6)</td>
<td>38 (18.6)</td>
<td>2 (6.3)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Hearing loss at hospital discharge</td>
<td>93/140 (66.4)</td>
<td>NA</td>
<td>22/32 (68.8)</td>
<td>15/28 (54)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients or median value (range). Data for Vietnam are from Mai et al. [16], data for China are from Tang et al. [33], data for Thailand are from Suankratay et al. [35] , and data for The Netherlands are from Arends et al. [4]. NA, not available.

*Estimated value.*
Figure 2. Skin findings in a patient with *Streptococcus suis* meningitis and septicemia.

geal signs. The duration of illness before hospital admission was 2–5 days [16, 25]. One striking feature is subjective hearing loss, which may be reported by up to one-half of patients at presentation or a few days later [9]. Six percent to 31% of patients also have skin findings, including petechiae, purpura, and ecchymoses, all of which can be extensive, and hemorrhagic bullae and skin necrosis (features of purpura fulminans) (figure 2). Gangrene of the fingers and toes may also be seen in a minority of patients at a later stage in the disease [16]. Less common manifestations of *S. suis* infection include acute and subacute endocarditis [26–28], acute pyogenic arthritis [28], endophthalmitis and uveitis [5, 9], spondylodiscitis [29], brain stem ophthalmoplegia [30], and epidural abscess [31]. Of importance, infective endocarditis was reported to be more common than meningitis in Chiang Mai, Thailand [13].

Meningitis is often accompanied by bacteremia, similar to *Streptococcus pneumoniae* and *Neisseria meningitidis* meningitis [32]. *S. suis* infection can be complicated by acute renal failure requiring renal replacement therapy, acute respiratory distress syndrome necessitating ventilation, and consumptive coagulopathy [1]. Recent outbreaks of *S. suis* infection in China have highlighted the importance and relative high frequency of a
severe sepsis syndrome—with some features suggestive of toxic shock syndrome—associated with a high mortality [17, 33]. The investigators observed erythematous blanching rash on the extremities, including blood spots and petechia, indicative of possible toxic shock syndrome [33]. However, no streptococcal superantigen was found on microbial analyses [33, 34]. Further investigations revealed that a pathogenicity island in the bacterial genome may be responsible for the more-severe cases that were found in China [34]. The exact role of this pathogenicity island is poorly understood, and it remains to be seen whether it has a function in S. suis virulence.

Hearing loss in S. suis meningitis is sensineural, is in the high frequency range [35], and can be profound; it was >80 dB on audiometric testing of Vietnamese adults [16]. The prognosis for hearing is guarded; some patients improve over time, and others do not. Among the Vietnamese adults, 93 (66.4%) of 140 evaluated patients had mild-to-severe hearing loss at hospital discharge, compared with 41 (47.7%) of 86 patients evaluated at 6 months after hospital discharge (table 1) [16]. Vestibular dysfunction (e.g., ataxia) has also been described in association with hearing loss [36].

**MICROBIOLOGICAL DIAGNOSIS**

*S. suis* is a gram-positive coccus that is frequently seen in pairs but can also be single or in short chains (figure 3). Determination of *S. suis* to the species level can be performed with biochemical tests, such as optochin, Voges-Proskauer, salicin, trehalose, and 6.5% sodium chloride [37]. Commercial systems (e.g., API Strep; Biomerieux) can also be used. Some commercial biochemical identification systems also report whether *S. suis* is biotype I or II. This should not be mistaken for serotype 1 or 2, as was done in some reports [38, 39]. The 35 *S. suis* serotypes can be identified by agglutination with a panel of antisera samples. Serotyping is performed in reference laboratories.

Although *S. suis* can be cultured from CSF or blood samples with use of standard microbiological techniques, it is often misidentified, or infection goes undiagnosed [40, 41]. In our experience and others’ experience, *S. suis* has been commonly misidentified and reported as Streptococcus species, α-hemolytic or viridans streptococci, Enterococcus faecalis, Aerococcus viridans, or even *S. pneumoniae* [36, 41].

Culture results can be negative as a result of, for example, antibiotic use prior to the obtainment of specimens. Molecular techniques with a *S. suis* serotype 2–specific PCR have improved the detection of *S. suis* cases in Asia, with the *cps2J* gene as a target [16, 42]. In a case series of 151 patients in Ho Chi Minh City, Vietnam, 117 were detected to have *S. suis* infection by CSF culture, and 149 had *S. suis* detected by real-time PCR. Cases in 22 patients would have remained undiagnosed if PCR was not available. After 1 week of treatment, *S. suis* DNA could still be detected by PCR in the majority of the patients’ samples [16]. The implementation of molecular techniques is not always feasible in regions where *S. suis* is highly prevalent. However, great improvements can be achieved by simple microbiological capacity building. As a rule of thumb, clinicians and microbiology laboratories in regions with pig farming industries should consider *S. suis* if optochin-resistant streptococci are cultured from a CSF sample obtained from a patient with meningitis (figure 3). The identification of α-hemolytic streptococci other than *Pneumococcus* species, cultured from a CSF sample, requires further microbiological investigation, because this may be *S. suis*.

The genetic diversity of *S. suis* serotype 2 strains has been studied using various typing techniques, including random amplification of polymorphic DNA, PFGE, and ribotyping, but with the exception of the Vietnamese strain collection, the number of human strains studied to date outside outbreak situations, has been small (range, 1–27 strains), and limited epidemiological data are available [43–47]. Analysis of Vietnamese strains with use of multilocus sequence typing [48] identified 98% of the strains as sequence type 1 and belonging to clonal complex 1. The strain that caused an outbreak of infection in pigs and humans in China in 2005 was sequence type 7 and also belonged to clonal complex 1 [49]. Although strains of clonal complex 1 thus appear to be important in human infection, serotype 2 strains of clonal complex 27 were recently described to cause infections in humans in Thailand [47], which suggests that the *S. suis* population infecting humans may vary by geographical region, similar to and potentially reflecting the situation in pigs.

**VIRULENCE**

Little is known about how *S. suis* invades the host and how it crosses the blood brain barrier. Inflammation is likely to contribute to the manifestations of disease in pigs and probably also in humans, as has been summarized elsewhere [10]. A series of potential virulence factors of *S. suis* serotype 2 have been identified, including the capsular polysaccharide, extracellular protein factor, muramidase-released protein, sulisyn, several adhesins, hyaluronate lyase, and surface antigen 1 [50–58]. With exception of the capsular polysaccharide, none of these were shown to be essential for virulence in animal models of infection, and the presence of extracellular protein factor and muramidase-released protein varied among human isolates [16, 59]. Two Chinese outbreak isolates were fully sequenced, and a proposed pathogenicity island was identified that may have been involved in the particular clinical manifestations observed during the outbreak in 2005 [34]. This pathogenicity island contains a 2-component regulatory system that may be
involved in virulence [60]. More research is needed to elucidate virulence in \textit{S. suis}.

**TREATMENT AND OUTCOME**

Similar to the protocol for any other patient with suspected bacterial meningitis, antibiotic treatment should be started without delay. Data from Vietnam show that \textit{S. suis} is susceptible to penicillin, ceftriaxone, and vancomycin [16]. Resistance was seen to tetracyclin (83.2% of isolates; \(\text{MIC}_{90} 16 \mu\text{g/mL} \); \(\text{MIC}_{90} 32 \mu\text{g/mL}\)), erythromycin (20%; \(\text{MIC}_{90} 0.064 \mu\text{g/mL} \); \(\text{MIC}_{90} 1256 \mu\text{g/mL}\)), and cloramphenicol (3.3%) [16]. Penicillin resistance has been reported in a single human case and in some pig isolates [61, 62]. In 1 European study, the drug susceptibility of 384 \textit{S. suis} strains from diseased pigs was assessed. The strains were susceptible to penicillin (\(\text{MIC}_{90} \leq 0.13 \mu\text{g/mL}\)). Low rates of resistance were observed for gentamicin (1.3% of isolates; \(\text{MIC}_{90} 8 \mu\text{g/mL}\)) and trimethoprim-sulfamethoxazole (6.0%; \(\text{MIC}_{90} 2 \mu\text{g/mL}\)), and a high rate of resistance was seen for tetracycline (75.1%; \(\text{MIC}_{90} 64 \mu\text{g/mL}\)) [63].

The principles of treatment are the same as those for other causes of bacterial meningitis. For empirical treatment, cef-
triexone with or without vancomycin (depending on the local epidemiology of bacterial meningitis and drug resistance) is a good choice until the diagnosis is laboratory confirmed. The same treatment dose and duration that is used for pneumococcal meningitis is also recommended for S. suis meningitis (i.e., ceftriaxone [2 g every 12 h for 14 days for adults]). This has achieved a high cure rate of 97% [16, 64]. Penicillin G (24 million U over 24 h for at least 10 days) has been used successfully for the treatment of S. suis meningitis [65]. Clinical experience with other drugs (e.g., in instances of penicillin allergy) is limited. Failure to improve during treatment or the development of a relapse should prompt a reevaluation, including a search for an intracranial abscess, a metastatic infection, a hospital-acquired infection, or the development of drug resistance. Some patients with S. suis meningitis have experienced relapse after 2 weeks of treatment with penicillin or ceftriaxone but responded to prolonged treatment (4–6 weeks) [10]. It must be stressed that the treatment recommendations may not be successful for all patients and may need to be tailored. For instance, in case of S. suis infection involving sites other than the CNS, such as endocarditis, endophthalmitis, or arthritis, the recommended guidelines should be observed in terms of duration of treatment, monitoring, and surgical intervention. There are no clinical data on the treatment of penicillin- or ceftriaxone-resistant S. suis infections.

The use of dexamethasone as an adjunctive treatment to reduce mortality and improve the outcome of bacterial meningitis remains controversial [66]. In a randomized, double-blind, placebo-controlled clinical trial in Vietnam, dexamethasone (0.4 mg/kg twice daily for 4 days) resulted in a significant reduction in the risk of death at 1 month (relative risk, 0.43; 95% CI, 0.20–0.94) and in the risk of death and disability at 6 months (OR, 0.56; 95% CI, 0.32–0.98) in patients with confirmed bacterial meningitis [64]. A significant proportion of these patients were infected with S. suis [16, 64]. Of importance, in the group of patients with S. suis meningitis, 20 (37.7%) of 53 patients who were given placebo were deaf in at least 1 ear, compared with 7 (12.3%) of 57 patients who were given dexamethasone ($P = .003$) [16, 64]. In a multivariate analysis, severe hearing loss was associated with older age (>50 years) and not receiving corticosteroid treatment [16]. Dexamethasone (0.4 mg/kg twice daily for 4 days) is now given to adult patients in southern Vietnam who have a short disease onset (<7 days), cloudy CSF, WBC count >1000 cells/μL (with >60% neutrophils), high CSF lactate level (>4 mmol/L), and low CSF glucose level (<50% of blood glucose) or to patients who have a positive result of at least 1 of the following tests: Gram stain, bacterial culture, bacterial antigen test, or PCR.

The reported case-fatality rates associated with S. suis meningitis vary and have generally been low in several meningitis series, compared with rates among patients in the same age group with meningitis due to S. pneumoniae and other bacterial agents (e.g., 2.6% in southern Vietnam [16] and 7% in The Netherlands [4]). An outbreak in China was associated with an overall case-fatality rate of 18%, but this reached 63% among patients with sepsis and septic shock [33].

**CONCLUSIONS**

The majority of the reported human S. suis cases originate from Southeast Asia, where the disease can be considered endemic. This finding can be explained by the high density of pigs in the region, slaughtering practices without preventive measures, and the consumption of uncooked or lightly cooked pig products. Currently, a human vaccine is not available, but simple preventive measures, such as wearing gloves during processing pig meat or slaughtering, hand washing after handling raw pork meat, and thorough cooking of pork, should prevent the majority of cases. Travelers should be aware that dietary habits in some countries may pose a risk for infectious diseases, including S. suis infection. A case-control study to identify risk factors for S. suis infection is lacking and is urgently required, because S. suis meningitis is one of the most common causes of adult meningitis in China, northern Thailand, and Vietnam.

Mapping of pig density and human S. suis cases clearly suggests where S. suis is likely to be present but, thus far, has not been reported. Increased awareness of both clinicians and microbiologists is needed to fully appreciate the importance of S. suis as a human pathogen.

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