

Original Article

Etiology and Clinical Features of Bacterial Meningitis in Adults at National Hospital for Tropical Diseases during 2015–2018

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ABSTRACT: To evaluate the etiology and clinical features of bacterial meningitis (BM) in adults during 2015–2018 in Vietnam, a retrospective study using 102 patients was performed at the National Hospital of Tropical Diseases. BM occurred throughout the year, peaking in July–September. A total of 80.4% BM patients were males over 40 years old. The proportion of patients with underlying diseases was 41.2% and those in contact with pigs or pork products was 30.4%. Common manifestations include stiff neck, Kernig's sign, headache, fever/hypothermia, and altered consciousness. The cerebrospinal fluid (CSF) had high protein concentration (median: 3.2 g/L, range: 1.3–6.2) and leukocytes (median: 1,312 cell/mm³, range: 234–2,943). Moreover, 29.4% meningitis cases were associated with septicemia. *Streptococcus suis* was the main cause (72.5%), followed by *Pneumococcus* (6.8%) and a few other bacteria. Factors associated with *S. suis* risk were male sex (OR: 8.29, 95% CI: 2.83–24.33), over 40 years old (OR: 3.55, 95% CI: 1.28–9.87), drinking habits (OR: 3.78, 95% CI: 1.03–13.72), headache (OR: 6.19, 95% CI: 2.17–17.65), fever/hypothermia (OR: 5.17, 95% CI: 1.97–13.56) and ≥ 2.0 ng/mL procalcitonin (OR: 2.72, 95% CI: 1.07–6.89). Education on *S. suis* and nosocomial infection prevention, as well as pneumococcal vaccination use, should be continued.

INTRODUCTION

Bacterial meningitis (BM) is an infection of the central nervous system that is considered a medical emergency. According to WHO reports, BM treatment is costly and the survivors also have severe sequelae, which affect the quality of life (1,2).

Due to the importance of BM, vaccination programs against *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, and *Neisseria meningitidis* have been implemented, which have limited the incidence of BM caused by these pathogens (2). In Vietnam, Hib vaccine has been implemented since the 2010s; however, *S. pneumoniae* vaccines have not been applied in the national immunization program. Moreover, in recent years, *S. suis*, a bacterial pathogen, has been the main cause of BM in adults in both North and South Vietnam (3,4). In particular, diseases caused by *S. suis* is associated with pork production, hygiene,

and eating habits (5). To limit *S. suis* infection risk in livestock, processing, and consumption of pork products, the Vietnamese health sector has recently increased propaganda and education. Assessing and monitoring the disease situation over time can help prevent diseases in the community. The National Hospital for Tropical Diseases (NHTD) is a 500-bed tertiary treatment center for infectious diseases in North Vietnam that treats patients with severe or difficult diagnoses. It is also the largest central nervous system infection treatment center.

This study analyzes the etiology and clinical characteristics of BM among adults in Northern Vietnam between 2015 and 2018. Our findings may provide evidence for help-oriented solutions to prevent BM in adults in the next phase.

MATERIALS AND METHODS

This was a retrospective descriptive study of adult BM patients admitted to the NHTD, during July 2015 to June 2018. The inclusion criteria were: age ≥ 18 years, one or more evidence of infection in the clinical and laboratory, one or more manifestations of meningitis syndrome, and evidence of bacteria in CSF based on culture or polymerase chain reaction. Patients with HIV infection were excluded from the study.

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The data for each patient were collected using a standardized data collection form. Baseline demographic data, underlying diseases, clinical manifestations, laboratory results, and CSF analysis were reviewed.

The study design was approved by the Ethics Committee of NHTD. Data were analyzed using the Statistical Program for Social Science software, version 20.0. Categorical variables were described as counts, percentages, and medians. To determine the risk factors associated with *S. suis* infection, univariate and multivariate logistic regression analyses were performed, with each potential factor as an independent variable and the presence or absence of *S. suis* as the dependent variable. Any variable with *P* - value ≤ 0.05 was potentially significant.

RESULTS

During the 3-year study period, we enrolled 102 BM patients based on bacteriological evidence. The characteristics of the study population are summarized in Table 1. BM patients were hospitalized around the year and the number of patients hospitalized increased from July to September. BM occurred in all ages from 18 to 83 years, and 80.4% patients were males. Most patients were farmers (48%) and vendors (45.1%). Factors associated with the risk of meningitis and *S. suis* infection, including direct contact with pigs or pork products (30.4%), drinking habits (25.5%), and underlying diseases (41.2%), were explored. Common clinical manifestations were neck stiffness (100%), positive Kernig's sign (100%), headache (80.4%), fever/hypothermia (74.5%), and altered mental status (73.5%). Other manifestations, such as hemorrhagic rash (14.7%), hearing loss (12.7%), convulsions (5.9%), and paralysis (2.0%), have also been recorded.

Peripheral blood tests showed >10 G/L leukocyte count, ≥ 10 g/L C-reactive protein (CRP), and ≥ 2.0 ng/mL procalcitonin in 79.4%, 95.8%, and 77.9% cases, respectively. The CSF color was abnormal in 97/102 (95.1%) patients, being turbid, yellow, and hemorrhagic in 91 (89.3%), 3 (2.9%), and 3 (2.9%) patients, respectively. CSF analysis indicated increased leukocyte count (median: 1,312 cells/mL) and protein concentration (median: 3.2 g/L). Table 2 summarizes the pathogens identified in 102 BM cases. *S. suis* was the most common cause (72.5%), followed by *S. pneumoniae* (6.8%), *Acinetobacter baumannii* (5.9%), *Escherichia coli* (3.9%), and *N. meningitidis* (2.9%). Other meningitis-causing bacteria, including *S. gallolyticus* and *Klebsiella pneumoniae* (2.0% frequency each) and *S. aureus*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis* (1% frequency each), were identified in this study.

The results of the univariate analysis of the *S. suis* risk-associated factors are presented in Table 3. The factors recorded included male sex (OR: 8.29, 95% CI: 2.83–24.33, $P < 0.0001$), over 40 years old (OR: 3.55, 95% CI: 1.28–9.87, $P < 0.015$), drinking habit (OR: 3.78, 95% CI: 1.03–13.72, $P < 0.045$), severe headache (OR: 6.19, 95% CI: 2.17–17.65, $P < 0.0007$), fever/hypothermia (OR: 5.17, 95% CI: 1.97–13.56, $P < 0.0008$), and ≥ 2.0 ng/mL procalcitonin (OR: 2.72, 95% CI: 1.07–6.89, $P < 0.035$). Risk factors were also

included in the multivariate model, but no risk factors were identified.

DISCUSSION

In this study, we evaluated all BM patients admitted at the NHTD during 2015–2018. All 102 patients diagnosed with BM based on bacteriological results were analyzed.

While *S. pneumoniae* and *N. meningitidis* primarily caused BM in adults in some countries during the same study period (6–8), we found that *S. suis* primarily caused BM in adults in Vietnam (72.5% cases), followed by *S. pneumoniae* (6.8%), and other bacteria (Table 2). *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were identified in seven patients with traumatic brain injury, three patients with diabetes mellitus, and two patients with prolonged corticosteroid use. These gram-negative bacteria have been commonly reported in people with chronic diseases such as diabetes, cirrhosis, and alcoholism, particularly in those undergoing cranial surgery. These patients were possibly infected from the hospital environment when they were hospitalized for a long time or during a direct intervention in the skull and under immunocompromised conditions (9,10).

S. suis infection is associated with pig production (livestock, slaughter, transportation) or consumption of undercooked pork products in not only Vietnam (4,11), but also Thailand (12,13) and Indonesia (14). Direct pig/pork contact was identified as a causative factor in 30.4% BM cases. If according to previous reports, *S. suis* infection was mainly associated with undercooked pork product consumption (5,11,15); however, in our study, this risk was lower (12.7%) than the risk of contact with pigs or raw pork products (17.8%). Thus, to reduce *S. suis* infection risk, education on food safety should be strengthened in addition to focusing on labor protection (16).

The results of our study showed that 80.4% BM patients were males (Table 1), while in some countries, such as Korea in Asia (17), Kenya in Africa (7), and the Netherlands in Europe (6), BM infection was not sex-dependent. Furthermore, most BM patients participating in our study were farmers or vendors (93.1%). These differences may be related to *S. suis* infection (3,14, 15). The results of our study showed that BM occurred throughout the year and increased sharply in July, August, and September due to the increase in the number of *S. suis*-mediated cases (3). This requires further investigation of the factors involved, although *S. suis* infections increase in hot months (3,15). The clinical manifestations were still characteristics of BM, such as manifestations of infection with fever/hypothermia (74.5%) and increased inflammatory indicators such as white blood cell count, CRP, and procalcitonin. Typical meningeal signs and CSF were markedly altered, with increased leukocyte cell count and protein concentration. Non-specific fever has been observed mainly in patients with underlying medical conditions. Therefore, in patients with doubtful diagnosis, inflammatory indices should be evaluated and early CSF indication would be helpful in the diagnosis (9,10). It is noteworthy that 35% *S. suis*-infected

Clinical Features and Etiology of Bacterial Meningitis

Table 1. Demographic, clinical signs, laboratory of bacterial meningitis

Variable	<i>S. suis</i> (n = 74)	Other bacteria (n = 28)	Total (N = 102)
Gender, no. (%)			
Male	67 (90.5)	15 (53.6)	82 (80.4)
Female	7 (9.5)	13 (46.4)	20 (19.6)
Age, years, no. (%)			
18–20	0 (0.0)	2 (7.1)	2 (2.0)
21–40	10 (13.5)	8 (28.6)	18 (17.6)
41–60	44 (59.5)	10 (35.7)	54 (52.9)
>60	20 (27.0)	8 (28.6)	28 (27.5)
Median (range)	52 (22–83)	47 (18–75)	52 (18–83)
Occupation, no. (%)			
Farmer	37 (50.0)	12 (42.9)	49 (48.0)
Vendor	31 (41.9)	15 (53.6)	46 (45.1)
Worker	3 (4.1)	1 (3.6)	4 (4.0)
Office staff	3 (4.1)	0 (0.0)	3 (2.9)
Distribution of BM cases by seasons in a year, no. (%)			
January–March	11 (14.9)	9 (32.1)	20 (19.6)
April–June	16 (21.6)	3 (10.7)	19 (18.6)
July–September	33 (44.6)	8 (28.6)	41 (40.2)
October–December	14 (18.9)	8 (28.6)	22 (21.6)
Predisposing conditions, no. (%)			
Direct contact with pig/pork			31 (30.4)
+ Recent contact with pigs or raw pork products	14 (18.9)	4 (14.3)	18 (17.8)
+ Recent consumption of raw pork product	11 (14.9)	2 (7.1)	13 (12.7)
Underlying disease ¹⁾	20 (27.0)	22 (78.6)	42 (41.2)
Alcohol habits	23 (31.1)	3 (10.7)	26 (25.5)
Days from the onset of illness to the admission, median (range)	3 (2–8)	4 (1–10)	3 (1–10)
Clinical signs, no. (%)			
Neck stiffness	74 (100.0)	28 (100.0)	102 (100.0)
Kernig	74 (100.0)	28 (100.0)	102 (100.0)
Headache	66 (89.2)	16 (57.1)	82 (80.4)
Fever/Hypothermia	62 (83.8)	14 (50.0)	76 (74.5)
Altered mental status	54 (73.0)	21 (75.0)	75 (73.5)
Vomiting/Nausea	48 (64.9)	19 (67.9)	67 (65.7)
Constipation/Diarrhea	14 (18.9)	4 (14.3)	18 (17.6)
Skin hemorrhages/Rash	12 (16.2)	3 (10.7)	15 (14.7)
Hearing loss	12 (16.2)	1 (3.6)	13 (12.7)
Convulsion	4 (5.4)	2 (7.1)	6 (5.9)
Paralysis	1 (1.4)	1 (3.6)	2 (2.0)
Blood test			
Leukocytes count >10 G/L, no. (%)	60 (81.1)	21 (75.0)	81 (79.4)
C-reactive protein ≥10 g/L, no. (%), (n = 95)	68 (91.9)	23 (82.1)	91 (95.8)
Procalcitonin ≥2.0 ng/ml, no. (%), (n = 95)	58 (78.4)	16 (57.1)	74 (77.9)
Cerebrospinal fluid profiles			
Color, no. (%)			
Turbid	65 (87.8)	26 (92.9)	91 (89.3)
Colorless	4 (5.4)	1 (3.6)	5 (4.9)
Yellow	2 (2.7)	1 (3.6)	3 (2.9)
Hemorrhage	3 (4.1)	0 (0.0)	3 (2.9)
Leukocytes cell/mm ³ , median (range)	1,698 (234–2,673)	1,281 (320–2,943)	1,312 (234–2,943)
Protein, g/L, median (range)	3.4 (1.6–4.6)	2.8 (1.3–6.2)	3.2 (1.3–6.2)
Glucose <2.2 mmol/L, no. (%)	12 (16.2)	4 (14.3)	16 (15.7)
Clinical classification			
Bacterial meningitis	48 (64.9)	24 (85.7)	72 (70.6)
Bacterial meningitis with septicemia	26 (35.1)	4 (14.3)	30 (29.4)
Outcome, no. (%)			
Complete recovery	45 (60.8)	23 (82.1)	68 (66.7)
Recovery with sequelae	19 (25.7)	1 (3.6)	20 (19.6)
Mortality	10 (13.5)	4 (14.3)	4 (13.7)

¹⁾: Underlying diseases including: chronic pulmonary disease (13 patients), diabetes mellitus (9 patients), traumatic brain injury (9 patients), otitis media (6 patients), cirrhosis (5 patients), use of immunosuppressive drugs (5 patients).

Table 2. Causative organisms

Bacteria identified	Total (n)	Proportion (%)
<i>Streptococcus suis</i> ¹⁾	74	72.5
<i>Streptococcus pneumoniae</i>	7	6.8
<i>Acinetobacter baumannii</i>	6	5.9
<i>Escherichia coli</i>	4	3.9
<i>Neisseria meningitidis</i>	3	2.9
<i>Streptococcus galloyticus</i>	2	2.0
<i>Klebsiella pneumoniae</i>	2	2.0
Other ²⁾	4	3.8
Total	102	100.0

¹⁾: *S. suis* was confirmed in CSF by culture in 65 patients and by PCR in 9 patients.

²⁾: Other includes *Staphylococcus aureus* (n = 1), *Pseudomonas aeruginosa* (n = 1), *Enterococcus faecalis* (n = 1), *Burkholderia pseudomallei* (n = 1).

Table 3. Regression analysis of factors associated with *S. suis* on clinical and laboratory Parameters

Indicator	<i>S. suis</i>	Other bacteria	Univariate analysis	
			P	OR (95% CI)
Male	67 (90.5)	15 (53.6)	0.0001	8.29 (2.83–24.33)
Age >40	64 (86.5)	18 (64.3)	0.015	3.55 (1.28–9.87)
Farmer	37 (50.0)	12 (42.9)	0.52	1.33 (0.55–3.20)
Vendor	31 (41.9)	15 (53.6)	0.292	0.62 (0.26–1.49)
July–September	33 (44.6)	8 (28.6)	1.145	2.01 (0.78–5.15)
Direct contact with pig/pork	25 (33.8)	6 (21.4)	0.230	1.87 (0.67–5.20)
Recent contact with pigs or raw pork products	14 (18.9)	4 (14.3)	0.585	1.40 (0.42–4.68)
Recent consumption of raw pork product	11 (14.9)	2 (7.1)	0.307	2.27 (0.47–10.96)
Underlying disease	20 (27.0)	22 (78.6)	<0.001	0.10 (0.03–0.28)
Alcohol habits	23 (31.1)	3 (10.7)	0.045	3.78 (1.03–13.72)
Headache	66 (89.2)	16 (57.1)	0.0007	6.19 (2.17–17.65)
Fever/Hypothermia	62 (83.8)	14 (50.0)	0.0008	5.17 (1.97–13.56)
Constipation/Diarrhea	14 (18.9)	4 (14.3)	0.585	1.40 (0.42–4.68)
Skin hemorrhages/rash	12 (16.2)	3 (10.7)	0.490	1.61 (0.42–6.21)
Hearing loss	12 (16.2)	1 (3.6)	0.12	5.22 (0.65–42.2)
Bacterial meningitis with septicemia	26 (35.1)	4 (14.3)	0.047	3.25 (1.02–10.38)
C-reactive protein ≥10 g/L	68 (91.9)	23 (82.1)	0.166	2.46 (0.69–8.84)
Procalcitonin ≥2.0 ng/mL	58 (78.4)	16 (57.1)	0.035	2.72 (1.07–6.89)
Recovery with sequelae	19 (25.7)	1 (3.6)	0.034	9.33 (1.18–73.40)

patients had associated sepsis.

We analyzed the epidemiological and clinical data of 102 patients to differentiate meningitis caused by *S. suis* from that by other etiologies. The results of the univariate analysis showed that male sex, age >40 years, drinking habit, severe headache, fever/hypothermia, and ≥2.0 ng/mL procalcitonin were the factors associated with *S. suis* infection risk. However, no risk factors were identified in the multivariate analysis. Compared to the results of previous studies, we also found that the factors suggesting *S. suis* infection have not been unified. In a case-control study conducted in Vietnam in 2011, the associated factors were eating high-risk foods, occupation involving pigs, and exposure to pigs or pork in the presence of skin injuries (5). Systematic reviews and meta-analyses of *S. suis* infection patients have also

documented the highest *S. suis* infection prevalence in Asia (15) associated with occupational exposure and contaminated food consumption (15,18). However, a previous study has also reported *S. suis* infection is more common in males, the elderly population, and those with history of skin injury, while underlying diseases only account for a small proportion of infection (18). It is noteworthy that Vietnam is a low-income agricultural country, and the risk of exposure to pigs and risky foods from pigs and drinking habits are very common (5,11). A study in Hanoi determined that consumption of food at risk of *S. suis* infection is associated with rural residence, age, sex, occupation, income, and marital status (11). The authors commented that the proportion of males consuming risky foods was higher than that of females and the difference was higher in urban areas

than that in rural areas. Therefore, risk assessment was influenced by sex and geography.

Furthermore, in addition to clinical syndromes (meningitis, sepsis, arthritis, and endocarditis), specific signs and symptoms differentiating between *S. suis* and non-*S. suis* meningitis were not evaluated in these studies. These are the indicators required for physicians to identify the cause in meningitis patients.

Our study was designed as a retrospective descriptive study; therefore, some limitations of this research method were unavoidable. Moreover, the number of non-*S. suis* meningitis patients was low ($n = 28$), which also led to limitations in the results. Therefore, a complete and comprehensive study of *S. suis* infections is needed to provide a full picture of this disease.

During 2015–2018, *S. suis* primarily caused meningitis in adults (72.5%), other causes were found in patients with underlying diseases. Several factors suggestive of *S. suis* infection should be considered, including male sex, age >40 years, drinking habits, severe headache, and marked fever. To prevent this disease, people should be continuously educated about hygiene in raising and consuming pork.

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Conflict of interest None to declare.

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