Zoonotic bacterial meningitis in adults: clinical characteristics, etiology, treatment and outcome

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CONTENTS

CHAPTER 1

INTRODUCTION

Since the early days of history, it has been known that diseases can be transmitted from animals to humans. Around 2300 BC, the Mesopotamian laws of Eshnunna stated: "If a dog is vicious and the authorities have brought the fact to the knowledge of its owner, [if nevertheless] he does not keep it in, it bites a man and causes [his] death, then the owner of the dog shall pay two-thirds of a mina of silver."[1] In 380 BC, Aristotle described this zoonotic disease, now known as rabies, as "fatal to the dog itself and to any animal that it may bite".[1]

Since then, more than 200 zoonotic diseases have been described. Some of these diseases have had a major impact on human civilization. For instance, the bubonic plague, that is transmitted to humans from infected rodents, wiped out 25% of Europe's population in the 14th century and is therefore considered one of the most devastating pandemics in human history.[2] Bovine tuberculosis, transmitted to humans through consumption of unpasteurized dairy products and contact with infected animals, was a significant cause of death in Europe in the 19th century.[3]

Due to modern sanitation and public health practice, the spread and mortality of many infectious diseases has decreased markedly. However, due to socio-economic and ecological changes, such as human population growth and loss of biodiversity, the incidence of emerging infectious diseases events has increased since 1940.[4,5] More than 60% of the roughly 400 emerging infectious diseases that have been identified are zoonotic.[4,6] In addition, the most recent pandemics and epidemics, *e.g.* Q-fever, severe acute respiratory syndrome (SARS) and avian influenza, are caused by zoonotic pathogens.[6] Zoonotic diseases are thus an increasing public health problem.[6]

Zoonotic pathogens may cause a variety of symptoms and diseases. One of the possible clinical manifestations of a zoonotic bacterial infection is meningitis. Bacterial meningitis is a neurologic emergency requiring prompt recognition and treatment. Despite fast initiation of antibiotic treatment, the mortality of bacterial meningitis remains high at 17%, and half of the patients surviving bacterial meningitis end up with neurological sequelae.[7] In patients presenting with bacterial meningitis, rapid identification of the bacteria causing the infection is essential for choice of treatment and for prediction of outcome. While meningitis caused by pathogens originating

from humans has been studied extensively, little is known about meningitis caused by zoonotic bacteria.

Aims and outline of this thesis

The aim was to investigate the epidemiology, etiology, clinical characteristics, treatment, outcome and prevention of zoonotic bacterial meningitis. In the following chapters, we will describe cases of meningitis caused by several zoonotic pathogens. In general, one zoonotic pathogen is described per chapter, combining cases identified in a nationwide cohort study of bacterial meningitis patients[7] and a review of the literature on meningitis caused by the described zoonotic pathogen.

In **Chapter 2**, we describe cases of *Streptococcus equi* meningitis and perform a literature review on *S. equi* meningitis. In **Chapter 3**, we describe cases of *Streptococcus suis* meningitis identified in a nationwide cohort study of bacterial meningitis patients in the Netherlands. In **Chapter 4**, we perform a systematic review and meta-analysis on the clinical characteristics, adjunctive treatment and outcome of *S. suis* meningitis. In **Chapter 5**, we describe the clinical characteristics, complications and outcome of meningitis caused by *Capnocytophaga canimorsus*. In **Chapter 6**, we describe cases of *Campylobacter fetus* meningitis and perform a review of the literature on *C. fetus* meningitis. In **Chapter 7**, we describe cases of *Streptococcus gallolyticus* meningitis. *S. gallolyticus*, formerly known as a member of the *Streptococcus bovis* group, is not a zoonotic pathogen, as it occasionally occurs as a commensal in the human gastro-intestinal tract.[6] Nevertheless, *S. gallolyticus* meningitis is described in this thesis, as the pathogen was first discovered in cattle and is commonly found in the gastro-intestinal tract of ruminants.[7] In **Chapter 8**, we describe leptospiral meningitis and report four cases of leptospiral meningitis in the Netherlands.

Finally, the thesis concludes with a general discussion in **Chapter 9**, in which we give an overview of the clinical characteristics, treatment and outcome of zoonotic bacterial meningitis. In this chapter, meningitis caused by the formerly mentioned zoonotic pathogens is described with addition of rare zoonotic pathogens not identified in our cohort study, such as *Bacillus anthracis* and *Francisella tularensis*.

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CHAPTER 2

STREPTOCOCCUS EQUI MENINGITIS

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Introduction

Streptococcus equi, part of the commensal flora of the upper respiratory tract in horses, is an uncommon cause of bacterial meningitis. Very little is known about its risk factors, presenting features and outcome. We report two cases of *S. equi* meningitis from a nationwide cohort study in the Netherlands performed from 2006 through 2014, and present a literature review.

Results

Case 1

The first case has been described previously[1] and concerned a 37-year-old previously healthy horsewoman presenting with fever, headache and nausea 4 days after a horse bite. Neurological examination showed neck stiffness and an altered consciousness (Glasgow Coma Scale E3M5V3). Cerebrospinal fluid (CSF) examination was consistent with bacterial meningitis (394 leukocytes/mm^3, protein 1.21 g/L, glucose 0.60 mmol/L), and she was treated with ceftriaxone and dexamethasone. After one day, cultures became positive for *S. equi* ssp. *zooepidemicus*, and antibiotic treatment was switched to penicillin. During admission, she developed right-sided hemiparesis and aphasia. Cranial imaging showed multiple brain abscesses. Penicillin was continued for 8 weeks and she was discharged to a rehabilitation centre. During the months after admission, her aphasia improved, but severe memory deficits persisted and she was unable to live independently.

Case 2

The second case identified was a 41-year-old previously healthy female who presented with headache and fever lasting 1 day. She had regular recreational contact with horses. On physical examination she had a temperature of 39.0°C and neck stiffness. She opened her eyes and localized in response to painful stimuli and made sounds but no recognizable words (Glasgow Coma Scale E2M5V2). Her blood leukocyte count was 21.1 x 10^9/L. Cranial CT showed brain oedema and CSF findings were consistent with bacterial meningitis (85 leukocytes/mm^3, protein 3.00 g/L, glucose 2.50 mmol/L);

CSF Gram stain showed Gram-positive bacteria. She was admitted to the ICU, but died on day 2 due to respiratory and circulatory failure despite treatment with ceftriaxone and dexamethasone. After 2 days, CSF cultures showed *S. equi* ssp. *zooepidemicus*. Blood cultures remained negative.

Table 1. Clinical characteristics, etiology and clinical outcome for *Streptococcus equi* meningitis; combination of our patients and patients reported in the literature

Characteristics	n/N (%)
Median age (range)	61 (0-83)
Male sex	18/32 (53)
Immunocompromised	5/25 (20)
Diabetes mellitus	2/25 (8)
Immunosuppressive medication	2/25 (8)
Haematological malignancy	1/25 (4)
Identified source of infection	32/32 (100)
Regular horse contact	21/32 (66)
Consuming unpasteurized dairy products	9/32 (28)
Mother had regular contact with horses	1/32 (3)
Contact with sick dogs	1/32 (3)
Clinical presentation	
Headache	19/34 (56)
Fever	34/34 (100)
Neck stiffness	27/34 (79)
Altered mental status	28/34 (82)
Classic meningitis triad[a]	22/34 (65)
Cerebrospinal fluid characteristics	
Median CSF leukocyte count/mm^3 (range)	1919 (31-11,000)
Median CSF protein (g/L) (range)	2.62 (0.71-62.29)
Median CSF glucose (mmol/L) (range)	2.02 (0.10-4.60)
Median blood leukocyte count (x 10^9/L)	16.8 (3.5-40.7)
Positive cultures	
Cerebrospinal fluid	31/33(94)
Blood	25/29 (86)
Complications	15/32 (47)
Sepsis	4/32 (12)
Endophthalmitis	3/32 (9)
Other	11/32 (34)
Outcome	
Death	7/34 (21)
Hearing loss	7/27 (26)
Impaired vision	3/27 (11)
Other sequelae	5/27 (19)

Abbreviations: CSF: cerebrospinal fluid
[a]Defined as fever, neck stiffness and altered mental status

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Table 2. Cases of *Streptococcus equi* meningitis reported in the literature, combined with our patients

Study	Age	Gender	Predisposing factor	Source of infection	Symptoms	CSF leukocyte count/mm³	Cranial CT	Complications	Outcome
This study[a]	37	Female	None	Bitten by horse	1;2;3;4	394	Brain abscesses	Brain abscesses	Severe amnesia
This study	41	Female	None	Regular horse contact	1;2;4	85	Brain edema	Respiratory and cardiac failure	Death
Madzar[6]	73	Male	None	Sick horse	1;2;3	3580	Normal	Endophthalmitis	Impaired vision
Pelkonen[7]	57	Male	N.R.	Regular horse contact	2;3;4	N.R.	N.R.	Septicaemia, endocarditis	Full recovery
Mori[8]	59	Male	None	Unpasteurized dairy products	1;2;3;4	1080	Mastoiditis	Pneumonia	Hearing loss
Brouwer[1]	37	Female	None	Bitten by horse	1;2;3;4	394	Brain abscesses	Brain abscesses	Severe amnesia
Eyre[9]	79	Male	N.R.	Trampled by horse	1;2;4	360	Normal	Multiple brain infarction	Hearing loss
Rajasekhar[10]	83	Male	None	Regular horse contact	2;4	31	Normal	None	Amnesia
Poulin[11]	59	Female	Diabetes mellitus	Regular horse contact	2;4	2560	N.R.	Endocarditis, endophthalmitis	Deafness, blindness
Minces[12]	51	Female	Diabetes mellitus	Regular horse contact	2;3	2140	Pansinusitis, mastoiditis	Respiratory failure	Full recovery
Rivas[13]	30	Female	None	Regular horse contact	2;3;4	1706	Edema, hypodensity	Intracranial hypertension	Full recovery
Jovanovic[14]	72	Female	None	Unpasteurized dairy products	2;3;4	2500	N.R.	None	Full recovery
Pati[15]	41	Male	None	Regular horse contact	1;2;3;4	166	Brain edema, sinusitis	N.R.	Full recovery
Bordes-Benitez[16]	83	Female	None	Unpasteurized dairy products	2;3	N.R.	N.R.	N.R.	Death
West[17]	66	Male	Immunosuppressive medication	Regular horse contact	1;2;3	4336	Pansinusitis	None	Mild vertigo

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Table 2. Continued

Study	Age	Gender	Predisposing factor	Source of infection	Symptoms	CSF leukocyte count/mm^3	Cranial CT	Complications	Outcome
Ural[18]	74	Male	None	Sick horse	2;3;4	583	N.R.	N.R.	Death
Downar[19]	49	Female	N.R.	Kicked by horse	1;2;3;4	3011	N.R.	N.R.	Diplopia
Shah[20]	13	Male	Immunosuppressive medication	Regular horse contact	1;2;3;4	6000	Normal	None	Hearing loss
Jenkins[21]	0	Male	None	Mother visited horse regularly	2;3;4	1750	Normal	None	Full recovery
Mattei[22]	66	Female	Leukaemia	Sick horse	1;2;3;4	4650	N.R.	Endophthalmitis	Impaired vision
Latorre[23]	62	Female	None	Unpasteurized dairy products	1;2;3;4	40	Normal	None	Full recovery
Ferrandière[24]	74	Male	None	Sick horse	1;2;3;4	2000	N.R.	None	Full recovery
Cheeseman[25]	24	Male	None	Regular horse contact	1;2;3;4	11,000	N.R.	None	Full recovery
Edwards[26]	73	Male	N.R.	Unpasteurized dairy products	2	N.R.	N.R.	Septicaemia	Death
Edwards[26]	73	Male	None	Unpasteurized dairy products	2;4	N.R.	N.R.	Septicaemia	Death
Edwards[26]	71	Male	N.R.	Unpasteurized dairy products	2;4	N.R.	N.R.	N.R.	Full recovery
Edwards[26]	80	Female	N.R.	Unpasteurized dairy products	1;2;3;4	N.R.	N.R.	Septicaemia	Death
Vergnes[27]	59	Female	None	Regular horse contact	2;3	5618	Brain abscess	Brain abscess	Full recovery
Ghoneim[28]	66	Male	None	Contact with sick dogs	2;3;4	520	Normal	None	Full recovery
Low[29]	24	Female	None	Regular horse contact	1;2;3;4	1818	N.R.	None	Changed behaviour

Table 2. Continued

Study	Age	Gender	Predisposing factor	Source of infection	Symptoms	CSF leukocyte count/mm^3	Cranial CT	Complications	Outcome
Mohr[30]	59	Male	None	Unpasteurized dairy products	1;2;3;4	3229	Normal	Pneumonia	Hearing loss
Patey[31]	77	Female	N.R.	N.R.	2;3;4	1200	N.R.	None	Death
Patey[31]	33	Male	N.R.	N.R.	1;2;3;4	5300	N.R.	None	Hearing loss
Elsayed[32]	13	Male	None	Regular horse contact	1;2;3;4	2175	Hydrocephalus	None	Hearing loss
Popescu[33]	75	Female	None	Regular horse contact	1;2;3;4	5200	Normal	None	Full recovery

Abbreviations: CSF: cerebrospinal fluid ; N.R: not reported

[a]This patient from our cohort has been described previously[4]

Symptoms: 1: headache; 2: fever; 3: neck stiffness; 4: altered consciousness

Review of the literature

A literature search identified 29 studies describing 33 episodes of *S. equi* meningitis, occurring between 1978 and 2015. Combining these data with our cases (Table 1, Table 2), we identified 34 patients with a median age of 61 years (range 0-83 years). Eighteen patients were male (53%) and five out of 25 patients (20%) were immunocompromised. A source of infection was identified in all 32 patients for whom it was reported, mainly regular horse contact (66%) and consuming unpasteurized dairy products (28%). The classic meningitis triad of fever, neck stiffness and an altered consciousness was present in 22 patients (65%). Examination of CSF produced abnormal findings in all. Blood cultures were positive in 25 out of 29 patients (86%) and CSF cultures in 31 out of 33 patients (94%). Subspecies *zooepidemicus* was identified in 32 cases and subspecies *equi* in 2 cases. Cranial CT was performed in 18 patients and showed abnormalities in 9 (50%): brain oedema and sinusitis each in three patients, mastoiditis and brain abscesses each in two, and hydrocephalus and cerebral hypodensity each in one patient.

Complications during admission were present in 15 out of 32 patients (47%) and consisted of sepsis in four patients, endophthalmitis in three, endocarditis, pneumonia, respiratory failure and brain abscesses each in two, and intracranial hypertension, cardiac failure and multiple brain infarction each in one patient. Three patients had multiple complications. Infections outside the brain were present in 12 out of 32 patients (37%). Outcome was reported in all 34 patients: seven patients died (21%). Of the surviving 27 patients, 14 patients had neurological sequelae (52%), consisting of hearing loss in six, impaired vision in two (after endophthalmitis), amnesia in two, and both deafness and blindness, vertigo, diplopia, and changed behaviour each in one patient.

Discussion

Meningitis caused by *S. equi* is a rare disease associated with high rates of unfavourable outcome (62%). Commonly identified risk factors were regular horse contact and consumption of unpasteurized dairy products. In 2005, a national study regarding horses in the USA showed that 4.6 million

Americans were involved in the horse industry and 2 million people owned horses.[2] The small number of cases identified reflects the low chance of developing *S. equi* meningitis after horse contact. Unpasteurized dairy products may harbour several pathogens, such as *Listeria monocytogenes* and *Campylobacter jejuni*, and consumption is therefore discouraged by the CDC.[3] An immunocompromised state was present in only 20% of the patients with *S. equi* meningitis, compared with 67% of the patients with *L. monocytogenes* meningitis being immunocompromised.[4]

Most cases of *S. equi* meningitis were caused by subspecies *zooepidemicus*, and only two cases were caused by subspecies *equi*. Both pathogens were sensitive to penicillin, cefotaxime and ceftriaxone in all cases described. Penicillin is the recommended antimicrobial therapy in patients with streptococcal meningitis caused by an equine pathogen.

Complications occurred in about half of patients with *S. equi* meningitis, most commonly distant infection foci, such as endophthalmitis and endocarditis. Endophthalmitis is a serious complication of *S. equi* infection that can lead to blindness. Endocarditis is an uncommon coexisting condition in bacterial meningitis identified in 2% of patients and is associated with high rates of unfavourable outcome (63%).[5] This condition needs to be treated with prolonged duration of antibiotics (6-8 weeks). Whether the primary focus of infection is the meningitis or endocarditis remains difficult to distinguish, because initial complaints of endocarditis can be nonspecific. Our findings indicate that endocarditis should be considered in all patients with *S. equi* meningitis.

In conclusion, *S. equi* meningitis is associated with horse contact and consuming unpasteurized dairy products. Although rare, the associated mortality is high and many survivors suffer from neurological sequelae. Endocarditis should be considered in all patients with *S. equi* meningitis.

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CHAPTER 3

STREPTOCOCCUS SUIS MENINGITIS IN THE NETHERLANDS

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Introduction

In 2008, a case report in *Journal of Infection* described four patients with *Streptococcus suis* meningitis in the Netherlands.[1] In 2006, a prospective nationwide cohort study of patients with community-acquired bacterial meningitis in the Netherlands was started.[1] In this new cohort study, 1732 episodes of bacterial meningitis were included between January 2006 and May 2015, of which 8 episodes were caused by *S. suis* in 7 patients.

Results

Case reports
The calculated annual incidence of *S. suis* meningitis in the Netherlands was 0.07 per 1,000,000 adult population. The median age was 54 years (range 28-77; Table 1). All cases concerned men who had professionally been in contact with pigs or pork: three pig farmers, two butchers and two abattoir workers. Headache was present in 6 out of 6 episodes (unknown in 2), fever and neck stiffness both in 5 out of 8, and altered consciousness in 7 out of 8 episodes. The classic meningitis triad consisting of fever, neck stiffness and an altered consciousness was present in 4 of 8 episodes. None presented with rash. All patients underwent a lumbar puncture and results of CSF analysis were abnormal in all. Blood culture was positive in 5 out of 7 episodes (71%) and serotype 2 was isolated in 4 out of 4 cases where serotype identification was performed (cases 1, 2, 3 and 8).

In seven episodes, initial antimicrobial therapy consisted of a cephalosporin (ceftriaxone in 5 episodes, cefotaxime in 2 episodes), combined with amoxicillin in 4 episodes (Table 1); after culture results became available, therapy was stepped down to penicillin in 3 episodes. One patient received penicillin monotherapy during admission. Adjunctive dexamethasone treatment according to the Dutch bacterial meningitis protocol (10mg QID, for 4 days)[2] was administered in 7 of 8 episodes. Six out of seven patients (86%) developed hearing loss.

Review of the literature

A literature search identified 6 articles describing 38 episodes of *S. suis* meningitis in 38 patients in the Netherlands (Table 2), occurring between 1988 and 2012.[1, 3-7] One article described a patient who was also included in our cohort.[3] When combining the data with our patients, 45 different episodes were described in 44 patients since 1988. The median age was 50 years, and 39 out of 44 patients (89%) were male. In 41 of 44 (93%) cases the source of infection could be established: 16 were pig farmers, 11 were abattoir workers, 10 were butchers, and 4 had occasional contact with pigs or pork. Predisposing factors were present in 7 patients (16%) and consisted of cancer in 4 patients, and alcohol, immunosuppressive medication and splenectomy in the remaining 3 patients. Hearing loss developed in 28 out of 43 survivors (65%).

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Discussion

S. suis meningitis in the Netherlands occurs in patients with professional contact with pigs or pork. Whilst the calculated annual incidence of *S. suis* meningitis in our cohort was 0.07 per 1,000,000 adults, Schultsz and co-workers reported an estimated annual risk for developing *S. suis* meningitis in Dutch persons having regular contact with pigs of 3.4-5.6 per 100.000.[8] *S. suis* thus remains an important risk for persons having regular contact with pigs and infection is probably underreported, partly due to misidentification of streptococci.[8] Invasive *S. suis* infections occur in pigs and humans.[9] In a recent study, it was shown that all cases of human *S. suis* infection in the Netherlands were caused by serotype 2: this study included the first three cases we described.[9] Infection in pigs was mainly caused by serotype 9.[9] The serotype causing *S. suis* meningitis in our cohort was not known in all patients, but no other serotypes but serotype 2 were found.

Hearing loss occurred in 86% of patients in our series, which is higher than described in patients with *S. suis* meningitis in Vietnam (50%),[10] and the earlier reviewed Dutch series (53%).[7] In a randomized clinical study on adjunctive dexamethasone in Vietnamese adults, dexamethasone was associated with reduced deafness (7 out of 57 in the dexamethasone group

compared with 20 out of 53 in the placebo group, p = 0.003).[10] Interestingly, all but one patient received adjunctive dexamethasone treatment. In conclusion, *S. suis* meningitis remains a rare disease in the Netherlands but should be considered in patients with professional pig contact. Hearing loss is a common complication despite adjunctive dexamethasone treatment.

Table 1. Cases of *Streptococcus suis* meningitis identified in our cohort

Case	Year	Age	Gender	Predisposing factors	Pig contact	Temperature (°C)	Headache	Neck stiffness	GCS
1	2006	39	M	None	Butcher	39.6	+	+	11
2	2006	28	M	None	Abattoir worker	36.0	?	-	11
3[a]	2007	50	M	None	Butcher	37.9	+	+	8
4	2007	62	M	None	Pig farmer	40.4	?	+	7
5	2008	40	M	M. Hodgkin	Pig farmer	38.0	+	+	10
6	2011	60	M	None	Abattoir worker	39.5	+	+	14
7	2012	77	M	Splenectomy	Pig farmer	38.8	+	-	10
8[a]	2015	58	M	None	Butcher	37.0	+	-	13

	CSF WBC	CSF glucose	CSF protein	CSF culture	Blood culture	Cranial CT	Antibiotics	DXM	Sequelae
1	8770	<0.1	10.59	+	+	Normal	Penicillin	+	Hearing loss, diplopia
2	1000	1.5	3.15	+	-	Normal	Cefotaxime	-	Hearing loss
3[a]	6760	0.6	3.34	+	-	Diffuse swelling	Amoxicillin, ceftriaxone	+	-
4	3400	3.1	2.5	+	+	Normal	Amoxicillin, ceftriaxone, penicillin	-	Hearing loss, ataxia
5	2750	0.5	3.81	+	+	Normal	Ceftriaxone	+	Hearing loss
6	6380	<0.1	5.46	+	+	Diffuse swelling	Ceftriaxone, penicillin	+	Hearing loss, cognitive impairment
7	4200	<0.1	5.28	+	+	Normal	Penicillin, amoxicillin, cefotaxime	+	Hearing loss, cognitive impairment
8[a]	2013	<0.1	3.66	+	Not done	Normal	Amoxicillin, ceftriaxone, penicillin	+	-

Abbreviations: CSF: cerebrospinal fluid; CT: Computed Tomography; DXM: dexamethasone; E: eye response; M: motor response; V: verbal response; WBC: white blood cell count
[a]Different episodes in same patient
CSF WBC: per mm^3; CSF glucose: mmol/L; CSF protein: g/L

Table 2. Cases of *Streptococcus suis* meningitis in the Netherlands reported in the literature, combined with our patients

	Episodes	Age	Male	Risk factors	Pig contact	Neck stiffness	GCS	CSF WBC[a] (/mm³)	CSF glucose (mmol/L)	CSF protein (g/L)	Blood culture positive	Hearing loss
De Ceuster[b,3]	1	60	Yes	No	Yes	Yes	14	6380	<0.1	5.46	Yes	Yes
Van de Beek[1]	4	53.5	3/4	No	4/4	3/4	10 (5-15)	1771 (213-4049)	1.6 (0.6-3.1)	4.4 (3.0-7.7)	2/4	3/4
Halaby[4]	1	63	Yes	No	Yes	Yes	8	3241	N.R.	N.R.	Yes	Yes
Arend[5]	1	57	Yes	Yes[c]	Yes	Yes	8	All pleiocytosis	<0.1	2.8	Yes	Yes
Coolen[6]	1	43	Yes	No	Yes	Yes	14	2160	N.R.	N.R.	No	Yes
Arends[7]	30	49	26/30	4/30[d]	27/30	N.R.	N.R.	1500 (50-110000)	1.5 (0.1-3.25)	3.0 (0.9-9.8)	17/30	16/30
This study	8	50	8/8	2/8	8/8	5/8	10.5	3800 (1000-8770)	0.30 (0.10-3.10)	3.74 (2.50-10.59)	5/7	6/8
Total	45	50	39/44	7/44	41/44	11/15	-	-	-	-	26/44	28/43

Abbreviations: CSF: cerebrospinal fluid; GCS: score on Glasgow Coma Scale; N.R.: not reported
[a]Continuous data is presented as median (range); [b]This patient was present in our cohort (case 6), in the summary this patient is counted only once; [c]Use of cortisone cream; [d]1 alcohol, 3 cancer

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CHAPTER 4

STREPTOCOCCUS SUIS
MENINGITIS: A SYSTEMATIC
REVIEW AND META-ANALYSIS

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Abstract

Introduction: *Streptococcus suis* is the most common cause of meningitis in pork consuming and pig rearing countries in South-East Asia. We performed a systematic review of studies on *S. suis* meningitis to define the clinical characteristics, predisposing factors and outcome.

Methods: Studies published between January 1, 1980 and August 1, 2015 were identified from main literature databases and reference lists. Studies were included if they were written in West-European languages and described at least 5 adult patients with *S. suis* meningitis in whom at least one clinical characteristic was described.

Results: We identified 913 patients with *S. suis* meningitis included in 24 studies between 1980 and 2015. The mean age was 49 years and 581 of 711 patients were male (82%). Exposure to pigs or pork was present in 395 of 648 patients (61%) while other predisposing factors were less common. 514 of 528 patients presented with fever (97%), 429 of 451 with headache (95%), 462 of 496 with neck stiffness (93%) and 78 of 384 patients (20%) had a skin injury in the presence of pig/pork contact. The case fatality rate was 2.9% and hearing loss was a common sequel occurring in 259 of 489 patients (53%). Treatment included dexamethasone in 157 of 300 (52%) of patients and was associated with reduced hearing loss in *S. suis* meningitis patients included in a randomized controlled trial.

Conclusion: *S. suis* meningitis has a clear association with pig and pork contact. Mortality is low, but hearing loss occurs frequently. Dexamethasone was shown to reduce hearing loss.

Introduction

Bacterial meningitis is a severe infectious disease with a high mortality and morbidity. The estimated incidence is 2.6-6 per 100,000 adults per year in developed countries and several times higher in low-income settings.[1] Most pathogens causing bacterial meningitis are transmitted between humans (*e.g.*, *Streptococcus pneumoniae* and *Neisseria meningitidis*), while others can be acquired through food ingestion (*e.g.*, *Listeria monocytogenes*). [1, 2] Transmission of pathogens causing bacterial meningitis can also occur directly from animals to humans, a condition referred to as zoonotic bacterial meningitis.

One of the most common zoonotic pathogens causing bacterial meningitis is *Streptococcus suis*. This pathogen has its natural reservoir in pigs and may cause meningitis, endocarditis and sepsis in humans after contact with pig or pork.[3, 4] Due to high pork consumption and frequent small scale pig rearing, *S. suis* infection is endemic in South-East Asia, where several outbreaks and cohort studies of *S. suis* meningitis have been reported.[5-8] Nevertheless, cases of *S. suis* meningitis occur all over the world,[9] particularly in patients having occupational contact with pigs or pork, such as abattoir workers and butchers.[10] The clinical manifestations, epidemiology and outcome of *S. suis* infection in humans were described in a recent systematic review and meta-analysis.[9] This review included studies through 2012 and did not review characteristics of *S. suis* meningitis separately (the condition comprised 68% of cases). We performed a systematic review on studies on *S. suis* meningitis to define the clinical characteristics, risk factors and outcome of *S. suis* meningitis.

Methods

We searched the main databases (PubMed, ScienceDirect, Google scholar) for published articles describing cases of *S. suis* meningitis, published from January 1980 to August 2015. We used the search terms "*Streptococcus suis* AND meningitis", and searched the literature for cohort studies using the term "*Streptococcus suis*". We also searched the reference lists of the articles

identified by this search strategy and selected those that we judged to be relevant. Articles written in English, Dutch, French, German, Spanish, Italian and Portuguese were included. Articles describing at least 5 patients with *S. suis* meningitis were included if at least one clinical characteristics or ancillary investigation was described, unless no sub-analysis for *S. suis* meningitis was performed (e.g. *S. suis* infection or streptococcal meningitis). All articles meeting the inclusion criteria were read and systematically processed into a database of clinical data. The variables were as follows: patient characteristics, predisposing factors, clinical presentation, ancillary investigations, and outcome. Predisposing factors were defined as 1) Contact with pigs or pork, defined as preparing pork, consumption of raw pork or other swine materials (e.g. raw pig blood), occupations related to pigs or pork (e.g. abattoir workers, butchers), or breeding pigs at home,[4] and/or 2) An immunocompromised status for bacterial meningitis caused by infection with Human Immunodeficiency Virus (HIV), a history of immunosuppressive medication, cancer, splenectomy, or alcoholism.[2] When patients were reported to be 'not immunocompromised', we assumed no immunosuppressive medication, splenectomy or HIV-infection in these patients. Skin injury was defined as cuts or scrapes, since skin rash could be misidentified as bruises (as seen in meningococcal sepsis).

As data description was heterogeneous between studies, all data are presented as number for which a characteristic was present out of the total number for which the characteristic was evaluated. We described the relevant characteristics using proportions with 95% confidence intervals (CIs) for categorical factors (sex, predisposing factors), and mean with standard deviation (SD) for continuous factors (age, laboratory parameters). For the latter, medians were converted to means by using proposed formulas.[11]

Results

Study characteristics
In total, 382 articles were assessed for eligibility (375 by searching the databases and 7 by cross-checking references) (Fig. 1). 54 articles did not meet the inclusion criteria as they described *S. suis* infection in animals. 304 articles were excluded from the review as no cases were described (183

articles), reporting less than 5 cases (88 articles), no sub-analysis possible for *S. suis* meningitis (10 articles), no *S. suis* infection described (9 articles), no meningitis described (7 articles), foreign language (5 articles) and duplicate articles (3 articles). The 24 articles included in the review described 913 patients.[7, 8, 10, 12-32] The number of included patients per study varied between 5 and 151 (median 21). The median described time-period of the studies was 6 years (ranging from 1 to 23 years). Studies were performed in Thailand (8 studies), Vietnam (6 studies), Hong Kong (5 studies), the Netherlands (3 studies), China (1 study) and Japan (1 study). Studies composed 10 single center studies, 4 multi-center studies and 10 nationwide studies. 11 studies included patients prospectively and 13 were retrospective studies.

Clinical characteristics

The pooled mean age was 48.8 years (SD 3.9, reported in 715 cases) and 581 of 711 patients (82%, 95% CI 79-85%) were male (Table 1). Predisposing factors consisted of exposure to pig or pork in 395 of 648 patients (61%, 95% CI 57-65%), alcoholism in 60 of 322 patients (19%, 95% CI 15-23%), diabetes mellitus in 11 of 209 patients (5%, 95% CI 2-8%), cancer in 5 of 85 patients (6%, 95% CI 1-11%), splenectomy in 5 of 507 patients (1%, 95% CI 0-2%) and immunosuppressive medication in 2 of 593 patients (0.3%, 95% CI 0-0.8%).

The clinical presentation of *S. suis* meningitis was characterized by fever in 514 of 528 patients (97%, 95% CI 96-98%), headache in 429 of 451 patients (95%, 95% CI 93-97%), neck stiffness in 462 of 496 patients (93%, 95% CI 91-95%), an altered consciousness in 35 of 113 patients (31%, 95% CI 23-39%) and nausea or vomiting
in 210 of 321 patients (65%, 95% CI 60-70%). The classic meningitis triad of fever, neck stiffness and altered consciousness was present in 4 out of 43 patients (9%, 95% CI 0-18%) [2]. Skin injury in the presence of pig/pork contact was present in 78 of 384 patients (20%, 95% CI 16-24%).

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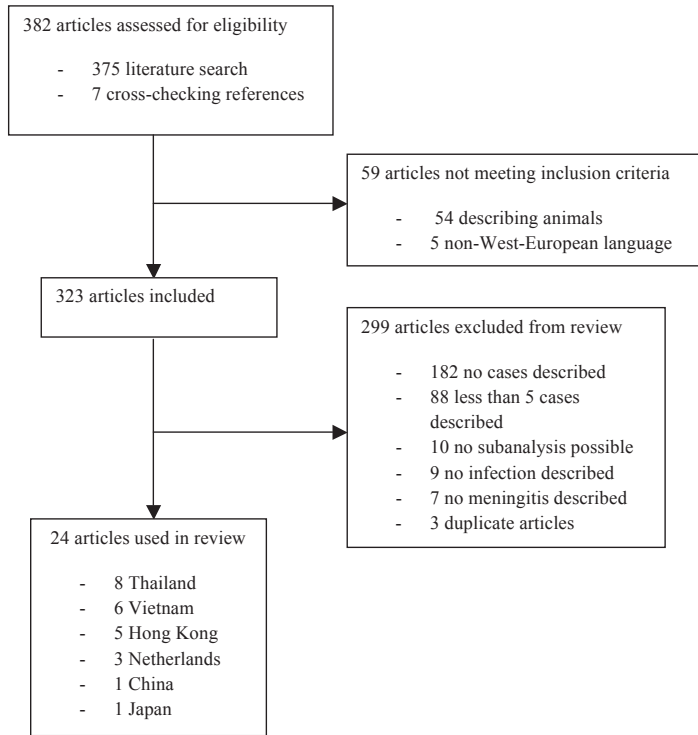
Figure 1. Flowchart systematic review *Streptococcus suis* meningitis

Ancillary investigations

The mean blood leukocyte count was 17.4 x 10^9/L (SD 0.9, reported in 322 cases). The mean blood thrombocyte count was 166.3 x 10^9/L (SD 19.1, reported in 213 cases). The mean cerebrospinal fluid (CSF) leukocyte count was 1920/mm³ (SD 757); it was reported in 395 patients and abnormal in all 913 patients. The mean CSF protein was 2.4 g/L (SD 0.8, reported in 380 patients) and the mean CSF glucose was 1.09 mmol/L (SD 0.60, reported in 177 patients).

Data on cerebrospinal fluid cultures were reported in all 913 patients, and were positive in 758 (83%, 95% CI 81-85%). Blood cultures were positive in 288 of 435 cases (66%, 95% CI 62-70%). Results of cranial CT were noted in 3 studies describing 27 patients [23, 28, 32] and consisted of cerebral edema in 8 of 27 patients (30%, 95% CI 10-50%).

Table 1. Clinical characteristics of patients with *Streptococcus suis* meningitis identified in the literature

Characteristics	n/N* (%)
Age (SD)[a,b]	48.8 (3.9)
Male	581/711 (82%)
Predisposing factors	
Alcoholism	60/322 (19%)
Diabetes mellitus	11/209 (5%)
Splenectomy	5/507 (1%)
Immunosuppressive medication	2/601 (0.3%)
Cancer	5/85 (6%)
Exposure to pigs/pork	395/648 (61%)
Clinical presentation	
Skin injury in the presence of pig/pork contact	78/384 (20%)
Headache	429/451 (95%)
Fever	514/528 (97%)
Neck stiffness	462/496 (93%)
Altered consciousness	35/113 (31%)
Classic meningitis triad[1]	4/43 (9%)
Nausea/vomiting	210/321 (65%)
Blood characteristics	
Leukocytes[a,c]	17.4 (0.9)
Thrombocytes[a,d]	166.3 (19.1)
Cerebrospinal fluid characteristics	
Leukocytes/mm^3 , SD[a,e]	1920 (757)
Protein (g/dL), SD[a,f]	2.4 (0.8)
Glucose (mmol/L), SD[a,g]	1.09 (0.60)
Positive cultures	
Cerebrospinal fluid	758/913 (83%)
Blood	288/435 (66%)
Adjunctive dexamethasone	157/300 (52%)
Outcome	
Death	17/581 (3%)
Hearing loss	259/489 (53%)
Other sequelae	35/286 (12%)
Full recovery	116/320 (36%)

N* number of patients in whom the symptom was reported
[1]Triad of fever, neck stiffness and altered consciousness
[a]Means are recalculated from means and medians; [b]reported in 715 cases; [c]reported in 322 cases;
[d]reported in 213 cases; [e]reported in 395 cases; [f]reported in 380 cases; [g]reported in 177 cases

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Treatment

The majority of patients was treated with ceftriaxone (250 patients) or penicillin (102 patients) monotherapy; no antibiotic resistance for these antibiotics was found in the 182 cases where the resistance pattern

was determined. Antibiotic resistance for tetracycline was reported in 2 studies.[7, 33] In some studies, patients were treated with either penicillin or ceftriaxone (101 patients), but the exact number of patients receiving either treatment was not reported.[23, 24, 29, 31] In 454 patients, the type of antibiotic treatment was unknown. 157 of 300 patients (52%, 95% CI 44-60%) received adjunctive dexamethasone. The majority of these patients were included in a randomized controlled trial in which 71 patients received adjunctive dexamethasone and 69 patients received placebo.[7] In the other studies, dexamethasone was given at the discretion of the treating physician.

Outcome

The case fatality rate was 2.9% (17 of 581 patients, 95% CI 1.9-3.9%) and 116 of 320 patients (36%, 95% CI 31-41%) recovered without sequelae. An association between dexamethasone and death could not be established because numbers of patients who died were small. Data from the RCT showed no patients died in dexamethasone group versus three in the placebo group.[34] Hearing loss was present in 259 of 489 patients (53%, 95% CI 49-57%). 68 of these patients were screened at admission for hearing loss and this was present in 60 patients (88%, 95% CI 80-96%). According to a study describing 41 patients with hearing loss in *S. suis* meningitis, 38 had hearing loss on admission and 3 developed hearing loss during admission.[23] Another study described 16 patients with *S. suis* meningitis and hearing loss, with hearing loss persisting in 7 patients (44%).[28] Other neurological sequelae were present in 35 of 286 patients (12%, 95% CI 8-16%) and consisted of ataxia in 19 patients, cognitive impairment in 2, tinnitus in 2, and were not specified in 12.

A randomized controlled trial showed that dexamethasone was significantly associated with a reduction in hearing loss in at least one ear (38% to 12%, p = 0.003) and a reduction in severe (>80 dB) hearing loss (odds ratio 0.23 [95% CI, 0.06–0.78]), using a multivariate analysis including age >50 and CSF bacterial load.[7] A recent case series from the Netherlands showed that despite dexamethasone treatment 6 out of 7 patients with *S. suis* meningitis had hearing loss upon discharge.[32]

Discussion

Meningitis is the most frequently described presentation of *S. suis* infection, occurring in approximately 50-60% of reported *S. suis* infected patients.[9] Despite the geographical distribution, there were no significant differences for clinical presentation and outcome in *S. suis* meningitis between the different studies and low-/high-income countries. In our meta-analysis the main risk factor for *S. suis* meningitis was exposure to pigs or raw pork. This confirms the findings by a single center case-control study from Vietnam of 101 patients with *S. suis* infection which showed an odds ratio of 6.33 for occupations related to pigs.[16] Another previously reported potential risk factor was alcoholism, which we identified in 16% of patients. Alcoholism was not an independent risk factor for contracting *S. suis* meningitis when corrected for other predisposing factors in Vietnam.[16] However, alcoholism has been associated with an increased risk of infection in general and of an unfavorable outcome of bacterial meningitis.[35]

Skin injury in the presence of pig/pork contact was described in 20% of the cases, which is similar to the previously observed 25% skin injuries in all types of *S. suis* infections.[9] *S. suis* may directly pass into the blood stream after exposure to pigs or pork in the presence of skin injuries, even without visible wound infection.[10, 16, 36] Patients with an increased risk of infection, e.g. because of splenectomy or use of immunosuppressive medication, should avoid direct pig or pork contact when skin lesions, particularly on the hands, are present. Skin protection has been suggested to reduce the incidence of *S. suis* infection.[16]

Direct exposure to pigs or pork was described for 61% of meningitis cases. Direct pig exposure was documented in the majority of the European cases of *S. suis* infection, but was reported in less than half of the Asian cases, suggesting that other mechanisms may be involved in those patients.[16] A recent study showed that the gastro-intestinal tract is an entry site for *S. suis,*[36] supporting the epidemiological evidence that ingestion of *S. suis* contaminated food is a risk factor for infection.[9, 16, 37]

The sensitivity of the classic triad of bacterial meningitis consisting of fever, neck stiffness, and altered mental status was low (9%). This was mainly due to the low frequency of altered mental status, since other symptoms and

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signs of bacterial meningitis were present in a large proportion of patients. In patients with a history of regular pig exposure or pork consumption, hearing loss and these symptoms, meningitis due to *S. suis* should be suspected, and CSF examination should be performed to get diagnostic certainty.[3]

We found that the mortality of *S. suis* meningitis was low (3%), especially when compared with pneumococcal meningitis (20%) and *Listeria monocytogenes* meningitis (36%).[38, 39] The mortality rate was also lower than reported for general invasive infection caused by *S. suis* (13%).[12] The difference between mortality in *S. suis* meningitis and other types of *S. suis* infection (such as sepsis) has been noted before,[6, 8, 9, 19] but the mechanism causing this difference needs to be further elucidated.[9] Similar differences between meningitis and sepsis case fatality rates have been reported for invasive meningococcal disease.[40]

The mortality rate was low but many surviving patients have sequelae. The most common sequel is hearing loss occurring in 53% of the patients; variable rates of hearing loss have been reported in other types of bacterial meningitis, with 8% in meningococcal meningitis and 22% in pneumococcal meningitis.[2] Hearing loss in *S. suis* meningitis may be a presenting symptom or develop during admission,[23] and does not always persist.[28] Different hypotheses for hearing loss in *S. suis* meningitis are described in the literature such as direct infection of the auditory nerve and suppurative labyrinthitis.[41] For patients with meningitis in whom *S. suis* is identified, it is important to consult the otorhinolaryngologist early in the clinical course for audiometry and evaluate whether cochlear implantation is possible.[42]

Dexamethasone has been shown to decrease mortality in pneumococcal meningitis and to decrease hearing loss and neurological sequelae in all bacterial meningitis cases.[43, 44] For *S. suis* meningitis, an effect on mortality has not been established.[34] One randomized controlled trial on dexamethasone in bacterial meningitis, performed in Vietnam, included a substantial number of *S. suis* meningitis.[34] A subsequent analysis of all *S. suis* patients showed dexamethasone reduced hearing loss in a multivariate analysis.[7] As a recent case-series showed, hearing loss is still observed in patients treated with dexamethasone,[32] additional randomized clinical trials

on the effect of dexamethasone in *S. suis* meningitis would be desirable to further evaluate whether there is a benefit. However, it is unlikely such a trial is going to be performed for practical and financial reasons. Based on the available evidence, dexamethasone treatment in regions with high rates of *S. suis* as cause of meningitis appears reasonable to potentially reduce the very high rate of post-meningitic hearing impairment.

This review has several limitations. First, most included studies show a selection bias due to a retrospective character. A recent study showed evidence of publication bias in *S. suis* meningitis.[9] *S. suis* meningitis is probably underreported, and often in numbers of less than 5 cases, which was an exclusion criterion for this study. Second, reporting of clinical characteristics, ancillary investigations and outcome was highly diverse between the included studies. We have presented the total number of patients in whom the specific characteristic was reported, but we could not perform a risk factor analysis due to heterogeneity in data. Third, cases of *S. suis* meningitis might have been missed due to a negative CSF culture caused by pre-treatment with antibiotics.

In conclusion, *S. suis* meningitis is predominantly seen in men after contact with pigs or pork and is endemic in pig rearing and pork consuming countries such as Vietnam, Thailand and China. The typical clinical presentation consists of hearing loss, fever, headache and neck stiffness, and skin injury in the presence of pig/pork contact is present in 20% of the cases. Although the mortality of *S. suis* meningitis is low compared with *S. suis* infection in general and other causes of bacterial meningitis, 53% of patients end up with hearing loss.

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CHAPTER 5

CAPNOCYTOPHAGA CANIMORSUS MENINGITIS: THREE CASES AND A REVIEW OF THE LITERATURE

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Abstract

Introduction: Bacterial meningitis is a disease with a high morbidity and mortality. It may be caused by the zoonotic pathogen *Capnocytophaga canimorsus*, which is part of the commensal oral flora in dogs and cats.

Methods: We report three cases of *C. canimorsus* meningitis in a nationwide cohort study of bacterial meningitis patients and performed a review of the literature.

Results: Three episodes of *C. canimorsus* meningitis were identified in three patients included in a nationwide cohort study from 2006 through 2014. The calculated annual incidence was 0.03 per million adults. When combined with the literature, 33 patients were identified of which 28 were male (85%). The median age was 63 years, and 13 (42%) were immunocompromised, which consisted of alcoholism in 7 (21%). Animal contact could be established in 29 of 30 patients (93%) and consisted of dog bites in 22 of 29 (76%). One patient died (3%) and 8 had neurological sequelae upon discharge (25%), most often hearing loss (n = 6, 19%).

Conclusion: *Capnocytophaga canimorsus* meningitis is associated with dog bites. Although mortality is relatively low, survivors often have neurological sequelae.

Introduction

In the Netherlands, the incidence of bacterial meningitis is 2.6-6 per 100.000 adults per year.[1] Bacterial meningitis is caused by *Streptococcus pneumoniae* and *Neisseria meningitidis* in approximately 85% of adults.[2] Most pathogens causing bacterial meningitis are transmitted between humans (*S. pneumoniae*, *N. meningitidis*, *Haemophilus influenzae*) while others can be acquired through food ingestion (*Listeria monocytogenes*).[2] Transmission of pathogens causing bacterial meningitis can also occur from animals to humans, known as zoonotic bacterial meningitis.

One of these zoonotic pathogens is *Capnocytophaga canimorsus*. This pathogen is part of the commensal oral flora in dogs and cats and may cause meningitis, other infections and sepsis, especially in the immunocompromised.[3] We report three cases of *C. canimorsus* meningitis of which two occurred in healthy individuals. Additionally, we performed a systematic review of the literature on cases of *C. canimorsus* meningitis.

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Methods

In a prospective nationwide observational cohort study in the Netherlands, we included episodes of community-acquired bacterial meningitis confirmed by culture of cerebrospinal fluid in adults. Methods have been described previously.[2] In summary, patients were at least 16 years of age and were listed in the database of the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) from January 2006 to December 2014. This laboratory receives cerebrospinal fluid (CSF) isolates from approximately 90% of all patients with bacterial meningitis in the Netherlands. The NRLBM provided daily updates of the names of the hospitals where patients with bacterial meningitis had been admitted in the preceding days. Physicians were contacted, and written informed consent was obtained from all participating patients or their legally authorized representatives. From this cohort, we selected all patients with *C. canimorsus* grown in CSF or blood. Episodes reported by physicians with negative CSF cultures could also be included if all of the following criteria were present: (i) blood cultures showed *C. canimorsus*, (ii) CSF analysis showed at least one individual predictor of

bacterial meningitis defined as a glucose level of <1.9 mmol/L, a ratio of CSF glucose to blood glucose of <0.23, a protein level of more than 2.20 g/L, or a leukocyte count of more than 2000/mm³;[4] and (iii) the clinical presentation was compatible with bacterial meningitis.

Excluded were the following: (i) patients with hospital-associated meningitis, (ii) patients with a neurosurgical device (implant) *in situ* and (iii) patients who had undergone a neurosurgical operation within one month before the onset of bacterial meningitis. An immunocompromised status was defined as: patients who used immunosuppressive drugs, patients with asplenia, diabetes mellitus, alcoholism, or infection by human immunodeficiency virus (HIV).[5]

The study was approved by the ethics committee of the Academic Medical Centre, Amsterdam, The Netherlands.

A literature search was performed using the terms 'canimorsus AND meningitis' and 'fermenter AND meningitis', as the former name of *Capnocytophaga canimorsus* was *dysgonic fermenter* type 2. All articles were checked for cross-references. Articles written in English, Dutch, French, Spanish, German, Italian and Portuguese were included. Articles written in other languages and articles concerning children or animals were excluded. We excluded articles in which subanalysis for *C. canimorsus* meningitis was impossible or lacking proper description of cases and articles describing patients in whom no CSF analysis was performed

Results

In our cohort, 1561 cases of bacterial meningitis were included. Bacterial meningitis was caused by *C. canimorsus* in 3 cases. The calculated annual incidence was 0.03 per million adults (Tables 1 and 2).

Case 1

A 78-year-old man without medical history was found unconscious at his home. Physical examination showed a temperature of 37.7°C, neck stiffness and an altered mental status; he opened his eyes on command and performed simple tasks, but did only speak a few words (score on Glasgow Coma Scale E3M6V3). Cranial CT was performed and showed no abnormalities.

A lumbar puncture revealed opalescent CSF with 901 leukocytes/mm^3, a protein concentration of 3.46 g/L and a glucose concentration of 1.4 mmol/L. The patient was admitted to the intensive care and treated with intravenous (i.v.) amoxicillin 2 g six times daily for 10 days, i.v. ceftriaxone 2 g two times daily for 2 weeks and i.v. dexamethasone 10 mg QID for 4 days. After 3 days, CSF and blood cultures showed *C. canimorsus*. He regained consciousness within 24 h and recovered completely. He remembered being bitten by his dog four days prior to admission. He was discharged without sequelae.

Case 2

A 37-year-old man presented on the emergency department with fever, headache and nausea. Medical history revealed alcohol abuse. He was bitten by a dog four days prior to admission. Physical examination showed a temperature of 38.5°C and a generalized rash, but no other abnormalities. Cranial CT showed no abnormalities. Lumbar puncture revealed opalescent CSF with 2376 leukocytes/mm^3, protein concentration of 2.61 g/L and glucose concentration of 3.7 mmol/L. He was treated with i.v. amoxicillin 2 g six times daily for 3 days, i.v. ceftriaxone 2 g two times daily for 20 days, i.v. acyclovir for 3 days and i.v. dexamethasone 10 mg QID for 4 days. After 5 days, CSF cultures showed *C. canimorsus*; blood cultures remained negative. The rash and fever disappeared, but headache, disorientation and concentration problems persisted; he was discharged to a rehabilitation facility.

Case 3

A 60-year-old man presented with fever and headache since three days. His medical history revealed a basal cell carcinoma on his right ear. Previous animal contact was unknown. Physical examination showed a generalized rash, a temperature of 38.5°C and an altered mental status; patient opened his eyes on command, localized to pain and produced sounds but no recognizable words (score on Glasgow Coma Scale E3M5V2). Lumbar puncture revealed clear CSF containing 828 leukocytes/mm^3, protein concentration of 1.9 g/L and glucose concentration of 3.0 mmol/L. The patient was treated with amoxicillin 2 g four times daily for 2 weeks, meropenem 2 g three times daily for 12 days, ceftriaxone 2 g two times

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daily for 1 day and dexamethasone 10 mg QID for 4 days. After 5 days, the CSF and blood culture showed *C. canimorsus*. The patient recovered and was discharged without sequelae.

Table 1. Clinical characteristics of patients with *Capnocytophaga canimorsus* meningitis identified in our cohort

Characteristics	Case 1	Case 2	Case 3
Year of admission	2008	2013	2013
Age	78	37	60
Gender	Male	Male	Male
Predisposing factor	None	Alcoholism	None
Dog contact	Bitten	Bitten	Unknown
Clinical characteristics			
Temperature (°C)	37.7	38.5	38.5
Headache	Unknown	Yes	Yes
Neck stiffness	Yes	No	No
Glasgow Coma Scale	12	15	10
Cerebrospinal fluid findings			
CSF leukocyte count/mm^3	901	2376	828
CSF protein (g/L)	3.46	2.61	1.90
CSF glucose (mmol/L)	1.4	3.7	3.0
Cerebrospinal fluid culture	+	+	+
Blood culture	+	-	+
Cranial CT	Normal	Normal	Not done
Empirical treatment			
Antibiotics	Amoxicillin, ceftriaxone	Amoxicillin, ceftriaxone	Amoxicillin, ceftriaxone, meropenem
Dexamethasone	Yes	Yes	Yes
Outcome	Complete recovery	Hearing loss, cognitive defects, ataxia	Complete recovery

Abbreviations: CSF: cerebrospinal fluid; CT: Computed Tomography

Review of the literature

We searched the literature and found 32 articles. Five additional articles were added by cross-reference checking. One article described a child and was therefore excluded. Fifteen more articles were excluded as no *C. canimorsus* meningitis cases were described (10 articles). Subanalysis for *C. canimorsus* meningitis was not possible in three articles. One article was excluded because it was in Danish and another article described a case that had been described elsewhere. For the review, 21 articles were

used, describing 30 cases.[6-26] (Table 3) We combined the cases identified in our cohort with the cases reported in the literature, describing a total of 33 cases of *C. canimorsus* meningitis. The median age was 63 years (range 26-83) and 28 of 33 patients were male (85%). Thirteen of 31 patients (42%) were immunocompromised: seven had a history of alcohol abuse, three had undergone a splenectomy, and three used immunosuppressive medication.

Table 2. Clinical characteristics, etiology and clinical outcome for adults with *Capnocytophaga canimorsus* meningitis; combination of our patients and patients reported in the literature

Characteristics	n/N (%)
Median age	63
Male sex	28/33 (85)
Immunocompromised	13/31 (42)
Alcohol	7
Splenectomy	3
Immunosuppressive medication	3
Animal contact	29/30 (97)
Bitten	22 (76)
Not bitten, but dog owner	5 (17)
Wounds licked by dog	1 (3)
Scratched by cat	1 (3)
Clinical presentation	
Headache	19/28 (68)
Fever	26/28 (93)
Neck stiffness	17/28 (61)
Altered mental status	14/28 (50)
≥2 predictive symptoms[a]	27/28 (96)
Meningitis triad[b]	8/28 (29)
Cerebrospinal fluid characteristics	
Median CSF leukocyte count/mm^3	951
Median CSF protein (g/L)	1.91
Median CSF glucose (mmol/L)	1.9
Individual predictive factors[c]	18/26 (69)
Positive cultures	
Cerebrospinal fluid	26/33 (79)
Blood	12/14 (86)
Complications	
Death	1/33 (3)
Hearing loss	6/32 (19)
Other sequelae	3/32 (9)

Abbreviations: CSF: cerebrospinal fluid
[a]At least two of the four symptoms of headache, fever, neck stiffness and altered mental status; [b]defined as fever, neck stiffness, and altered mental status; [c]defined as a CSF leukocyte count above 2000/mm^3, a CSF protein above 2.2g/L, or a CSF glucose <1.9mmol/L

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Table 3. Cases of *Capnocytophaga canimorsus* meningitis reported in the literature, combined with our patients

Study	Age	Gender	Predisposing conditions	Animal contact	Symptoms	CSF leukocyte count / mm³	CSF protein (g/L)	CSF glucose (mmol/L)	Day of positive culture	Complications
Popiel[6]	56	M	Alcoholism	Dog bite	1;2;4	855	2.70	0.2	CSF: negative, blood: 7	Ventriculitis
Monrad[7]	66	M	Alcoholism	Dog bite	2;3;5	1814	2.76	0.2	CSF: 11	Hearing loss
Monrad[7]	67	F	Splenectomy	Dog bite	1;2	2120	1.91	1.8	CSF: 5	Transient paresis right arm, hearing loss
Monrad[7]	79	M	No	Dog bite	2;3;4	234	2.21	0.2	CSF: 6	Hearing loss
Gasch[8]	64	M	No	Dog bite	1;2;3;5	730	0.79	3.1	CSF: 2	Hearing loss
Gibou[9]	60	M	No	Dog bite	1;2;3;6	420	0.81	2.6	CSF: 5, blood: 6	No
Gibou[9]	60	M	No	Dog bite	1;2;3;5;6	70	0.62	3.6	CSF: 6	Hearing loss
De Boer[10]	69	M	Immunosuppressants	Dog bite	2;3;4;6	1024	1.73	1.7	CSF: 12	No
De Boer[10]	58	M	No	No	1;2	1566	1.3	2.0	CSF: negative, blood: 9	No
Risi[11]	65	F	Myelography[a]	Dog owner	3;4	1138	1.92	0.1	CSF: negative	No
Risi[11]	65	M	No	Dog bite	1;2;3;4	1226	3.28	2.0	CSF: 2	No
Drouet[13]	60	M	No	Dog owner	1;2;3;4	4000	5.02	1.0	CSF: 18	No
Gottwein[14]	54	M	Alcoholism	Dog bite	1;2;3	1001	1.69	1.8	CSF: 5, blood: 7	No
Biedermann[15]	63	M	Alcoholism	Dog licked wounds	1;2	1720	3.89	1.9	CSF: negative, blood: 2	Hyponatremia, disorientation
Le Moal[16]	45	M	Alcoholism	Dog bite	1;2;3;4	1240	1.65	1.8	CSF: 9	No
Mendioroz[17]	64	M	Immunosuppressants	Dog bite	1;2	3200	2.73	3.3	CSF: 3	No
Kampinga[18]	63	M	No	Dog bite	1;2;4	597	2.10	3.0	CSF: 3, blood: 4	No
Lion[19]	54	M	Alcoholism	Dog bite	2;3;4	N.R.	N.R.	N.R.	CSF: 4, blood: 3	No
Lion[19]	57	M	No	Dog bite	2;3;4	N.R.	N.R.	N.R.	CSF	No
Pers[20]	74	M	No	Dog bite	N.R.	240	Elevated	Low	CSF	Cardiac arrest, death
Pers[20]	80	M	No	Dog bite	N.R.	>1700	Elevated	Low	CSF	No

Study	Age	Sex	Risk factor	Exposure	Symptoms	Cell count	Protein	Glucose	Culture	Sequelae
Pers[20]	83	M	Immunosuppressants	N.R.	N.R.	245	Elevated	Low	CSF	No
Pers[20]	42	M	Unknown	N.R.	N.R.	>1700	Elevated	Low	CSF: negative	No
Pers[20]	74	M	Unknown	Dog owner	N.R.	>1700	Elevated	Low	CSF	No
Blanche[21]	57	M	No	Dog bite	1;2;4	434	1.59	2.4	CSF: 5, blood: 5	No
Krol-van Straaten[22]	75	F	Splenectomy	Dog bite	2;3;4	2000	N.R.	N.R.	CSF: 4	No
Imanse[23,b]	39	F	No	Dog owner	1;2;3;5	480	0.32	3.7	CSF: negative, blood: 1	Hearing loss
Chan[24]	63	M	No	Dog bite	2;6	1121	1.75	2.1	CSF: 1	No
Carpenter[25]	26	M	Splenectomy	Cat scratch	1;2;6	520	1.43	1.1	CSF: negative, blood: 3	No
Ofori-Adjei[26]	66	F	No	Dog owner	1;2;3;6	575	2.4	1.2	CSF: 5	No
This study	78	M	No	Dog bite	3;4	901	3.46	1.4	CSF: 3, blood: 3	No
This study	37	M	Alcoholism	Dog bite	1;2	2376	2.61	3.7	CSF: 5, blood: negative	Cognitive impairment, ataxia, tinnitus
This study	60	M	Basal cell carcinoma	Unknown	1;2;4	828	1.90	3.0	CSF: 5, blood: 5	No

Abbreviations: N.R.: not reported; M: male; F: female; CSF: cerebrospinal fluid
[a]This patient underwent a myelography by a dog-owning radiologist and radiology technician; [b]this patient was not treated with antibiotics
Symptoms: 1: headache; 2: fever; 3: neck stiffness; 4: altered mental status; 5: hearing loss; 6: photophobia

Animal contact was known in 30 of 33 patients (91%). In one of these 30 patients, no animal contact could be identified.[10] For the other patients, the majority was bitten by a dog (22 of 29, 76%); none of these had a wound infection at the site of the bite. In the remaining seven patients, five owned a dog,[11, 13, 20, 23, 26] one was scratched by a cat,[25] and one patient let his dog lick his varicose wounds.[15]

The clinical presentation was reported in 28 patients. Headache was present in 19 patients (68%), fever (temperature ≥38°C) in 26 (93%), neck stiffness in 17 (61%), altered mental status (score on Glasgow Coma Scale ≤13) in 14 patients (50%) and four patients (14%) presented with hearing loss. Twenty-seven patients (96%) had at least two of the four symptoms of headache, fever, neck stiffness and altered mental status. The classic meningitis triad of fever, neck stiffness and altered mental status was present in eight patients (29%).

Lumbar puncture was performed in all patients, and results of CSF analysis were reported for 31 cases. Typical abnormalities predictive of bacterial meningitis were present in 18 of 26 patients (69%).
CSF leukocyte count was reported for 28 cases. CSF leukocytes were elevated in all patients. The median CSF leukocyte count was $951/mm^3$, ranging from 70 to $2376/mm^3$. Fourteen of 31 patients (45%) had a leukocyte count under $1000/mm^3$. CSF protein was reported in 25 cases and showed a median CSF protein of 1.91 g/L, ranging from 0.32 to 5.02 g/L. CSF glucose concentration was reported in 25 cases and showed a median CSF glucose of 1.9 mmol/L.

CSF culture was performed in all and was negative in seven patients (21%). In six of those patients, the blood culture became positive, and *C. canimorsus* meningitis was diagnosed based on the positive blood culture combined with CSF abnormalities. In the other patient, the cultures remained negative, but after 8 weeks CSF broad PCR targeted at the bacterial 16S rRNA gene followed by sequencing was performed which showed *C. canimorsus*.[11] CSF cultures became positive after a median of 5 days (range: 2-18, 25-75% range: 3-6; known for 21 cases). In six cases, CSF cultures became positive after the fifth day (29%). Results of blood culture were reported for 14 patients and were positive in 12. Median time to blood culture positivity was 4.5 days (range 1-9); blood cultures remained negative in two cases.

Complications during admission were present in two patients; one patient developed ventriculitis and one patient developed hyponatremia. One patient died due to cardiac arrest (mortality 3%).[20] Sequelae were present in eight of 32 surviving patients (25%) and consisted of hearing loss in six (19%), cognitive impairment in two, and ataxia and tinnitus in one patient. There was no significant difference for complications between patients with and without an immunocompromised status (five complications in 13 patients (38%) versus five complications in 20 patients (25%), p = 0.46, Fisher's Exact test). The rate of complications was higher in patients with alcoholism compared with those without (four in seven patients (57%) versus six in 26 patients (23%), p = 0.16, Fisher's exact test), although this did not reach statistical significance.

Discussion

Capnocytophaga canimorsus meningitis has a calculated annual incidence of 0.03 per million in the Netherlands. Only 30 cases have been reported in the literature, reflecting the rarity of *Capnocytophaga canimorsus* as cause of bacterial meningitis. Dog or cat contact could be established in all but one patient. Approximately 164 million American households (63%) have at least one cat or dog,[27] and over 350 000 Americans are treated for non-fatal dog bite-related injuries on annual basis.[27] As *C. canimorsus* is present in respectively 21% and 19% of the oral flora of cats and dogs,[28] the chance of developing *C. canimorsus* meningitis after a dog bite is very low. However, post-exposure antibiotic therapy after a dog bite probably prevents infection by canine pathogens.

Male gender and an immunocompromised state (mostly splenectomy and alcoholism) were found to be relatively frequent in *C. canimorsus* meningitis patients. Seven patients diagnosed with *C. canimorsus* meningitis in this study had a previous history of alcoholism. Alcoholism is a risk factor of bacterial meningitis and has been associated with a high rate of unfavourable outcome.[29] Three cases identified in the literature were found to occur in patients who had undergone splenectomy. Patients without functional spleen due to splenectomy or functional asplenia are at increased risk for

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(fulminant) bacterial sepsis and meningitis, and require regular vaccination against common pathogens of meningitis such as pneumococci.[30] In the population of *C. canimorsus* meningitis, the number of splenectomised patients is relatively high, suggesting this to be a risk factor. Prophylactic treatment of splenectomised patients who are bitten by dogs should therefore be considered.[31]

C. canimorsus sepsis is reported to have a more fulminant course involving more complications in immunocompromised patients compared with immunocompetent patients.[19, 32] In our meta-analysis, we did not find that immunocompromised patients had a worse outcome compared with immunocompetent patients.

We found that the median time for the CSF culture to turn positive in *C. canimorsus* is 5 days, with a range of 1-19 days, and 29% of CSF cultures become positive after the fifth day. This implies that cultures from meningitis patients with dog contact should not be discontinued early. *C. canimorsus* is a slow-growing, gram-negative rod which is difficult to culture on blood agar.[18] The gold standard for detecting *C. canimorsus* in culture-negative CSF is 16S rRNA gene amplification followed by sequencing of the PCR product, which is a highly sensitive molecular method and has been widely implemented.[12, 32] In patients with meningitis after dog bites and negative CSF cultures after 24 h, 16S rRNA gene amplification followed by sequencing of the PCR product might be used to detect *C. canimorsus*, as was described in one case.[11]

Capnocytophaga canimorsus strains can also be identified with MALDI-TOF (matrix-assisted laser desorption/ionisation time-of-flight analyser): in one study, it was able to identify six of six blood *C. canimorsus* strains, 13 of 14 wound strains and two of two ATCC reference strains.[33]

Other pathogens than *C. canimorsus* originating from dogs have been described to cause meningitis. *Capnocytophaga cynodegmi*, a similar pathogen, may cause several infections, varying from a local wound infection to endocarditis and meningitis, and is more frequently found in the immunocompromised.[34] The clinical characteristics are similar to those of *C. canimorsus* meningitis and it may be hard to distinguish between *C. cynodegmi* and *C. canimorsus* microbiologically.[33, 35] As both respond to the

recommended empirical antibiotic treatment used for meningitis,[2] the exact subtyping is clinically less relevant. Another pathogen found in the oral cavity of healthy dogs is *Pasteurella multocida*. This pathogen is reported to cause infections in previously healthy individuals after animal bites and animal kissing.[36, 37] Patients with *P. multocida* meningitis occasionally have accompanying neurological diseases such as encephalitis.[37, 38] In the literature, the most frequently used therapy is penicillin, but resistance has been reported; therefore, the recommended antimicrobial therapy is meropenem or vancomycin.[36]

Limitations of this study were that only patients with culture-proven *C. canimorsus* meningitis were included in our cohort study and the literature review, as 21% of the reported patients in our meta-analysis have a negative CSF culture and 16S rRNA analysis is not performed standardly. As post-exposure antibiotic prophylaxis is regularly administered after a dog bite, this may be a cause of negative CSF cultures. Furthermore, not all patients with suspected bacterial meningitis may undergo a lumbar puncture, for example patients with coagulopathy due to sepsis or those with space occupying lesions on cranial imaging. This may have led to a possible underestimation of the incidence of *C. canimorsus* meningitis. In our meta-analysis, specific characteristics of interest were not always available in the retrieved case reports. Therefore, we have presented the total number of patients for whom the specific characteristic was reported. In addition, we restricted our cases to the adult population. The main focus of our research is bacterial meningitis in adults, and we excluded children from the literature review. Finally, publication bias may play a role in the small number of cases reported.

In conclusion, *C. canimorsus* meningitis is a rare disease. It has a clear association with dog bites and an immunocompromised status. As CSF cultures may remain negative during the first days, molecular diagnostic tools based on16S rRNA gene amplification of bacterial DNA in CSF following PCR is recommended in patients with meningitis after a dog bite and negative initial CSF cultures. When bacterial meningitis occurs after a dog bite, other pathogens originating from dogs as a cause of the bacterial meningitis should be kept in mind when the choice for empirical antibiotic treatment is made.

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CHAPTER 6

CAMPYLOBACTER FETUS MENINGITIS IN ADULTS: REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

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Abstract

Introduction: The zoonotic pathogen *Campylobacter fetus* is a rare cause of bacterial meningitis. Little is known about the clinical characteristics, predisposing factors and outcome of *C. fetus* meningitis in adults.

Methods: We report cases of *C. fetus* meningitis in a nationwide cohort study of adult bacterial meningitis patients in the Netherlands and performed a review of the literature.

Results: Two patients with *C. fetus* meningitis were identified from January 2006 through May 2015. The calculated annual incidence was 0.02 per million adults. Combined with the literature, we identified 22 patients with a median age of 48 years. An immunocompromised state was present in 16 patients (73%), mostly due to alcoholism (41%) and diabetes mellitus (27%). The source of infection was identified in 13 out of 19 patients (68%), consisting of regular contact with domestic animals in 5 and working on a farm in 4. Recurrent fever and illness was reported in 4 patients (18%), requiring prolonged antibiotic treatment. Two patients died (9%) and 3 survivors (15%) had neurological sequelae.

Conclusion: *C. fetus* is a rare cause of bacterial meningitis and is associated with an immunocompromised state. Based on the apparent slow clinical response seen in this limited number of cases, the authors of this study recommend a prolonged course of antimicrobial therapy when *C. fetus* is identified as causative agent of bacterial meningitis. Cases appeared to do best with carbapenem therapy.

Introduction

Bacterial meningitis is a severe infectious disease requiring prompt antibiotic treatment. Most cases are caused by *Neisseria meningitidis* and *Streptococcus pneumoniae*, which are both part of the commensal nasopharyngeal flora in humans.[1] Bacterial meningitis is rarely caused by bacteria having their natural reservoir in animals. One of these so-called zoonotic pathogens is *Campylobacter fetus* (formerly *Vibrio fetus, Spirillum serpens*), which is part of the commensal flora in the gastro-intestinal tracts of sheep and cattle.[2] *C. fetus* meningitis occurs worldwide, but little is known about its clinical characteristics, predisposing factors and outcome. We report 2 cases of *C. fetus* meningitis from a nationwide cohort of bacterial meningitis patients in the Netherlands. Additionally, we performed a review of the literature on *C. fetus* meningitis.

Methods

We included patients with community-acquired bacterial meningitis in a nationwide prospective cohort study in the Netherlands between January 2006 and May 2015. Methods have been described previously.[1] Patients were listed in the database of the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM), which receives >90% of the cerebrospinal fluid (CSF) isolates of all adult patients (>16 years) with CSF culture confirmed bacterial meningitis. The NRLBM provided daily updates of the hospitals where the patients were admitted and the patients' physicians, who were subsequently contacted. Physicians could also include patients without report of the NRLBM. Written informed consent was obtained from all patients or their legally authorized representatives. The study was approved by the medical ethical review board of the Academic Medical Center, Amsterdam, the Netherlands.

From the cohort, we selected patients with *C. fetus* meningitis. Additional information on risk factors was retrospectively collected from the discharge letters. Patients were considered immunocompromised if they had cancer, diabetes mellitus, alcoholism, asplenia, HIV-infection, or use of immunosuppressive medication.[1]

Individual predictive factors in the cerebrospinal fluid were defined as follows: a glucose level of < 34 mg/dL (1.9 mmol/L), a ratio of CSF glucose to blood glucose of < 0.23, a protein level of > 220 mg/dL, or a leukocyte count of > 2000/mL (Spanos criteria).[3]

Review of the literature

We performed a literature search using the search terms "*Campylobacter fetus* AND meningitis," "*Vibrio fetus* AND meningitis," and "*Spirillum serpens* AND meningitis". Studies written in English, German, French, Dutch, Spanish, Italian, and Portuguese were included. Articles describing animals and articles describing children were excluded. We also excluded articles in which no subanalysis for *C. fetus* meningitis cases was performed, or when no clinical characteristics were described. Additional studies were identified by cross-checking references.

In a meta-analysis of clinical data we systematically scored clinical presentation, predisposing factors, ancillary investigations, and outcome. Differences between groups were calculated by means of Fisher's Exact Test.

Results

Case reports in prospective nationwide cohort study

Two patients with *C. fetus* meningitis were identified in our nationwide cohort consisting of 1732 patients (0.1%). The calculated annual incidence of *C. fetus* meningitis in the Netherlands was 0.02 per 1,000,000 adults.

Case 1

A 23-year-old woman presented at the emergency department with fever, headache, and earache since 4 weeks and severe neck pain since 3 days. She was previously healthy and had been in regular contact with horses, dogs, rabbits, and guinea pigs. Physical examination showed fever and neck stiffness but no other abnormalities. Blood laboratory examination was normal. CSF examination was consistent with meningitis (Table 1) and the patient was treated with amoxicillin, ceftriaxone, and acyclovir. Cultures became positive for *C. fetus* subspecies *fetus* after 9 days. Amoxicillin and

acyclovir were discontinued and ceftriaxone was continued for 2 weeks. The patient was discharged, but mild vertigo and a decreased sense of smell remained. One week after discharge, the patient presented with a subfebrile temperature (38-38.5°C) and headache. Repeated CSF examination was consistent with meningitis (Table 1). Despite prolonged treatment with meropenem, the patient's complaints lasted for a total of 4 weeks. Extensive ancillary investigations did not reveal any underlying illness. The patient was not able to resume her studies due to persisting fatigue and cognitive defects.

Case 2

A 52-year-old previously healthy farmer presented at the emergency department with headache and fever since 10 days and a stiff neck since 2 days. Physical examination showed fever and neck stiffness. Blood laboratory examination showed 11.9 x 10^9 leukocytes /L and a C-reactive protein of 206 mg/L. CSF examination was consistent with meningitis (Table 1). The patient was treated with ceftriaxone and amoxicillin for 2 weeks and received adjunctive dexamethasone 10 mg 4 times a day for 4 days. CSF and blood cultures were positive for *C. fetus* subspecies *fetus*. The patient was discharged in good clinical condition, but after a week, he came back to the hospital because of recurrent headache and fever. Physical examination showed fever but no other abnormalities. Blood laboratory examination showed 10.8 x10^9 leukocytes/L, and CSF examination was consistent with bacterial meningitis (Table 1). CSF cultures were not repeated. The patient was treated with meropenem for 3 weeks and fully recovered.

Review of the literature

We identified a total of 18 relevant articles published between 1960 and 2013 (Figure 1).[4-21] Combined with our cases, 22 adult patients with *C. fetus* meningitis were identified (Table 2, Table 3) with a median age of 48 years (range 23-84 years). Sixteen patients were men (73%). An immunocompromised state was present in 16 out of 22 patients (73%, 95% CI 54-92%) and consisted of alcoholism in 9 patients, diabetes mellitus in 6, use of immunosuppressive medication in 2, and leukemia and asplenia in 1 patient each. The source of infection was identified in 13 out of 19 patients (68%, 95% CI 47-89%) and consisted of frequent contact with domestic

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animals in 5 patients (38%, 95% CI 12-64%), working on a farm in 4 (31%, 95% CI 10-52%), frequent contact with rats in 3, consuming raw meat in 2, and working in an abattoir and chewing khat in an animal sanctuary in 1 patient each (Table 1). One patient cared for sick animals before developing meningitis.[20] Both an immunocompromised state and an identified source of infection were present in 7 out of 19 patients (37%, 95% CI 15-59%).

Table 1. Clinical characteristics, etiology and clinical outcome for cases of *Campylobacter fetus* meningitis in our cohort

Characteristics	Case 1		Case 2	
Year of admission	2013		2015	
Age	23		52	
Gender	Female		Male	
Predisposing factor	-		-	
Source of infection	Domestic animals, worked on a farm		Farmer	
	First episode	Readmission	First episode	Readmission
Clinical presentation				
Temperature (°C)	38.5	38.5	39.3	Fever
Headache	+	+	+	+
Neck stiffness	+	-	+	-
Glasgow Coma Scale	15	15	15	15
Cerebrospinal fluid characteristics				
CSF leukocyte count/mm^3	308	28	243	2501
CSF protein (g/L)	0.90	0.22	1.76	1.32
CSF glucose (mmol/L)	1.7	2.7	1.0	2.5
CSF culture	+	Not done	+	Not done
Blood culture	-	Not done	+	Not done
Empirical treatment				
Antibiotics	Amoxicillin, ceftriaxone	Meropenem	Amoxicillin, ceftriaxone	Meropenem
Dexamethasone	-	-	+	-
Outcome	Concentration problems		Full recovery	

Abbreviations: CSF: cerebrospinal fluid

Presenting symptoms were reported in all 22 patients and consisted of headache in 14 (64%, 95% CI 44-84%), fever in 20 (91%, 95% CI 79-100%), neck stiffness in 13 (59%, 95% CI 38-80%), and an altered consciousness in 10 patients (45%, 95% CI 24-66%). The classic triad of fever, neck stiffness, and an altered consciousness was present in 4 patients (18%, 95% CI 2-34%). At least 2 of the 4 symptoms of headache, fever, neck stiffness, and an

altered consciousness were present in all patients. There was no association between the presence of fever and an immunocompromised state (p = 0.48)

The results of blood investigations were reported in 15 patients. The median leukocyte count was 12.2 x 10⁹/L (range 5.4-29.3 x 10⁹). The blood leukocyte count was considered normal (range 4.0-10.0 x 10⁹/L) in 4 patients.

CSF examinations were performed in all patients; CSF was abnormal in all (Table 2, Supplementary table 1). Individual CSF predictive factors were present in 10 out of 19 patients (53%, 95% CI 31-75%), mostly due to a decreased CSF glucose (6 patients). The CSF leukocyte count was less <1000 per mL in 11 patients (52%, 95% CI 31-73%), ranging from 48 to 11,000 leukocytes per mL. There was no association between a CSF leukocyte count of < 1000 per mL and an immunocompromised state (p = 1.00) or alcoholism (p = 0.66).

CSF cultures were positive in 17 out of 22 patients (77%, 95% CI 59-95%); in 5 patients, CSF cultures were negative, whereas blood cultures were positive (23%, 95% CI 5-41%). Blood cultures were positive in 19 out of 22 patients (86%, 95% CI 71-100%). Both CSF and blood cultures were positive in 14 out of 22 patients (64%, 95% CI 44-84%). *C. fetus* subspecies *fetus* was the causative organism in all cases.

Antibiotic treatment was highly diverse and the primary antibiotic treatment mainly consisted of beta-lactam antibiotics, such as penicillin (between 1960 and 1970), amoxicillin, ampicillin, and ceftriaxone (from 1985 onwards). In 11 patients (50%, 95% CI 29-71%), the antibiotic treatment was altered after the cultures became positive for *C. fetus*. The duration of antibiotic treatment was reported in 9 patients: 7 patients were treated for 4 weeks, 1 patient for 5 weeks (case 2), and 1 patient for 6 weeks (case 1).

Outcome was reported in all 22 patients: 2 patients died (9%, 95% CI 0-21%).[9, 16] Three out of 20 survivors (15%, 95% CI 0-31%) had an unfavorable outcome: 1 patient remained comatose, 1 patient had a persisting hemiparesis, and 1 patient had persisting fatigue and concentration problems (case 1). There was no association between any cause of an immunocompromised state and unfavorable outcome (p = 0.59).
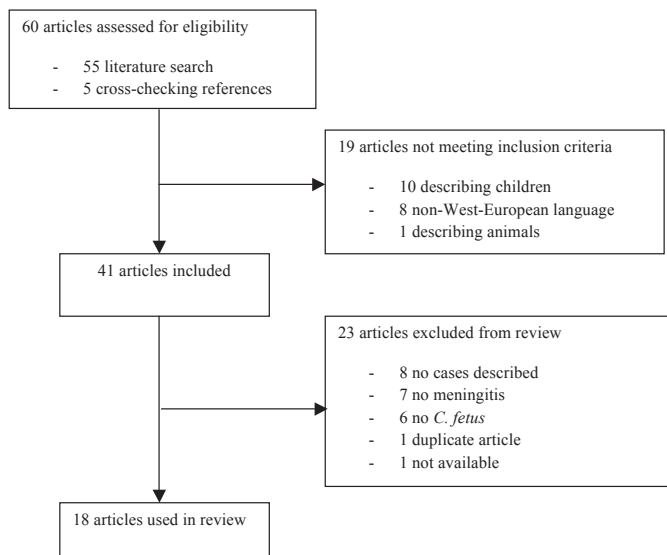
Figure 1. Flowchart review of the literature *Campylobacter fetus* meningitis

4 out of 22 patients (18%, 95% CI 2-34%) had persisting or recurrent fever and headache, for which they were readmitted to the hospital for antibiotic treatment.[8, 18] In 1 patient, the isolated *C. fetus* strain was resistant to the prior administered antibiotics (penicillin), and repeated blood and CSF cultures remained positive until another antibiotic agent (tetracycline) was administered.[18] However, in the other 3 patients, the *C. fetus* isolate was susceptible to the antibiotics administered during the first admission (ceftriaxone and amoxicillin in 2 and cefotaxime and vancomycin in 1). After a 3-week treatment with meropenem (2 cases) and ofloxacin and gentamicin (1 case), fever and headache disappeared. In 2 of these 3 patients (case 1 and case 2), no new cultures were performed before this treatment, and in the other patient, new CSF and blood cultures remained negative.[8]

Table 2. Clinical characteristics, etiology, and clinical outcome for *Campylobacter fetus* meningitis; combination of our patients and patients reported in the literature

Characteristics	n/N (%)
Median age (range)	48 (23-84)
Male sex	16/22 (73)
Immunocompromised	16/22 (73)
Alcoholism	9/16 (56)
Diabetes mellitus	6/16 (38)
Immunosuppressive medication	2/16 (13)
Haematological malignancy	1/16 (6)
Splenectomy	1/16 (6)
Identified source of infection	13/19 (68)
Frequent contact with domestic animals	5/13 (38)
Working on a farm	4/13 (31)
Frequent contact with rats	3/13 (23)
Consuming raw meat	2/13 (15)
Working in an abattoir	1/13 (8)
Chewing khat in an animal sanctuary	1/13 (8)
Clinical presentation	
Headache	14/22 (64)
Fever	20/22 (91)
Neck stiffness	13/22 (59)
Altered mental status	10/22 (45)
Classic meningitis triad[a]	4/22 (18)
Cerebrospinal fluid characteristics	
Median CSF leukocyte count/mm^3 (range)	577 (48-11,000)
Median CSF protein (g/L) (range)	1.00 (0.33-5.08)
Median CSF glucose (mmol/L) (range)	2.88 (0.30-6.83)
Positive cultures	
Cerebrospinal fluid	17/22 (77)
Blood	19/22 (86)
Outcome	
Death	2/22 (9)
Neurological deficits	2/20 (10)
Comatose	1/20 (5)

Abbreviations: CSF; cerebrospinal fluid
[a]Defined as fever, neck stiffness and altered mental status

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Table 3. Cases of *Campylobacter fetus* meningitis reported in the literature, combined with our patients

Study	Age	Gender	Predisposing factor	Source of infection	Symptoms	CSF leukocyte count/mm³	CSF culture	Blood culture	Outcome
Suy[4]	75	Male	DM	Raw sheep liver ingestion	2;4	1430	+	+	Full recovery
Martinez[5]	28	Male	No	Khat chewing	1;2	170	-	+	Full recovery
Umehara[6]	40	Male	Prednisolone	Unknown	1;2	115	+	+	Full recovery
Herve[7]	71	Male	DM	Unknown	3;4	11100	+	+	Full recovery
Dronda[8]	47	Male	Alcoholism	Dogs, cats	1;2,3	300	-	+	Full recovery[a]
Wilhelm[9]	84	Male	Alcoholism	N.R.	2;4	577	+	+	Death
Kato[10]	55	Male	Alcoholism, DM	Unknown	1;2;3;4	400	+	+	Full recovery
Clavelou[11]	39	Female	Alcoholism	N.R.	2;3	1800	+	+	Full recovery
Clavelou[11]	36	Male	Alcoholism	N.R.	2;4	154	-	+	Full recovery
Rao[12]	47	Male	DM, ISM	Raw calve liver ingestion	1;2	48	+	+	Full recovery
Malbrunot[13]	38	Male	No	Cats	2;3	2040	+	-	Full recovery
Gubina[14]	46	Male	Alcoholism	Farmer, domestic animals	1;2	N.R.	-	+	Full recovery
Gubina[14]	40	Male	No	Domestic animals	1;2	2821	+	+	Full recovery
Gunderson[15]	53	Male	Alcoholism	Unknown	1;2;3;4	7250	+	+	Comatose
Reyman[16]	69	Female	DM, splenectomy	Unknown	2;4	1230	+	+	Death
Stille[17]	50	Male	DM	Abattoir worker	1;2;3	3436	+	-	Full recovery
Collins[18]	55	Male	Leukaemia	Rats at work place	1;2;3	330	+	+	Full recovery[a]
Robin[19]	47	Female	Alcoholism	Unknown	1;2;3;4	2128	+	+	Full recovery
Killam[20]	48	Female	No	Farmer, cared for sick calves	3;4	1399	-	+	Hemiparesis
Edwards[21]	50	Female	Alcoholism	Lived in rat-infested neighbourhood	1;2;3;4	100	+	+	Full recovery
This study	23	Female	No	Farmer, domestic animals	1;2;3	308	+	-	Concentration problems[a]
This study	52	Male	No	Farmer	1;2;3	243	+	+	Full recovery[a]

Abbreviations: CSF: cerebrospinal fluid; DM: diabetes mellitus;
ISM: immunosuppressive medication; N.R: not reported
[a]These patients were readmitted due to persisting symptoms
Symptoms: 1: headache; 2: fever; 3: neck stiffness; 4: altered consciousness

Discussion

Meningitis caused by *C. fetus* is a rare disease, which is associated with an immunocompromised state. Nine patients diagnosed with *C. fetus* meningitis had a previous history of alcoholism, and 5 patients had diabetes mellitus. Alcoholism and diabetes mellitus are both risk factors for bacterial meningitis[22] and have been associated with a high rate of unfavorable outcome.[23, 24] Cancer has been reported to be a risk factor for *C. fetus* bacteremia,[25] but was only present in 1 patient with *C. fetus* meningitis.

Although *C. fetus* is a zoonotic pathogen, contact with animals or animal products could only be identified in 68% of patients with *C. fetus* meningitis. In most patients in whom a source of infection was identified, frequent contact with domestic animals was reported to be the source of infection (38%). However, ~164 million American households have domestic animals,[26] implying that the risk at developing *C. fetus* meningitis after frequent domestic animal contact is very low.

CSF abnormalities were present in all patients with *C. fetus* meningitis. However, only 53% of the cases had at least 1 individual CSF predictor for bacterial meningitis,[3] as compared to 88% of the patients with community-acquired bacterial meningitis in a large prospective cohort study.[27] Furthermore, CSF cultures were negative in 23% of the *C. fetus* meningitis cases, whereas blood cultures were positive. As blood cultures were positive in 86% of all cases, they can therefore be useful to confirm the diagnosis of *C. fetus* meningitis in the case of CSF abnormalities and a negative CSF culture. When *C. fetus* meningitis is suspected but cultures remain negative, PCR targeting 16S rRNA encoding gene sequencing followed by sequencing of the PCR product may provide the diagnosis.[28]

C. fetus has been described to be resistant to several antimicrobial agents. In a multicenter study of 25 isolates of *C. fetus* ssp. *fetus* recovered from blood and synovial fluid samples, a significant proportion of isolates was interpreted as intermediate or resistant to ampicillin (12%), cefotaxime (80%), and erythromycin (100%).[29] Several case reports describe human *C. fetus* isolates resistant to ceftriaxone,[30] cefotaxime,[4, 7, 8] and penicillin.[8, 12] In *C. fetus,* the genes tet(44) and ant(6)-lb have been associated with

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resistance to tetracycline, minocycline, and streptomycin.[31] Other genes may play a role in reduced susceptibility of *C. fetus* for antimicrobial agents which are commonly used for the treatment of bacterial meningitis, such as ceftriaxone.[32] In our study, 4 patients were known to be readmitted to the hospital because of persisting fever and CSF abnormalities, and received prolonged treatment with antibiotics, although the *C. fetus* isolate was sensitive to the primarily received antibiotics in 3 of these cases. There might even be some cases where the patients might have persisting or recurrent fever but not readmitted to the hospital for treatment. Relapsing and persisting infection have also been reported in other manifestations of *C. fetus*.[33] This is interesting and suggests inconsistency between the in vivo and in vitro susceptibility of *C. fetus*. However, as repeated cultures remained negative in most cases, it is also possible that the recurrent clinical parameters are a postinfectious syndrome or inflammatory response. Nevertheless, cases appeared to do best with carbapenem therapy. Based on the apparent slow clinical response seen in this limited number of cases, the authors of this study recommend a prolonged course of antimicrobial therapy when *C. fetus* is identified as a causative agent of bacterial meningitis.[28]

Our study had several limitations. First, only patients with a positive CSF culture were included. In our literature review, 23% of the patients had a negative CSF culture, which means we could have missed cases of *C. fetus* meningitis. Second, patients may not have undergone a lumbar puncture due to space-occupying lesions on cranial CT or coagulation problems. Furthermore, we did not include neonates with *C. fetus* meningitis, as predisposing factors, etiology, and clinical characteristics in neonates are not comparable to those in adults.
Also, specific characteristics of interest were not always available in the retrieved case-reports included in our meta-analysis. Therefore, we reported the number of patients in who the specific characteristic was known.
Finally, the recommendations that can be made are limited by small numbers of affected patients.

In conclusion, *C. fetus* is a rare cause of bacterial meningitis and is associated with an immunocompromised state. Based on the apparent slow clinical response seen in this limited number of cases, the authors of this study

recommend a prolonged course of antimicrobial therapy when *C. fetus* is identified as the causative agent of bacterial meningitis. Cases appeared to do best with carbapenem therapy.

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CHAPTER 7

SUSPECTED LEPTOSPIRAL MENINGITIS IN ADULTS: REPORT OF FOUR CASES AND REVIEW OF THE LITERATURE

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Abstract

Introduction: Leptospirosis is a widespread zoonotic disease characterised by headache and fever. These symptoms are often suggestive of meningitis, but only a proportion of patients have leptospiral meningitis.

Methods: We report episodes of leptospiral meningitis in patients admitted to a tertiary referral centre in the Netherlands, in whom lumbar puncture was performed, and conducted a literature search of adult cases of leptospiral meningitis to describe clinical characteristics and outcome.

Results: Between 2011 and 2014, 19 patients with leptospirosis were identified. Seven underwent a lumbar puncture for suspected meningitis (37%), of which six had been in contact with fresh water in a tropical area. Four patients with suspected meningitis (57%) had cerebrospinal fluid pleocytosis indicative of leptospiral meningitis and presented with headache, fever and neck stiffness. In a review of the literature we identified 366 patients with leptospiral meningitis with a median age of 33 years (range 17-77). Risk factors for leptospirosis were identified in 32 of 33 patients. Typical cerebrospinal fluid abnormalities consisted of a mildly elevated leukocyte count (median 206 leukocytes/mm^3, range 6-2072) with a lymphocytic predominance (median 95%). Outcome was generally favourable, with a mortality rate of 3% and neurological sequelae in 5% of the survivors.

Conclusion: Leptospirosis in the Netherlands has a low incidence. In the case of suspected meningitis and a history of visiting tropical areas or direct or indirect contact with animal urine, leptospiral meningitis should be considered. Cerebrospinal fluid examination is vital for the differential diagnosis of leptospirosis. Outcome is generally favourable in patients with leptospiral meningitis treated with antibiotics.

Introduction

Leptospirosis (infection with *Leptospira* spp) is a widespread zoonotic disease. Although the majority of the case load is seen in tropical areas,[1, 2] it also occurs in Europe with a reported incidence of 0.13 per 100,000 individuals.[3] Leptospirosis is caused by the transmission of a spirochete of the *Leptospira* genus through direct contact with infected animals or through indirect contact with a contaminated environment, e.g. fresh water.[4] A wide variety of mammalian hosts, both feral and domestic/semi-domestic, serve as infection reservoirs and can excrete *Leptospira* spp in the urine.[4]

Leptospira infection may cause a variety of clinical syndromes. The most severe form is Weil's disease, which has a high mortality and is characterised by high fever, bleeding, icterus and renal insufficiency,[2, 5] Leptospiral infection may also present with neurological symptoms, such as meningitis, bilateral facial palsy or opsoclonus-myoclonus syndrome.[4, 6-8] Many patients with leptospiral infection present with headache, fever and neck stiffness and therefore bacterial, tuberculous or viral meningitis may often be suspected prior to the eventual diagnosis of leptospirosis.[9-11] Symptoms of meningitis due to leptospirosis occur with and without cerebrospinal fluid (CSF) abnormalities.[12]

In the Netherlands, approximately 30-40 cases of leptospirosis are reported per year.[11] We reviewed the cases of leptospirosis with suspected meningitis identified in a tertiary referral hospital in the Netherlands and performed a review of the literature on leptospiral meningitis.

Methods

We identified all adult patients (≥ 16 years of age) with confirmed leptospirosis in the Netherlands between January 2011 and December 2014. Cases were defined as patients with a positive serology (microscopic agglutination test (MAT), enzyme-linked immunosorbent assay (ELISA)), positive polymerase chain reaction (PCR) and/or a positive culture for *Leptospira* species. These tests were performed by the World Health Organisation, Food and

Agriculture Organisation of the United Nations, World Organisation for Animal Health, and the National Collaborating Centre for Reference and Research on Leptospirosis (NRL) at KIT Biomedical Research, the Royal Tropical Institute in the Netherlands. NRL confirms approximately 99% of the suspected cases of leptospirosis in the Netherlands, and thus could provide the authors with nationwide epidemiological data for this article.

From this dataset we selected patients with leptospirosis admitted at the Academic Medical Centre, Amsterdam, a tertiary referral hospital in the Netherlands, to study clinical characteristics, treatment and outcome. We analysed whether symptoms consistent with bacterial meningitis (neck stiffness, fever and headache) were associated with CSF abnormalities. All patients with abnormal CSF (defined as CSF white blood cell count > 5/mm^3, total protein > 0.6 g/L or CSF/serum glucose ratio < 0.6) were considered to have leptospiral meningitis.[13] We retrospectively collected clinical characteristics, data on ancillary investigations and outcome. The data were processed anonymously. Oral and written informed consent was obtained from all patients with leptospiral meningitis.

Review of the literature

Subsequently, we performed a literature search for leptospiral meningitis on PubMed, using the search terms "leptospir* AND meningitis", and ""Neurologic Manifestations"[MeSH] AND leptospir*". We also searched for cohort studies and reviews about leptospirosis using the search term "leptospir*". The search was updated until 20 March 2015.

Articles reporting children or animals, duplicate articles and articles in which no specific data were given for leptospiral meningitis patients were excluded. Leptospiral meningeal involvement was defined as a combination of 1) fever with one of the following signs: neck stiffness, altered consciousness or other meningeal signs,[12] and 2) detection of *Leptospira* species in blood and/or CSF by PCR or culture, and/or detection of leptospiral antibodies by serology (MAT and/or ELISA). When CSF was abnormal (see Methods section), the diagnosis of meningitis was established. In an analysis of clinical data we systematically scored baseline and presenting characteristics, clinical course and outcome.

Differences between groups were calculated by means of Fisher's Exact test. Articles with neither an abstract nor access to the full text were excluded.

Studies written in English, German, French, Dutch, Spanish, Italian and Portuguese were included.

Results

Between January 2011 and December 2014, 196 cases of leptospiral infection were identified at the NRL in the Netherlands, of which 104 contracted leptospirosis abroad (53%) and 92 contracted leptospirosis in the Netherlands (47%) (Figure 1). The mean calculated annual incidence from 2011 to 2014 was 0.30 per 100,000 inhabitants.
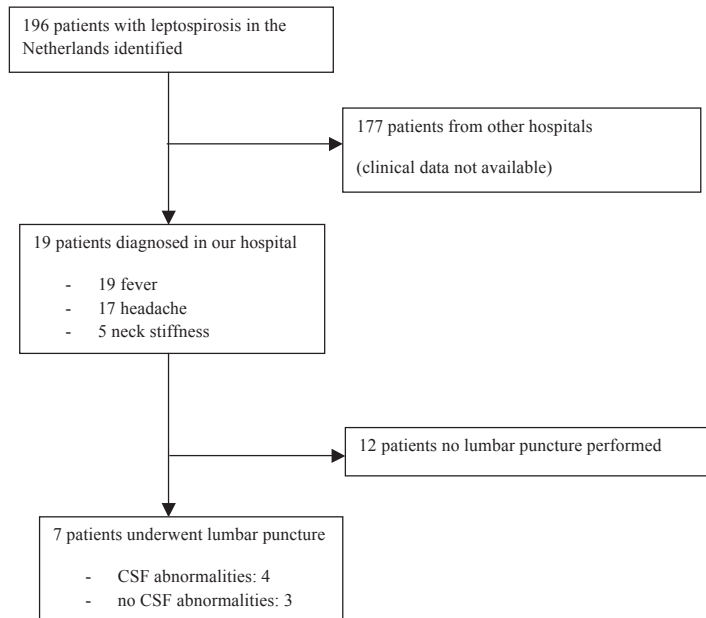

Figure 1. Flowchart of patients with leptospirosis in the Netherlands

Within this period we observed a threefold increased incidence in 2014 (0.57 per 100,000) compared with 2011-2013 (average 0.21 per 100,000). Furthermore, in 2014, leptospirosis was contracted in the Netherlands in 62% of the cases, compared with an average of 33% in 2011-2013.

In our hospital, 19 adult cases of leptospirosis (10%) were identified based on a positive serology and/or PCR and/or culture. All 19 patients presented with fever, 17 (89%) presented with headache and five (26%) with neck stiffness. The median age was 27 years (range 17-61 years) and 15 patients were male (79%). Eighteen patients contracted leptospirosis abroad (95%) and one patient contracted leptospirosis in the Netherlands (5%).

In seven patients (37%) there was a clinical suspicion of meningitis, for which a lumbar puncture was performed. Four patients with CSF abnormalities were diagnosed with leptospiral meningitis. Three patients had no CSF abnormalities (Figure 1), of which one patient had not been abroad and had not been in contact with animals. The incidence of meningitis in leptospirosis in our hospital was 21% (4 out of 19 patients). The patients with leptospiral meningitis are described below.

Case 1

A 27-year-old Dutch patient was admitted to the hospital in Laos with fever, myalgia, shivers and vomiting. He had been travelling through Vietnam, Laos, Cambodia and Thailand, where he had been swimming. He was treated with antibiotics but no source of infection was found. When he returned to the Netherlands a few days later, he presented with recurrent fever (temperature 38.5°C) and progressive headache. Physical examination showed conjunctivitis and neck stiffness. Laboratory examinations showed the following: creatinine 62 µmol/L, leukocytes 6.4×10^9/L, C-reactive protein (CRP) 3.6 mg/L, serum glutamic oxaloacetic transaminase (SGOT) 23 U/L, serum glutamic pyruvic transaminase (SGPT) 15 U/L, and bilirubin 5 µmol/L. Lumbar puncture showed turbid CSF with 734 leukocytes/mm^3 (75% polymorphonuclear leukocytes), protein level of 0.63 g/L, and CSF to blood glucose ratio of 0.45. The IgM ELISA for leptospirosis was positive. The patient was treated with 1 million IU penicillin intravenously four times a day for seven days. He was discharged in a good clinical condition without sequelae.

Case 2

A 45-year-old Dutch patient presented with fever, headache, nausea and diarrhoea. He had been travelling through Singapore, Thailand and Indonesia two weeks prior to admission, where he had suffered from gastroenteritis

after he fell off a boat during rafting and ingested fresh water. Physical examination showed bilateral conjunctivitis but no other abnormalities. Laboratory examination showed the following: erythrocyte sedimentation rate (ESR) 101 mm/h, CRP 106 mg/L, leukocytes 10.8 x 10^9/L, creatinine 413 µmol/L, SGPT 36 U/L, and bilirubin 8 µmol/L. The *Leptospira* IgM lateral flow test was positive and patient was treated with oral amoxicillin and discharged. However, the next day, he presented again with aggravated headache. Neurological examination now showed neck stiffness, for which a lumbar puncture was performed. This showed turbid CSF containing 628 leukocytes/mm^3 (86% polymorphonuclear leukocytes), protein level of 0.92 g/L and a CSF to blood glucose ratio of 0.41. The IgM ELISA and MAT were both positive, the probable infecting serogroup was *Grippotyphosa*. Patient was treated with 12 million IU penicillin intravenously daily for three days followed by oral amoxicillin (750 mg three times daily) for one week. He was discharged in a good clinical condition without sequelae.

Case 3

A 20-year-old Dutch patient presented with headache, fever, nausea and diarrhoea. The symptoms appeared a week after returning from a holiday in Borneo, where he had swum in fresh water. Physical examination showed bilateral conjunctivitis and neck stiffness. Laboratory examination showed the following: CRP 45.7 mg/L, leukocytes 6.2 x 10^9/L, SGOT 354 U/L, SGPT 305 U/L, bilirubin < 2 µmol/L, and creatinine 236 µmol/L. Lumbar puncture showed turbid CSF containing 1200 leukocytes (predominantly lymphocytes, percentage not specified), protein level of 0.89 g/L and a CSF to blood glucose ratio of 0.52. The MAT and IgM ELISA for leptospirosis were positive and showed *Leptospira* serogroup Australis. Patient was treated with 12 million IU penicillin intravenously for four days followed by oral amoxicillin (750 mg three times daily) for 5 days. He was discharged in a good clinical condition without sequelae.

Case 4

A 22-year-old Dutch patient presented with fever, headache, cough and nausea. The symptoms appeared a week after returning from a backpack trip in Malaysia, Borneo and Thailand for two months. She had not swum in fresh water, but had slept in rice fields in Thailand. Physical examination

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showed a temperature of 40.5°C and neck stiffness. Laboratory examination showed the following: leukocytes 12.9 x 10^9/L, CRP 62.3 mg/L, creatinine 93 μmol/L, SGOT 58 U/L, SGPT 18 U/L, and bilirubin 8 μmol/L. Lumbar puncture showed clear CSF with 11 leukocytes/mm^3 (100% mononuclear cells), a protein level of 0.21 g/L and a CSF to blood glucose ratio of 0.60. The MAT, IgM ELISA and PCR for leptospirosis were positive and showed *Leptospira* serogroup Mini. Patient was treated with 100 mg doxycycline twice daily for seven days. She was discharged in a good clinical condition without sequelae.

Review of the literature for leptospiral meningitis

A total of 41 relevant articles published between 1947 and 2014 were identified, describing 366 adults with leptospiral meningitis (Figure 2).[9, 12, 14-52] The number of included patients per study varied between one and 162 patients. Studies were performed in Europe (25), Asia (9) and America (7) (Figure 2).

The median age of the patients was 33 years (range 17-77 years) and 51 of 62 (82%, 95% CI 72-92%) were male (Table 1). Two out of 26 (8%) patients were immunocompromised (95% CI 0-16%). A known etiology was reported in 32 of 33 patients (97%, 95% CI 91-100%); seven had been in contact with fresh water (five swimming, one fishing, and one window cleaning in an endemic area), six worked with cattle, five had been in contact with dogs, five had been in contact with rats, four were farm workers, two lived in a rural area endemic for leptospirosis, one worked in sewers, one was a horse trainer and one was a hunter. In one patient, no etiology was found. In an article describing 162 patients with leptospiral meningitis, no etiology per patient was reported, but the patient group mainly consisted of farmers.[47]

Headache was reported in 65 of 69 patients (94%, 95% CI 88-100%). Fever was reported in 100 of 102 patients (98%, 95% CI 93-100%), neck stiffness in 77 of 83 (93%, 95% CI 87-99%) and altered consciousness in 8 of 54 patients (15%, 95% CI 5-25%). The classic triad of fever, altered consciousness and neck stiffness[53] was present in 5 of 39 patients (13%, 95% CI 3-23%).
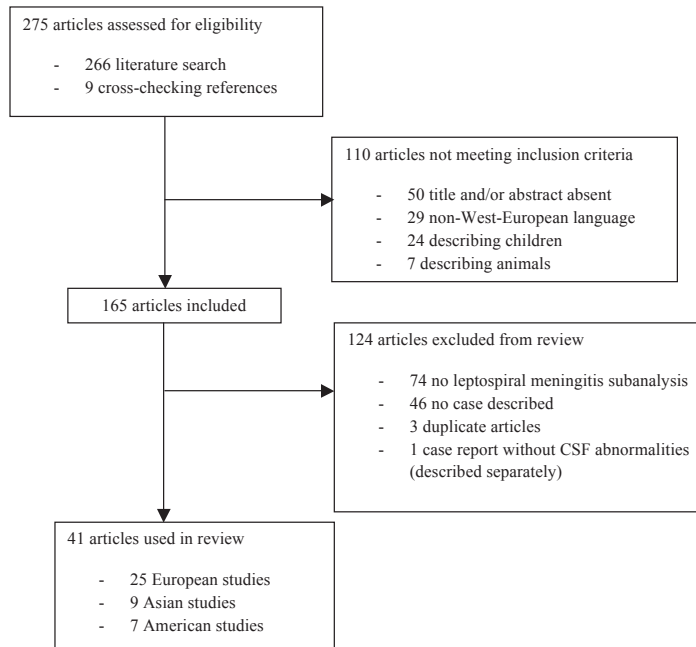
Figure 2. Flowchart review of the literature for leptospiral meningitis

The median CSF leukocyte count was 206 leukocytes/mm^3 (range 6-2072). All but one of the patients in whom the CSF leukocyte counts were known had a leukocyte count under 2000, with a predominance of lymphocytes (95%, 95% CI 92-98%) in most patients (224 of 236; 95%, 95% CI 92-98%). The CSF protein was known in 39 patients and the CSF glucose in 27 patients. The median CSF glucose was 2.5 mmol/L, while the median CSF protein was 1.10 g/L. In 190 of 208 patients (91%, 95% CI 87-95%), CSF protein was normal, and CSF glucose was normal in 201 of 207 patients (97%, 95% CI 95-99%), while CSF leukocytes were elevated (> 5/mm^3). In all patients, antibodies to *Leptospira* were detected by blood serology (either ELISA or MAT); no *Leptospira* were detected in CSF by culture or PCR.

A total of 245 patients (91%) were treated with antibiotics (mostly penicillin and doxycycline). Twenty-three patients were not treated with antibiotics. One patient was treated with dexamethasone and received antibiotics

(penicillin) as well.[48] Eight of 229 patients (3%, 95% CI 1-5%) died during hospital admission, of which five had received antibiotics. The cause of death was reported in two cases and consisted of respiratory insufficiency[46] and gastro-intestinal bleeding.[27] The mortality rate in patients who were not treated with antibiotics was 13% compared with 2% in patients treated with antibiotics (Fisher's exact test, p = 0.04).

Three of 56 patients (5%) had sequelae; one patient was not able to walk until two months after discharge,[48] one patient had transient renal insufficiency [38] and one patient had neurocognitive defects which resolved after a few weeks.[22]

Table 1. Clinical characteristics, etiology, laboratory findings, treatment and clinical outcome for 366 adults with leptospiral meningitis identified in the literature, compared with our patients

Characteristics	n/N	Cases
Median age	33	25
Male sex	51/62 (82%)	3/4 (75%)
Immunocompromised	2/26 (8%)	0/4 (0%)
Alcohol	1 (4%)	0 (0%)
Diabetes mellitus	1 (4%)	0 (0%)
Identified source of infection	32/33 (97%)	4/4 (100%)
Animal contact	24 (75%)	0 (0%)
Water	8 (25%)	4 (100%)
Clinical presentation		
Headache	65/69 (94%)	4/4 (100%)
Fever	100/102 (98%)	4/4 (100%)
Neck stiffness	77/83 (93%)	4/4 (100%)
Altered consciousness	8/54 (15%)	0/4 (0%)
Meningitis triad	5/39 (13%)	0/4 (0%)
Cerebrospinal fluid characteristics		
Median CSF leukocyte count/mm^3 (range)	206 (5-2072)	681 (11-1200)
Empirical treatment		
Antibiotics	245/267 (92%)	4/4 (100%)
Outcome		
Death	8/229 (3%)	0/4 (0%)
Sequelae	3/56 (5%)	0/4 (0%)

Abbreviations: CSF: cerebrospinal fluid

Two articles describing two case reports of patients with meningeal symptoms but normal CSF were identified. [25, 54] When combining these patients and our three patients with meningeal symptoms without CSF abnormalities, we identified five male patients with a median age of 27 years (range 20-47). Two had had animal contact, two travelled to a tropical area and one (one

of our patients) worked in the municipal cleansing department. All five presented with headache and fever and two with neck stiffness. Diagnosis was established by blood tests; no leptospiral antibodies or DNA were detected in the CSF. All recovered without neurological sequelae.

Discussion

We found a low incidence of leptospirosis in the Netherlands: 0.30 per 100,000 inhabitants in the period 2011-2014. In the period 2011-2013, the calculated annual incidence was 0.21 per 100,000 inhabitants, while the annual incidence in Europe in 2010 was 0.13 per 100,000 inhabitants.[3] In 2014, however, a threefold increase was observed in the incidence of leptospirosis in the Netherlands: 0.57 per 100,000 inhabitants. The contribution of travelling to leptospirosis in the Netherlands has been up to 50% since 1995[10, 11, 55] and was 33% in the period 2011-2013, but in 2014, the majority of patients (62%) contracted leptospirosis in the Netherlands. This increase is currently being investigated (unpublished data).

In our hospital, 18 out of 19 patients and 6 out of 7 patients with suspected meningitis contracted leptospirosis after fresh water contact while travelling in Southeast Asia, which has been reported to be the main risk factor for leptospiral infection worldwide.[56] The high contribution of travelling to leptospirosis in our hospital compared with the national results, is probably caused by most patients being diagnosed at the AMC Department of Tropical and Travel Medicine. Only one patient had not been abroad, but worked at the municipal cleansing department where he could have been infected through contact with sewage water.[47]

From the 19 patients with leptospirosis identified in our hospital, all had fever (100%), 17 had headache (89%) and 5 had neck stiffness (26%). In general, headache and fever are common symptoms in leptospirosis which have been reported in 60-100%,[4] and neck stiffness is found in 10-20% of the cases,[10] which confirms our findings.

The incidence of meningitis in leptospirosis is relatively low despite the high frequency of headache and neck stiffness, although there could be an underestimation since not all patients undergo a lumbar puncture. In a

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cohort study of 63 cases, 12 patients (19%) were diagnosed with leptospiral meningitis,[4] which is similar to the incidence of meningitis in leptospirosis in our hospital (21%).

In our review of leptospiral meningitis, headache was seen in 94%, fever in 98% and neck stiffness in 93% of cases. When a patient presents with meningeal symptoms after fresh water contact in tropical regions or direct or indirect contact with animal urine, the diagnosis of leptospiral meningitis should be considered.

Our review showed that most patients with leptospiral meningitis have a mildly elevated CSF leukocyte count and a normal CSF glucose and protein. In a cohort study performed in 2008, CSF pleocytosis was seen ranging from 16 to 850 leukocytes/mm^3.[4] In this cohort study CSF analysis of patients with suspected leptospiral meningitis showed that 50% of patients had CSF pleocytosis,[4] which is similar to our case series (4 out of 7, 57%). In most patients in our study, CSF leukocytes mainly consisted of lymphocytes, but two of our cases with leptospiral meningitis had predominantly polymorphonuclear leukocytes in their CSF. This may be due to the timing of the lumbar puncture; polymorphonuclear leukocytes are often predominant early in the clinical course, and later replaced by lymphocytes.[16]

The necessity of a lumbar puncture in patients with leptospirosis has not been studied. In general, if the diagnosis of leptospirosis has not been confirmed in patients with suspected meningitis, cerebrospinal fluid examination is vital to determine whether the patient has meningitis, and what the cause is. However, in patients with confirmed leptospirosis, cerebrospinal fluid examination does not have additional value since the treatment is similar in patients with and without leptospiral meningitis, unless a second diagnosis is being considered.

In our review, we found a significantly increased mortality in patients not treated with antibiotics compared with those who were treated with antibiotics (13% versus 2%; p = 0.04). However, only a small number of the patients (8%) did not receive antibiotics and the reasons for not treating those patients were unknown. In a recent Cochrane review, there was insufficient evidence for using antibiotics in leptospirosis, but

no conclusions for 'severe leptospirosis' (not specified) could be drawn.[57] No association was established between the different antibiotic treatments ceftriaxone, doxycycline, cefotaxime and penicillin in leptospirosis and outcome. Most patients with leptospiral meningitis are treated with doxycycline or penicillin, which is the currently advised treatment regimen for leptospirosis (doxycycline 100 mg twice a day, or penicillin 1.5 million units four times a day).[54, 57, 58]

Our study has several limitations. We did not have clinical information about patients with leptospirosis attending other hospitals in the Netherlands, and therefore our case series is not representative for leptospirosis in the Netherlands. This is reflected in the high proportion of patients in our hospital who contracted leptospirosis abroad (95%) compared with the national average (53%). Furthermore, patients may have contracted leptospirosis and thus have a positive serology, but may have other diseases as well, such as Epstein-Barr viral infection or hepatitis.

For our review, we could not include articles written in non-West-European languages, e.g. Polish and Russian, due to insufficient knowledge of the language. Finally, there could be a publication bias since physicians may not report patients with leptospirosis and meningeal symptoms in whom no CSF abnormalities are found, when CSF culture was negative, or when no lumbar puncture was performed.

In conclusion, leptospirosis in the Netherlands had an annual incidence of 0.30 per 100,000 inhabitants in the period 2011-2014 and was contracted abroad in 53% of the cases. In the case of suspected meningitis and a history of travel to tropical areas or direct/indirect contact with animal urine, tests for leptospirosis should be considered. Leptospirosis commonly presents with headache and fever, but only a proportion of patients have meningitis. Approximately 50% of patients with suspected leptospiral meningitis have CSF pleocytosis and most have a normal CSF glucose and protein. When the diagnosis of leptospiral infection has been confirmed, lumbar puncture does not have clinical consequences, unless there is a differential diagnosis that needs to be considered. Treatment with penicillin or doxycycline usually leads to a favourable outcome.

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CHAPTER 8

STREPTOCOCCUS GALLOLYTICUS MENINGITIS IN ADULTS: REPORT OF FIVE CASES AND REVIEW OF THE LITERATURE

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Abstract

Introduction: We describe the incidence and patient characteristics of *Streptococcus gallolyticus* meningitis.

Methods: We identified *S. gallolyticus* meningitis in a nationwide cohort of patients with community-acquired bacterial meningitis, and performed a systematic review and meta-analysis of all reported adult cases in the literature.

Results: Five cases were identified (0.3%) in a cohort of 1561 episodes of bacterial meningitis. In one patient, bowel disease (colon polyps) was identified as predisposing condition for *S. gallolyticus* infection, whereas no patients were diagnosed with endocarditis. In a combined analysis of our patients and 37 reported in the literature, we found that the median age was 59 years. Predisposing factors were present in 21 of 42 patients (50%), and mainly consisted of immunosuppressive therapy (seven patients), cancer (four patients), and alcoholism (four patients). Colon disease was identified in 15 of 24 patients (63%) and endocarditis in five of 27 patients (18%). Co-infection with *Strongyloides stercoralis* was identified in 14 of 34 patients (41%), ten of whom were infected with human immunodeficiency virus or human T-lymphotropic virus. Outcome was described in 37 patients; eight died (22%) and one (3%) had neurological sequelae.

Conclusion: *S. gallolyticus* is an uncommon cause of bacterial meningitis, with specific predisposing conditions. When it is identified, consultation with a cardiologist and gastroenterologist is warranted to rule out underlying endocarditis or colon disease. Stool examinations for *Strongyloides stercoralis* should be performed in patients who have travelled to or originate from endemic areas.

Introduction

Bacterial meningitis is usually caused by *Streptococcus pneumoniae* and *Neisseria meningitidis*.[1] These bacteria form part of the normal human nasopharyngeal flora, and can cause meningitis in both immunocompromised and healthy individuals. Other bacteria causing meningitis are commonly associated with specific risk factors, such as *Listeria monocytogenes* and *Staphylococcus aureus*.[2]

Streptococcus gallolyticus, formerly known as a member of the *Streptococcus bovis* group, is a bacterium that has been described to cause meningitis and endocarditis.[3, 4] Three subspecies of *S. gallolyticus* are known: *gallolyticus*, *macedonicus* and *pasteurianus*.[5] The bacteria were first discovered in cattle, and have been reported to be a colonic commensal in 10-15% of healthy humans.[6] Among patients with *S. gallolyticus* bacteraemia, 50-70% have been reported to have colon carcinoma or benign colon abnormalities, such as diverticulosis and colon adenomas.[5, 7] *S. gallolyticus* infection is also associated with strongyloidiasis, for which different hypotheses have been suggested: (a) *Strongyloides stercoralis* makes the bowel wall more permeable to bacteria like *S. gallolyticus*, which can invade the body and cause sepsis and/or meningitis; and (b) the migrating *Strongyloides* larvae penetrate the gut mucosa and enter the portal circulation, carrying with them *S. gallolyticus*.[8, 9] The incidence and patient characteristics of *S. gallolyticus* meningitis are unknown.

We describe five cases of bacterial meningitis caused by *S. gallolyticus* identified in a prospective nationwide cohort study on community-acquired bacterial meningitis, and the results of a systematic review of the literature. In this review, we describe the epidemiology, clinical characteristics, risk factors and outcome of *S. gallolyticus* meningitis.

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Methods

Case series
In a prospective observational cohort study in The Netherlands, we included episodes of community-acquired bacterial meningitis in adults confirmed by cerebrospinal fluid (CSF) culture. The methods have been described

previously.[10] In summary, all patients were aged ≥16 years, and were listed in the database of the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) from January 2006 to December 2014. This laboratory receives CSF isolates from approximately 90% of all patients with bacterial meningitis in The Netherlands. The NRLBM provided daily updates of the names of the hospitals to which patients with bacterial meningitis had been admitted in the preceding 2–6 days and the names of physicians. Physicians were contacted, and informed consent was obtained from all participating patients or their legally authorized representatives. Physicians could also contact the investigators without a report by the NRLBM for inclusion of patients.

Episodes with negative CSF cultures could also be included if the following criteria were present: (a) blood cultures showed *S. gallolyticus*; (b) CSF analysis showed at least one individual predictor of bacterial meningitis, defined as a glucose level of < 34 mg/dL (1.9 mmol/L), a CSF glucose/ blood glucose ratio of <0.23, a protein level of >220 mg/dL, or a leukocyte count of > 2000/mL,[1] and (c) the clinical presentation was compatible with bacterial meningitis.

 All patients with *S. gallolyticus* meningitis were selected from this cohort. *S. gallolyticus* subspecies were identified with VITEK 2 (BioMérieux, Marcy-l'Etoile, France). *S. gallolyticus* subspecies of case 2 and 4 were identified by an in-house-developed molecular biological technique sequencing a part of the gene encoding ribosomal protein S2 (*rpsB*). The primers targeting *rpsB* were Str_F4 (3'-ATGGCAGTAATTTCAATG-5') and Str_R2 (3'-GAATTTTTCAAGACG-5'). Sequences of the amplicon were clustered with reference sequences obtained from GenBank by use of the neighbour-joining algorithm in MEGA 6.06 with 1000 bootstraps.

Patients with hospital-associated meningitis, with a neurosurgical device or who had undergone a neurosurgical operation within 1 month before bacterial meningitis onset were excluded. Patients using immunosuppressive drugs, with asplenia, with diabetes mellitus, with alcoholism or with infection with human immunodeficiency virus (HIV) were considered to be immunocompromised.[10] Additional clinical data on specific risk factors, i.e. colon disease and endocarditis, were retrospectively collected from the discharge letters. At discharge, all patients underwent a neurological examination performed by a neurologist. The study was approved by

the ethics committee of the Academic Medical Centre, Amsterdam, The Netherlands.

Review of the literature

We performed a literature search in PubMed with the terms "*Streptococcus bovis* AND meningitis", *"Streptococcus gallolyticus* AND meningitis", and "*Streptococcus caprinus* AND meningitis". *S. gallolyticus* meningitis was defined as described in 'Case series'. Articles reporting on children or animals, duplicate articles and articles in which no specific data were given for *S. gallolyticus* meningitis patients (*e.g.* articles in which there was only an analysis of the whole group, and no sub-analysis for *S. gallolyticus*) were excluded. Articles with neither an abstract nor access to the full text were excluded. Studies written in English, German, French, Dutch, Spanish, Italian and Portuguese were included. In a meta-analysis of clinical data, we systematically scored baseline and presenting characteristics (including predisposing conditions), clinical course, and outcome.

Results

We identified five cases of *S. gallolyticus* meningitis among 1561 episodes (0.32%) included in our cohort study (Table 1). The median age of the patients was 77 years (range, 50-91 years). Three patients were immunocompromised (Table 1). All patients presented with fever and neck stiffness, and headache was reported in three. Blood cultures were positive in all patients, and CSF cultures were positive in three patients. None of the patients was diagnosed with endocarditis, though two died quickly before this had been investigated, and echocardiography results were not known for one other patient. Colonoscopy was reported in two patients, and showed colon polyps in one. Two patients died from the meningitis, and three patients recovered without sequelae.

Case 1

A 74-year-old man presented with fever and confusion after a holiday in Thailand. His medical history revealed chronic lymphocytic leukemia and transitional cell carcinoma of the bladder. Physical examination showed

fever, disorientation and neck stiffness. CSF examination was consistent with bacterial meningitis (Table 1). Blood cultures were positive for *S. gallolyticus*; CSF cultures were negative. Amoxycillin 2 g six times daily, ceftriaxone 2 g twice daily and dexamethasone 10 mg four times daily were started. The patient was discharged after 11 days. Investigations for endocarditis, colon disease and strongyloidiasis were not performed.

Case 2

A 91-year-old woman presented with headache, vomiting, and aphasia. Her medical history revealed hypertension, anaemia, and atrial fibrillation, for which she used antihypertensives and acenocoumarol. Physical examination showed fever, neck stiffness, and aphasia. After correction of the coagulation status, lumbar puncture was performed, and showed CSF abnormalities consistent with meningitis (Table 1). The patient was treated with amoxycillin 2 g six times daily, cefotaxime 2 g six times daily, and dexamethasone 10 mg four times daily. She died 1 day after admission. Blood cultures became positive for *S. gallolyticus ssp. gallolyticus* (Figure 1); CSF cultures were negative.

Case 3

A 77-year-old man with a medical history including haemodialysis for renal failure presented with fever. Physical examination showed neck stiffness and a right-sided hemiparesis. Cranial computed tomography showed a hypodensity consistent with left-hemisphere cerebral infarction. CSF examination was consistent with
bacterial meningitis (Table 1). The patient was treated with penicillin 6 MU six times daily and dexamethasone 10 mg four times daily. He developed respiratory failure and died the same day. Blood and CSF cultures were positive for *S. gallolyticus*.

Table 1. Clinical characteristics, etiology, laboratory findings, treatment and clinical outcome for five adults with *Streptococcus gallolyticus* meningitis

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5
Age	74	91	77	50	84
Gender	Male	Female	Male	Male	Female
Predisposing factor(s)	Leukaemia	None	Immunosup-pressants, renal failure	None	Diabetes
Clinical presentation					
Temperature (°C)	40.0	38.5	40.4	39.2	39.7
Neck stiffness	Yes	Yes	Yes	Yes	Yes
Headache	Unknown	Yes	Unknown	Yes	Yes
Score on Glasgow Coma Scale	14	9	3	15	14
Neurological deficits	Disorientation	Aphasia	Right-sided hemiparesis	None	Disorientation
CSF characteristics					
Leukocyte count/mm³	2880	2896	36300	6780	2280
Protein level (g/L)	2.16	8.5	5.6	Unknown	7.6
CSF/blood glucose ratio	0.40	0.23	0.30	0.32	0.36
Cranial CT	Normal	Normal	Infarction in left cerebral hemisphere	Normal	Normal
Cultures					
CSF culture	Negative	Negative	Positive	Positive	Positive
Blood culture	Positive	Positive	Positive	Positive	Positive
S. gallolyticus-associated disease					
Endocarditis	Unknown	Unknown	Unknown	No	No
Bowel abnormalities	Unknown	Unknown	Unknown	Normal	Colon polyps
Empirical treatment					
Antibiotics	Amoxycillin, ceftriaxone	Amoxycillin, cefotaxime	Penicillin	Ceftriaxone	Penicillin
Dexamethasone	Yes	Yes	Yes	Yes	Yes
Outcome	Recovery	Death	Death	Recovery	Recovery

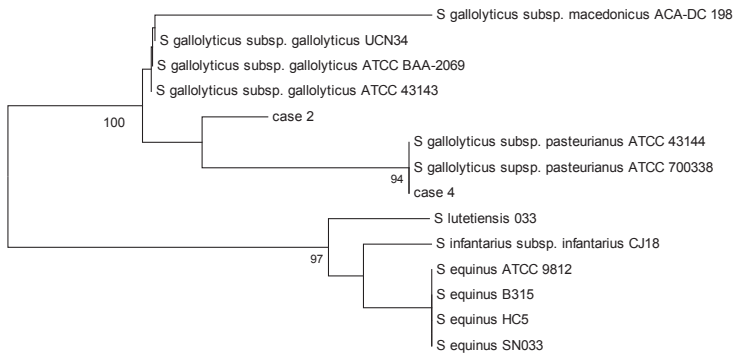Abbreviations: CSF: cerebrospinal fluid; CT: computed tomography

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Figure 1. Cluster analysis of rpsB sequences of isolates of case 2 and 4 with sequences from references strains extracted from Genbank
Bootstrap values larger than 905 are shown at branch points.

Case 4

A 50-year-old man complained of fever and progressive headache lasting for 3 days. His medical history showed no abnormalities. Physical examination showed fever and neck stiffness. CSF examination was consistent with bacterial meningitis (Table 1). Treatment with ceftriaxone 2 g twice daily and dexamethasone 10 mg four times daily was started. *S. gallolyticus* ssp. *pasteurianus* (Figure 1) was cultured from CSF and blood. Transthoracic ultrasound and colonoscopy did not show endocarditis or colon abnormalities. The patient was discharged after 11 days in good clinical condition.

Case 5

An 84-year-old woman presented with headache and confusion. Her medical history showed atrial fibrillation, diabetes, and heart failure. Physical examination showed disorientation and no neck stiffness. CSF examination was consistent with bacterial meningitis (Table 1). Empirical treatment was started with amoxicillin 2 g six times daily, ceftriaxone 2 g daily, and dexamethasone 10 mg four times daily. *S. gallolyticus* was cultured from blood and CSF, and antibiotic treatment was switched to penicillin 2 MU six times daily. Transthoracic ultrasound did not show endocarditis; colonoscopy showed colon polyps. The patient was discharged after 19 days in good clinical condition.

Review of the literature

In total, 86 studies were identified, of which 28 studies met the inclusion criteria, describing 37 patients (Figure 2). The identified studies were performed between 1975 and 2015.

Combining these data with our patients (Table 2, Table 3), we found that the median age was 59 years, and that 27 of 41 patients (66%) were male. Predisposing factors were described for 18 of 42 patients (43%), and mainly consisted of immunosuppressive therapy (seven patients), cancer (four patients) and alcoholism (four patients) (Table 2). Three patients had an anatomical defect (CSF leak, ventriculostomy, and postoperative cystic cavity communicating with the intradural space). Fourteen patients suffered from strongyloidiasis, and in 13 the strongyloidiasis infection was associated with an underlying disease (human T-lymphotropic virus (HTLV)-I infection in eight, HIV infection in two, and immunosuppressive medication in three).

Presenting symptoms were reported for 31 patients (Table 2). Colon abnormalities were identified in 15 out of 24 patients (63%): diverticulosis (five patients), colon adenoma (five patients), colon carcinoma (two patients), and ulcers, radiation enterocolitis, and radiation proctitis (each in one patient). Endocarditis was diagnosed in five of 28 patients (18%). One patient had both colonic diverticulosis and endocarditis.

CSF cultures were positive in 36 out of 41 patients (88%), and blood cultures were positive in 33 out of 38 patients (87%) (Table 1). For nine patients, the subspecies of the *Streptococcus gallolyticus* was reported; eight were *S. gallolyticus* ssp. *pasteurianus*.[11-17]

Fourteen of 42 patients (33%) received adjuvant treatment with dexamethasone. Complications of *S. gallolyticus* meningitis were reported in eight of 36 patients (22%), and consisted of atrial fibrillation, respiratory insufficiency, pneumonia, hearing loss, transient facial nerve paralysis, seizures, hyponatraemia, and progression despite treatment, occurring in one patient each.

Eight of 37 patients died (22%) and three survivors (10%) had sequelae, consisting of hearing loss in one patient and persisting nausea in two patients; both patients appeared to have strongyloidiasis, and the nausea disappeared after treatment.

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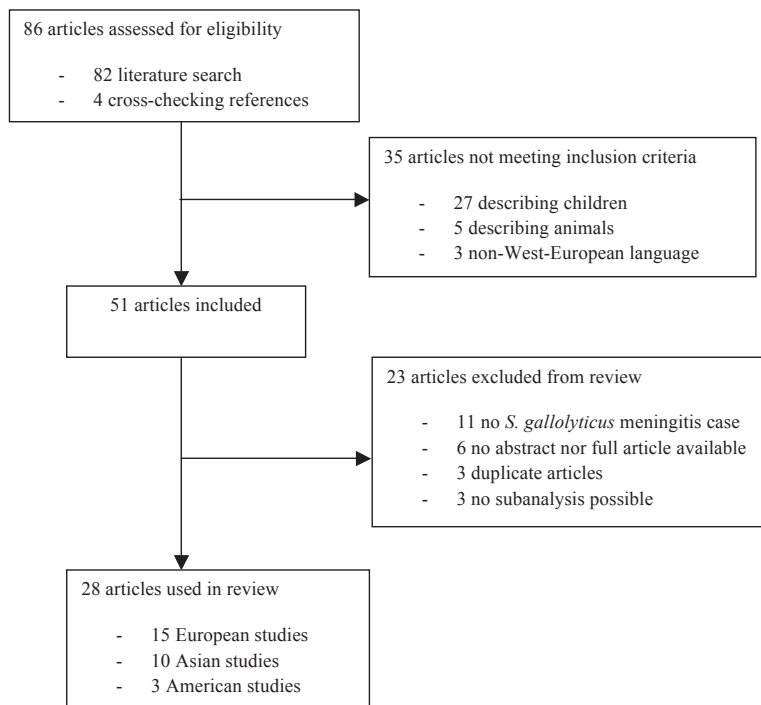
Figure 2. Flowchart review of the literature *Streptococcus gallolyticus* meningitis

Discussion

S. gallolyticus is a rare cause of community-acquired bacterial meningitis. Only five of 1561 patients in our cohort (0.3%) were infected with *S. gallolyticus*. In the literature, cases of *S. gallolyticus* meningitis have been described in cohorts of patients with specific risk factors. In a cohort of patients with bacterial meningitis and liver cirrhosis, one of 12 patients had *S. gallolyticus* meningitis, and in a case series of patients with bacterial meningitis and coexisting strongyloidiasis, one of six patients had *S. gallolyticus* meningitis.[20, 25] In two cohorts of patients with streptococcal meningitis, the relative incidence rates of *S. gallolyticus* meningitis were one in 26 cases and one in 29 cases.[28, 29]

Table 2. Clinical characteristics, etiology and clinical outcome for adults with *Streptococcus gallolyticus* meningitis; combination of our patients and patients reported in the literature

Characteristics	n/N (%)
Median age (range)	59 (23-91)
Male sex	27/41 (66)
Immunocompromised	18/42 (43)
Immunosuppressants	7 (17)
Cancer	4 (10)
Alcoholism	4 (10)
HIV-infection	3 (7)
Diabetes mellitus	3 (7)
Renal failure	2 (7)
Splenectomy	1 (2)
Clinical presentation	
Headache	21/31 (68)
Fever	26/31 (84)
Neck stiffness	20/31 (65)
Altered consciousness	13/31 (42)
Nausea	6/31 (19)
Photophobia	6/31 (19)
S. gallolyticus-associated disease	
Strongyloidiasis	14/34 (41)
Endocarditis	5/28 (18)
Colon abnormalities	15/24 (63)
Positive cultures	
Cerebrospinal fluid	36/41 (88)
Blood	33/38 (87)
Both	27/37 (43)
Complications	8/36 (22)
Outcome	
Death	8/37 (22)
Sequelae	3/29 (10)
Full recovery	26/29 (90)

Abbreviations: HIV: human immunodeficiency virus

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Table 3. Cases of *Streptococcus gallolyticus* meningitis reported in the literature, combined with our patients

	Age	Gender	Predisposing conditions	*S. stercoralis*	Symptoms	GCS	Bowel abnormalities / endocarditis	GOS
Shimasaki[18]	49	M	HTLV-1	Yes	1;2	N.R.	Colon adenoma	5
	40	F	HTLV-1	Yes	N.R.	N.R.	Not performed	5
Pukkila[11]	37	M	Immunosuppressants	Yes	1;3	15	Endocarditis	5
Khan[19]	27	M	Immunosuppressants	Yes	1;2;3	15	N.R.	4
Sasaki[20]	49	M	HTLV-1	Yes	N.R.	N.R.	Colon adenoma	5
	46	M	HTLV-1	Yes	N.R.	N.R.	Not performed	1
	66	M	HTLV-1	Yes	N.R.	N.R.	Diverticulosis	5
	44	M	HTLV-1	Yes	N.R.	N.R.	Not performed	5
	40	F	HTLV-1	Yes	N.R.	N.R.	Not performed	5
	66	M	HTLV-1	Yes	N.R.	N.R.	Not performed	5
Neves[21]	75	F	No	No	1;2	15	Diverticulosis	4
Hager[22]	69	F	No	Yes	1;3;4	N.R.	Not performed	5
Da Costa[23]	44	M	After scoliosis surgery[a]	No	2;3	15	N.R.	5
Shipway[24]	75	M	No	No	1;2;3;4	13	Colon carcinoma	1
Barahona[25]	N.R.	N.R.	Alcoholism	No	N.R.	N.R.	N.R.	N.R.
Smith[12]	61	F	No	No	1;2;3	15	Hemorrhoids	5
Sturt[13]	75	M	Prostate carcinoma (past)	No	1;2;3	N.R.	Radiation proctitis	N.R.
De Silva[26]	23	F	HIV	Yes	1;2;3	15	Colon ulcers	5
Namiduru[14]	70	M	No	No	2;3;4	13	No	5
Carnero[27]	74	M	Spleen infarction	No	1;2	N.R.	Endocarditis, diverticulosis	5
Vilarrasa[15]	45	M	No	N.R.	1;2;3;4	9	N.R.	5
Möller[28]	67	F	Breast cancer	No	N.R.	N.R.	N.R.	N.R.
Cabellos[29]	38	M	Ventriculostomy	No	N.R.	N.R.	N.R.	1
Link[9]	64	M	Immunosuppressants	Yes	1;2	N.R.	No	4

Study	Age	Sex	Predisposing condition	Communication	Symptoms	GCS	Associated condition	GOS
Cohen[16]	53	M	HIV; splenectomy	No	1;2;3	15	No	5
	70	M	DM; alcoholism; renal failure	No	1;2	15	Colon adenoma	1
Jain[30]	37	F	HIV	Yes	2;3;4	13	No	1
Ferrer[17]	61	M	Immunosuppressants	No	1;2	15	Diverticulosis	5
Harley[31]	41	M	No	No	4	13	Colon adenoma	5
Purdy[32]	32	F	CSF leakage	No	2;3	15	No	5
	79	M	No	No	1;2;3;4	13	Diverticulosis	5
Jacobson[4]	59	M	DM2; alcoholism	No	1;2;3	14	No	5
Jadeja[33]	56	F	Lymphoma; immunosuppressants	No	1;4	13	Radiation enterocolitis	5
Gavryck[34]	66	M	Immunosuppressants	No	2	14	Endocarditis	5
Weitberg[35]	90	F	No	No	2	14	Coloncarcinoma	1
Lerner[36]	56	M	Alcoholism	N.R.	4	13	Endocarditis	N.R.
	49	F	No	N.R.	N.R.	N.R.	Endocarditis	N.R.
This study	74	M	Leukemia	Unknown	2;3	14	Unknown	5
	91	F	No	Unknown	1;2;3;4	9	Not performed	1
	77	M	Immunosuppressants; renal failure	Unknown	2;3;4	3	Not performed	1
	50	M	No	Unknown	1;2;3	15	No	5
	84	F	DM2	Unknown	1;2;3	14	Colon polyps	5

Abbreviations: CSF: cerebrospinal fluid; DM2: diabetes mellitus type 2; F: female; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; M: male; N.R.: not reported

aThis patient had undergone scoliosis surgery. There was communication between an infectious cyst in the bone cavity and the intradural space
Symptoms: 1: headache; 2: fever; 3: neck stiffness; 4: altered consciousness

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Risk factors for *S. gallolyticus* meningitis are endocarditis[3] and colon disease.[5, 7] *S. gallolyticus* infection is the cause of 2-10% of cases of bacterial endocarditis, and is associated with advanced age as compared with bacterial endocarditis caused by other pathogens.[37] Endocarditis has been described to be caused by *S. gallolyticus* ssp. *gallolyticus* more frequently than by ssp. *pasteurianus* – reported rates vary between 43% and 100%, as compared with rates of 8% to 29%.[38, 39] In our study, one patient was infected with *S. gallolyticus* ssp. *pasteurianus*, and none of the patients was diagnosed with endocarditis. The rate of endocarditis could have been under-reported, because only two patients underwent echocardiography. In our meta-analysis, five of 28 patients were diagnosed with endocarditis, and colonoscopy was abnormal in 15 of 24 patients. When *S. gallolyticus* is identified in patients with bacterial meningitis, consultation by a gastroenterologist and cardiologist is warranted to identify whether a colonic disease or endocarditis is present as risk factor for *S. gallolyticus* meningitis, in most cases by colonoscopy and echocardiography.[40]

Strongyloidiasis has been described as a risk factor for *S. gallolyticus* meningitis.[18, 20] This is due to increased permeability of the bowel wall, through which *S. gallolyticus* can invade the bloodstream and thus cause sepsis and meningitis. In endemic areas such and Brazil and Thailand, *Strongyloides stercoralis* infection has an estimated prevalence of 10-40%.[41] One of our patients had visited Thailand prior to developing *S. gallolyticus* meningitis, where he could have been infected with *Strongyloides stercoralis*. Strongyloidiasis has been described as a disease imported by travelers to endemic areas even 60 years after travel.[41] In our patient, no stool examination was performed to detect *Strongyloides stercoralis*. So far, all patients with *S. gallolyticus* meningitis due to *Strongyloides stercoralis* infection reported in the literature have lived in an endemic area, and imported cases have not been described. Strongyloidiasis may cause mild gastrointestinal symptoms such as diarrhoea, pulmonary symptoms, or no symptoms at all, and may therefore go unnoticed. High-risk groups for *Strongyloides stercoralis* infection are alcoholics, HIV-infected and HTLV-1-infected persons, cancer patients, and other patients who are immunocompromised. All but one of the patients with strongyloidiasis in our meta-analysis were immunocompromised. It has previously been

reported that immunocompromised patients with strongyloidiasis are prone to meningitis or sepsis with enteric organisms.[42] Testing for *Strongyloides stercoralis* and (if positive) HIV testing should be performed in patients with *S. gallolyticus* meningitis who have travelled to or originate from areas endemic for strongyloidiasis.

Our study has several limitations. As this is an observational cohort study, patients did not undergo diagnostic procedures or testing according to a prespecified protocol. Therefore, the patients were not routinely tested for HIV, HTLV-1, and strongyloidiasis, and colonoscopy and echocardiography were not performed in all patients; risk factors for *S. gallolyticus* meningitis could therefore have been missed. Furthermore, not all patients with suspected bacterial meningitis may undergo a lumbar puncture, e.g. patients with coagulopathy due to sepsis or those with space-occupying lesions on cranial imaging. These patients were not included in our cohort, which may have led to a possible underestimation of the incidence of *S. gallolyticus* meningitis. In our meta-analysis, it was often the case that not all characteristics of interest were reported in the retrieved case reports. Therefore, we have presented the total number of patients for whom the specific characteristic was reported. Furthermore, there are inherent difficulties in identifying *S. gallolyticus* accurately to the subspecies level, in particular because of the use of multiple methods for identification, changing nomenclature, and the wide variations in time and geographical regions analysed.

We conclude that *S. gallolyticus* is a rare cause of bacterial meningitis. When it is identified, consultation with a gastroenterologist and cardiologist is warranted, to identify whether a concomitant colon disease or endocarditis is present. Stool examinations for *Strongyloides stercoralis* should be performed in patients who have travelled to or originate from endemic areas.

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CHAPTER 9

GENERAL DISCUSSION: ZOONOTIC BACTERIAL MENINGITIS IN ADULTS

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Diederik van de Beek

Abstract

Introduction: We describe the epidemiology, etiology, clinical characteristics, treatment, outcome and prevention of zoonotic bacterial meningitis in human adults.

Methods: We identified 16 zoonotic bacteria causing meningitis in adults.

Results: Zoonotic bacterial meningitis is uncommon compared to bacterial meningitis caused by human pathogens, and the incidence has a strong regional distribution. Zoonotic bacterial meningitis is mainly associated with animal contact, consumption of animal products and an immunocompromised state of the patient. In a high proportion of zoonotic bacterial meningitis cases, CSF analysis showed only a mildly elevated leukocyte count. The recommended antibiotic therapy differs per pathogen, and the overall mortality is low.

Conclusion: Zoonotic bacterial meningitis is uncommon but is associated with specific complications. The suspicion should be raised in patients with bacterial meningitis who have recreational or professional contact with animals, and in patients living in regions endemic for specific zoonotic pathogens. An immunocompromised state is associated with a worse prognosis. Identification of risk factors and underlying disease is necessary to improve treatment.

Introduction

Community-acquired bacterial meningitis is a severe infectious disease with a high morbidity and mortality. In 85% of the cases of meningitis in adults, the infection is caused by *Streptococcus pneumoniae* and *Neisseria meningitidis*.[1] These bacteria are part of the normal human nasopharyngeal flora and cause meningitis in both immunocompromised and healthy individuals. Other microorganisms causing bacterial meningitis are more commonly associated with specific risk factors. For example, meningitis caused by *Listeria monocytogenes* is more common in elderly and immunocompromised patients than in healthy individuals. *Staphylococcus aureus*, a bacterium living on the human mucosal surfaces, mainly causes meningitis in patients with endocarditis and CSF drains.[2]

In patients presenting with bacterial meningitis, rapid identification of the bacteria causing the infection is essential for choice of treatment and for prediction of outcome. An uncommon but potentially important risk factor for bacterial meningitis is contact with animals or animal products. Bacteria originating from animals that are able to cause disease in humans are referred to as zoonotic pathogens and are present in domestic animals, livestock and wildlife. Meningitis caused by pathogens originating from humans has been studied, but little is known about the clinical presentation, risk factors, complications and prognosis of meningitis caused by bacteria originating from animals. The aim of this review was to describe the epidemiology, etiology, clinical characteristics, treatment, outcome and prevention of zoonotic bacterial meningitis in adults.

Search strategy and selection criteria

We defined zoonotic bacterial meningitis as meningitis caused by bacteria that have their natural reservoir in animals and are not part of the commensal human flora. To identify these bacteria, we searched the websites of the Centers for Disease Control and Prevention[3] and the World Health Organization for lists of zoonotic infectious diseases. We searched the names of the identified zoonotic bacteria on PubMed, Google Scholar and Embase, combined with the word "meningitis" (e.g., "*Streptococcus suis*

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AND meningitis"), to investigate which zoonotic bacteria cause meningitis in adults. Other pathogens causing meningitis such as spirochetes, e.g., *Borrelia burgdorferi*, parasites, e.g., *Ehrlichia*, and virusus, e.g., rabies, were excluded. Also, the pathogen *L. monocytogenes* was excluded since this is mainly a foodborne pathogen and it has been described extensively. In total, we identified 16 zoonotic bacteria that have been reported to cause meningitis (Figure 1). Meningitis caused by *Yersinia pestis* (carried by rats) and *Streptococcus iniae* (carried by fish) are not described in this review.

Epidemiology

Zoonotic bacterial meningitis is uncommon compared to bacterial meningitis caused by human pathogens. In cohort studies of patients with bacterial meningitis, zoonotic pathogens are identified in less than 1% of episodes.[4-6] Moreover, fewer than 100 cases of meningitis have been reported per zoonotic pathogen (Table 1), except for *Streptococcus suis* and *Leptospira*.[7,8] However, it must be kept in mind that cases of zoonotic bacterial meningitis are likely to be underreported.

The incidence and causes of zoonotic bacterial meningitis have a strong regional distribution. Most zoonotic pathogens are endemic in subtropical and tropical regions, such as *Leptospira* and *Brucella*.[8,9] *S. suis* is the most common cause of bacterial meningitis in Southeast Asia, attributed to pig rearing and pork consumption.[7] On the contrary, cases of meningitis caused by pathogens having their natural reservoir in cats, dogs and horses, such as *Capnocytophaga spp* and *Streptococcus equi*, are mainly reported in Europe and the United States - however, this could be attributable to publication bias.

Most cases of zoonotic bacterial meningitis follow contact with animals or consumption of animal products (Table 1,2). The animals carrying the zoonotic pathogens may be sick, as in anthrax or tularaemia,[10,11] or not clinically affected, as in *S. suis* infection or *Capnocytophaga canimorsus* infection.[12,13] Other factors associated with zoonotic bacterial meningitis are an immunocompromised state[14,15] and person-to-person transmission.[16,17]

Rare causes of zoonotic bacterial meningitis are bioterrorism agents[18,19] and iatrogenic transmission.[20,21]

Animal contact

Animal contact is the main risk factor for zoonotic bacterial meningitis (Table 1,2, Figure 1). For example, *S. equi* meningitis is associated with regular horse contact,[22] and *Coxiella burnetii* meningitis and *Campylobacter fetus* meningitis are associated with regular contact with cattle, goats and sheep (Table 1, Figure 1).[15,23] Moreover, several occupations are associated with zoonotic bacterial meningitis: butchers and abattoir workers have an increased risk of contracting *S. suis* meningitis,[12] and *Brucella* meningitis is mainly reported in farmers and veterinarians.[9] The presence of skin lesions increases the risk of contracting *S. suis* meningitis when working with pigs[24] and of contracting *Bacillus anthracis* meningitis when working with cattle.[25]

Zoonotic bacterial meningitis is occasionally associated with animal scratches and animal bites. For example, *Bartonella henselae* meningitis follows cat scratches.[26] A history of dog bites is often described in patients with meningitis caused by the canine pathogens *C. canimorsus, Pasteurella multocida* and *Capnocytophaga cynodegmi*.[13,27] Although these pathogens are present as a commensal in 21% and 19% of the oral flora of cats and dogs, respectively, animal bites rarely result in meningitis: only approximately 30 cases of *C. canimorsus* meningitis and 40 cases of *P. multocida* meningitis have been reported worldwide in adults (Table 1).[13,27] In addition, only one case of *C. cynodegmi* meningitis has been described so far.[28]

Zoonotic bacterial meningitis is not always related to direct animal contact. For instance, leptospiral meningitis often follows swimming in (sub)tropical fresh water sources contaminated with animal urine. Furthermore, some zoonotic pathogens are harboured by meat and dairy products. Ingestion of contaminated undercooked pig products is the main risk factor for *S. suis* infection in Southeast Asia. Unpasteurized dairy products may contain several zoonotic pathogens[29,30] (Table 1) and consumption of these products is therefore discouraged by the Centers for Disease Control and Prevention.[31] Nonetheless, several outbreaks of zoonotic bacterial meningitis have been reported after consumption of unpasteurized dairy products.[29,30]

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Not all zoonotic bacteria causing meningitis in human adults cause meningitis in animals. However, most zoonotic pathogens do cause some kind of infection in animals, such as endometritis in *C. fetus* infected goats or kidney failure in *Leptospira* infected dogs. Some zoonotic pathogens do not cause any disease in animals, such as *C. canimorsus* in dogs and *B. henselae* in cats; however, these pathogens are usually more virulent in immunocompromised patients.[13,32,33]
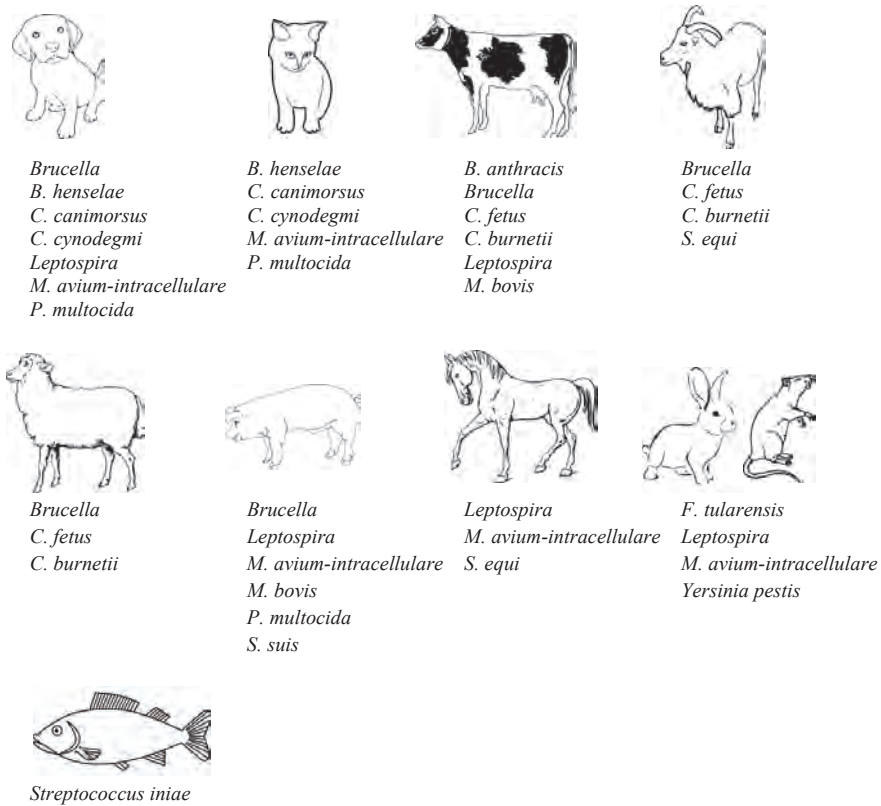

Brucella
B. henselae
C. canimorsus
C. cynodegmi
Leptospira
M. avium-intracellulare
P. multocida

B. henselae
C. canimorsus
C. cynodegmi
M. avium-intracellulare
P. multocida

B. anthracis
Brucella
C. fetus
C. burnetii
Leptospira
M. bovis

Brucella
C. fetus
C. burnetii
S. equi

Brucella
C. fetus
C. burnetii

Brucella
Leptospira
M. avium-intracellulare
M. bovis
P. multocida
S. suis

Leptospira
M. avium-intracellulare
S. equi

F. tularensis
Leptospira
M. avium-intracellulare
Yersinia pestis

Streptococcus iniae

Figure 1. Animals carrying zoonotic pathogens that may cause bacterial meningitis

Immunocompromised state

Bacterial meningitis in general occurs relatively more frequently in patients with an immunocompromised state, which has been defined as the use of immunosuppressive drugs, asplenia, diabetes mellitus, cancer, and infection

with the human immunodeficiency virus (HIV).[2] Meningitis caused by *Mycobacterium bovis*, *Mycobacterium avium-intracellulare* and *B. henselae* has been associated with HIV infection.[33-35] *C. cynodegmi* meningitis has only been reported in a splenectomised patient.[28] *C. canimorsus* meningitis has been associated with splenectomy and alcoholism.[13] *S. suis* meningitis and *P. multocida* meningitis have mainly occurred in previously healthy individuals.[7,27]

Person to person transmission

The pathogens causing zoonotic bacterial meningitis are rarely transmitted between individuals. However, a few case reports describe person-to-person transmission of Q-fever, bovine tuberculosis and *C. fetus* infection.[16,17,36] In pregnant women with *C. fetus* gastro-enteritis, *C. fetus* has been reported to pass through the placenta, leading to premature labour and *C. fetus* septicaemia and meningitis in the neonate.[37]

Bioterrorism agents

Several zoonotic pathogens have been considered to be a serious potential bioterrorist threat. In 2001, anthrax powder was used in a series of attacks on the offices of several United States senators.[11] The bacteria caused infection by inhalation, which rarely resulted in meningitis as manifestation of the disease.[11] *Francisella tularensis*, *Brucella* and *Coxiella burnetii* have not been used as bioterrorism agents, but have been considered to be a threat, since the bacteria are very infectious through aerosol route, and even a small number of bacteria can cause disease.[10,18,19] Nevertheless, bioterrorism has not been described as a cause of zoonotic bacterial meningitis so far.

Iatrogenic transmission

Several cases of *M. bovis* meningitis have been reported after BCG vaccination and intravesical BCG instillation.[20,38] All cases were reported in patients who were immunocompromised due to cancer or HIV. Intravesical BCG instillation may induce disseminated infection in immunocompromised patients.[20] In patients with HIV, the attenuated *M. bovis* bacilli in the BCG vaccination may cause meningitis even years after vaccination.[38] All patients with iatrogenic *M. bovis* meningitis recovered after lengthy treatment with tuberculostatic agents.

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Table 1. Epidemiology and etiology of zoonotic bacterial meningitis; collected data from several systematic reviews and case reports

Name of pathogen (systemic infection)	Main reservoir	Main continent	Number of cases	Age (median)	Male gender
Bartonella henselae	Cats, dogs	North America, South America	4[26,32,33]	44	100%
Campylobacter fetus	Cattle, goats, sheep	North America, Western Europe	22[15]	48	73%
Capnocytophaga canimorsus	Cats, dogs	North America, Europe	33[13]	63	85%
Capnocytophaga cynodegmi	Cats, dogs	North America	1[28]	72	0%
Pasteurella multocida	Cats, dogs, pigs	Europe, North America	36[27,54]	54	50%
Streptococcus equi	Donkeys, goats, horses, dairy[b]	Europe, North America	34[22]	61	53%
Streptococcus suis	Pigs	South-east Asia	913[7]	49	82%
Bacillus anthracis (anthrax)	Cattle	North America, Europe	70[40]	41	77%
Brucella (brucellosis)	Camels, goats, sheep (ssp. *melitensis*), cattle (ssp. *abortus*), dogs (ssp. *canis*), pigs (ssp. *suis*), dairy[b]	Middle-East, USA	18[55]	38	61%
Coxiella burnetii (Q-fever)	Cattle, goats, sheep, dairy[b]	USA, Australia, Middle-East	21[41]	34	67%
Francisella tularensis (tularaemia)	Rabbits, rodents	USA, Western Europe	5[49]	51	60%
Leptospira (leptospirosis)	Cattle, dogs, horses, pigs, rodents, wildlife, water[c]	Asia, Europe	366[8]	33	82%
Mycobacterium avium-intracellulare (avian tuberculosis)	Birds, cats, deer, dogs, horses, pigs, rabbits, water[c]	USA, Europe, Africa	31[35]	33	45%
Mycobacterium bovis (bovine tuberculosis)	Cattle, deer, pigs, wild carnivores, dairy[b]	Europe	5[a,34,36,56-58]	39	80%

[a]Non-iatrogenic cases of *M. bovis* meningitis, [b]Unpasteurized dairy products, [c]Fresh water contaminated with animal excretions

Clinical presentation

Bacterial meningitis typically presents with headache, fever, neck stiffness and an altered mental status (Glasgow Coma Scale score <14).[39] In a prospective nationwide cohort of 1412 adults with culture-proven bacterial meningitis, 83% presented with headache, 74% with fever, 74% with neck

stiffness and 71% with an altered mental status.[39] In zoonotic bacterial meningitis, headache, fever and neck stiffness are common symptoms, but an altered mental status is less frequently encountered (Table 2). An exception is *B. anthracis* meningitis, which is characterized by an altered mental status early in the clinical course since both the meninges and the brain parenchyma are affected, and therefore, it must be considered more on the encephalitis spectrum of disease than meningitis.[40]

In several zoonotic diseases, meningitis occurs as part of a systemic infection. Meningitis caused by *Leptospira*, *Brucella* and *C. burnetii* occurs in patients with leptospirosis, brucellosis, and Q-fever, respectively.[8,41,42] Patients with these systemic infections often present with a flu-like illness characterized by headache, myalgia and fever. However, many of these patients do not have meningitis. In leptospirosis, only 20% of the patients presenting with headache and fever had CSF abnormalities and thus *Leptospira* meningitis.[8] *Brucella* meningitis was seen in 5% of the brucellosis patients,[42] and only 1% of Q-fever patients had *C. burnetii* meningitis.[23] Compared to non-zoonotic bacterial meningitis, meningitis caused by *Leptospira, Brucella* and *C. burnetii* is generally less severe and has a better outcome. Other systemic infections in which meningitis has been reported are cat scratch disease and tularaemia. Cat scratch disease is caused by *B. henselae* and is characterized by fever and lymph node enlargement.[26] Tularaemia is caused by *F. tularensis* and is characterized by high fever, lymph node enlargement, eye infection and pneumonia.[10] Meningitis is a rare manifestation of both infections.

Several zoonotic pathogens present with specific symptoms and concomitant infections. *S. suis* meningitis is characterized by hearing loss early in the clinical course.[7] In late-stage cutaneous anthrax, patients have painless necrotic eschars with regional lymphadenopathy.[27] *S. equi* meningitis and *P. multocida* meningitis often present with severe concomitant infections, such as endocarditis, pneumonia, endophthalmitis, encephalitis and epidural empyema.[53] *B. henselae* meningitis is often complicated by neuroretinitis.[35]

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Table 2. Etiology, clinical characteristics and outcome of zoonotic bacterial meningitis; collected data from several systematic reviews and case reports

Name of pathogen	Identified source of infection	Immuno-compromised	Headache	Fever	Neck stiffness	Mortality	Sequelae in survivors
B. henselae	100%	33% (1/3)	N.R.	100%	N.R.	0% (0/2)	0% (0/2)
C. fetus	68%	73%	64%	91%	59%	9%	15%
C. canimorsus	97%	42%	68%	93%	61%	3%	25%
C. cynodegmi	100%	100%	100%	100%	N.R.	100% (1/1)	N/A[a]
P. multocida	88%	N.R.	63%	100%	88%	20%	13%
S. equi	100%	20%	56%	100%	79%	21%	52%
S. suis	61%	0.3-19%	95%	97%	93%	3%	64%
B. anthracis	70%	N.R.	45%	71%	37%	94%	29%
Brucella	100%	N.R.	83%	44%	28%	0%	22%
C. burnetii	N.R.	N.R.	19%	57%	38%	0%	24%
F. tularensis	100%	N.R.	60%	100%	N.R.	0%	0%
Leptospira	97%	8%	94%	98%	93%	3%	5%
M. avium-intracellulare	N.R.	71%	32%	48%	N.R.	77%	N.R.
M. bovis	40%	20%	75% (3/4)	100%	75%	20%	25%

Abbreviations: N.R.: not reported. [a]No survivors

Ancillary investigations

Obtaining cerebrospinal fluid (CSF) through lumbar puncture is essential for establishing the diagnosis of bacterial meningitis.[44] In community-acquired bacterial meningitis, typical CSF abnormalities predictive for bacterial meningitis have been defined as a CSF glucose level of less than 1.9 mmol/L, a ratio of CSF glucose to blood glucose of less than 0.23, a CSF protein level of more than 2.20g/L, or a CSF leukocyte count of more than 2000/mm^3.[39] However, in zoonotic bacterial meningitis, these typical CSF abnormalities were often reported to be absent, especially in *C. fetus* meningitis and *C. canimorsus* meningitis.[13,15] Meningitis caused by *Brucella, C. burnetii, B. henselae, M. avium-intracellulare, M. bovis* and *Leptospira* presented with a mildly elevated CSF leukocyte count and a predominance of CSF lymphocytes (Table 3).[8,33-35,41,42] Meningitis caused by *B. anthracis* is typically hemorrhagic and may therefore be mistaken for a subarachnoidal hemorrhage.[25]

CSF culture is the gold standard for diagnosing bacterial meningitis.[44] Blood cultures and CSF cultures were positive in a high proportion of zoonotic bacterial meningitis cases, but regularly remained negative in meningitis caused by *C. canimorsus*, *Leptospira*, *C. burnetii*, *B. henselae* and non-tuberculous mycobacteria.[8,13,33-35,41] If cultures remain negative in suspected zoonotic bacterial meningitis,16S-rRNA PCR might be useful for identifying the causative agent. This is a highly sensitive molecular method in which a conserved region of bacterial RNA is replicated and sequenced, and then the strain-specific 16-rRNA sequence can be identified. 16S-rRNA PCR has for instance been described for the identification of *C. canimorsus*.[13] Meningitis caused by *Leptospira, C. burnetii* and *B. henselae* is typically diagnosed by means of blood serology combined with CSF abnormalities.[8,33,41] A recently described method to diagnose bacterial meningitis is next generation deep sequencing, in which all bacterial DNA is amplified to detect the pathogen. This has been described to identify neuroleptospirosis in an immunocompromised patient.[45]

Mycobacterial meningitis is notoriously difficult to diagnose in the cerebrospinal fluid. Mycobacteria can be identified by acid-fast bacilli staining and mycobacterial culture. In the case of CSF smears positive for acid-fast bacilli, the T-SPOT.TB test or interferon-gamma release assays (IGRA) can be used to differentiate the non-tuberculous mycobacteria *M. avium* and *M. bovis* from *M. tuberculosis*. Mycobacterial culture is the gold standard for diagnosing non-tuberculous mycobacterial meningitis.[46]

Patients with space-occupying lesions can often not undergo a lumbar puncture due to the risk of brain herniation.[44] Described abnormalities on cerebral imaging in zoonotic bacterial meningitis are brain abscesses (in *S. equi* meningitis, *F. tularensis* meningitis and *Brucella* meningitis),[22,47,48] brain edema (in *S. suis* meningitis)[7] and subarachnoidal bleedings and intraparenchymous bleedings (in *B. anthracis* meningitis).[40] In all patients, blood cultures should be drawn early during presentation, as these identify the causative organism in a large proportion of patients (60-80%).[44] In patients in whom lumbar puncture is not possible, blood cultures may be the only source from which the bacteria can be cultured.[44] In the case of brain abscesses, brain biopsy can be helpful to identify the causative agent.[47]

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Table 3. Cerebrospinal fluid characteristics in zoonotic bacterial meningitis; collected data from several systematic reviews and case reports

	Median CSF leukocyte count/mm³ (range)	Median CSF protein, g/L (range)	Median CSF glucose, mmol/L (range)	Positive CSF culture	Predominance of cells
B. henselae	N.R.	N.R.	N.R.	0%	Lymphocytes
C. fetus	577 (48-11000)	1.00 (0.33-5.08)	2.88 (0.30-6.83)	77%	PMN
C. canimorsus	951 (70-2376)	1.91 (0.32-5.02)	1.9 (0.1-3.7)	79%	Lymphocytes
C. cynodegmi	24 (N/A)	1.27 (N/A)	7.0 (N/A)	100%	Neutrophils
P. multocida	245 (5-622)	3.16 (N.R.)	2.52 (N.R.)	N/A[b]	Neutrophils
S. equi	1919 (31-11000)	2.62 (0.71-62.29)	2.02 (0.10-4.60)	94%	Neutrophils
S. suis	1920 (N.R.)[a]	2.4 (N.R.)[a]	1.09 (N.R.)[a]	83%	PMN
B. anthracis	N.R. (0-10,000)	N.R. (0.1-28)	N.R. (1.1-2.2)	100%	PMN
Brucella	N.R.	N.R.	N.R.	N.R.	Lymphocytes
C. burnetii	375 (16-1393)	1.43 (0.55-3.68)	N.R.	0%	Lymphocytes
F. tularensis	1956 (1200-2926)	1.75 (0.33-2.77)	2·1 (1.67-5.2)	80%	PMN
Leptospira	206 (6-2072)	1.10 (N.R.)	2.5 (N.R.)	0%	Lymphocytes
M. avium-intracellulare	598 (4-3000)	0.52 (0.38-2.41)	2.83 (1.78-3.00)	N/A[b]	Lymphocytes
M. bovis	258 (41-735)[a]	N.R.	N.R.	N.R.	Lymphocytes

Abbreviations: CSF: cerebrospinal fluid; PMN: polymorphonuclear leukocytes
[a]Mean instead of median was reported; [b]A positive CSF culture was an inclusion criterion for this study

Treatment

The recommended antibiotic treatment in patients with community-acquired bacterial meningitis depends on age, predisposing conditions and local epidemiology.[1] Resistance of bacterial pathogens to common antibiotics has been reported to be an increasing problem. Examples are vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus*. Microbial resistance to antibiotics has been reported for several zoonotic pathogens as well: reduced susceptibility of *C. canimorsus* for trimethoprim-sulfamethoxazole and gentamicin has been described,[13] of *S. zooepidemicus* for clindamycin,[22] of *P. multocida* for ceftriaxone[43] and of *C. fetus* for penicillin and cefotaxime.[15]

The recommended antibiotic therapy for zoonotic bacterial meningitis differs per pathogen (Table 4). *C. fetus* meningitis often required lengthy treatment with carbapenem antibiotics such as meropenem or imipenem.[15] *F. tularensis* is generally unresponsive to ceftriaxone, and *F. tularensis* meningitis should therefore be treated with chloramphenicol and streptomycin.[49] Leptospirosis and brucellosis are generally treated with doxycycline,[50] but no specific treatment has been investigated for *Leptospira* meningitis and *Brucella* meningitis; however, ceftriaxone is recommended for *Leptospira* meningitis. In Q-fever, doxycycline is used to shorten the course of the disease.[42]

The recommended treatment for non-tuberculous mycobacterial meningitis consists of rifampicin, ethambutol and isoniazid, with addition of azithromycin or clarithromycin for *M. avium-intracellulare* meningitis.[35,51] Tuberculous meningitis is treated by four antituberculosis drugs for at least the first 2 months of therapy, followed by treatment with rifampin and isoniazid for an additional 7 to 10 months.[52] For non-tuberculous mycobacterial meningitis, the duration of treatment has not been investigated.

Dexamethasone administration has been associated with a better outcome and survival in bacterial meningitis in general.[39] In tuberculous meningitis, adjunctive treatment with dexamethasone improved survival.[52] In *S. suis* meningitis, dexamethasone has been shown to improve hearing loss,[7] and in *B. anthracis* infection, it has been associated with a better outcome.[25] Dexamethasone administration has not been studied in meningitis caused by the other zoonotic pathogens or non-tuberculous mycobacterial meningitis, but is advised in the acute treatment of bacterial meningitis in general.[39]

Outcome and prognostic factors

The mortality of zoonotic bacterial meningitis is variable. *B. anthracis* meningitis had the worst prognosis, with a mortality of 94%.[25] *M. avium-intracellulare* meningitis had a mortality of 77%, which was associated with HIV-positivity.[35] *S. equi* meningitis had a mortality of 21% and sequelae were reported in 52% of survivors.[22] In pigs, unfavourable outcome of *S. equi* infection has been associated with specific bacterial genetic factors; these

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may also influence disease severity in humans.[22] Other factors associated with an unfavourable outcome in zoonotic bacterial meningitis are splenectomy in *C. canimorsus* meningitis and *C. cynodegmi* meningitis,[13,28] and a positive CSF culture and HIV-positivity in *M. bovis* meningitis.[51] Sequelae occurred in 0% (*F. tularensis* meningitis)[49] to 64% (*S. suis* meningitis)[7] of all cases and mainly consisted of hearing loss. For patients in whom *S. suis* is identified as causative organism of bacterial meningitis, it is important to consult the otorhinolaryngologist early for audiometry and to evaluate whether cochlear implantation is possible.[7]

Prevention

Because of the low incidence of zoonotic bacterial meningitis, it is unlikely that preventive measures lead to a decrease of the incidence. However, in case of a wound inflicted by an animal, immunocompromised patients should be considered to be treated with post-exposure prophylactic antibiotics to prevent infection.[13] Since complications have been more frequently reported in patients with meningitis after splenectomy,[13,28] these patients should be extra careful when handling animals and are advised not to choose a profession with regular animal handling. Post-exposure prophylactic antibiotics are advised in immunocompromised patients after animal bites[13] and in immunocompromised patients travelling to leptospirosis-endemic countries.[50] Prophylactic tuberculostatic agents are advised in HIV positive patients with less than 50 CD4+ T-lymphocytes/µL for prevention of *M. avium-intracellulare* infection.[35,53]

Vaccines are available for several bacteria causing zoonotic meningitis. These vaccines are generally administered to the animals serving as natural reservoir for these pathogens, such as *S. equi* in horses, *Leptospira* in dogs and *Brucella* in cattle. Human vaccines are available for infection with *Leptospira*, *C. burnetii* and *B. anthracis*, but none of these vaccines has been widely implemented. The *M. bovis* bacilli Calmette-Guérin (BCG) vaccine, used to protect humans against *Mycobacterium tuberculosis* infection, has been associated with *M. bovis* meningitis in immunocompromised patients and is therefore discouraged in patients with HIV infection.[38]

Table 4. Recommended antibiotic treatment for several causes of zoonotic bacterial meningitis

Pathogen	Recommended treatment	Alternative treatment	Post-exposure prophylaxis or prevention
B. henselae[26]	Doxycycline plus rifampicin	-	-
C. fetus[15]	Meropenem		-
C. canimorsus[13]	Penicillin, ceftriaxone	Ciprofloxacin, doxycycline	Amoxicillin
C. cynodegmi[13]	Penicillin, ceftriaxone	Ciprofloxacin, doxycycline	Amoxicillin
P. multocida[27]	Penicillin, ceftriaxone	Meropenem	-
S. equi[59]	Ceftriaxone	Penicillin	-
S. suis[7]	Ceftriaxone	Penicillin	-
B. anthracis[25]	Ciprofloxacin plus penicillin/ampicillin	Ciprofloxacin plus meropenem/ rifampicin / vancomycin	Ciprofloxacin, doxycycline
Brucella[60]	Doxycycline plus rifampicin/streptomycin	Doxycycline plus gentamicin	Doxycycline plus rifampicin
C. burnetii[41]	Doxycycline	-	-
F. tularensis[49]	Chloramphenicol plus streptomycin	Chloramphenicol plus gentamicin	-
Leptospira[8]	Ceftriaxone	Penicillin	Doxycycline
M. avium-intracellulare[35]	Rifampicin plus isoniazid plus ethambutol plus azitromycin /claritromycin	-	Rifabutin[35]
M. bovis[51]	Rifampicin plus isoniazid plus ethambutol	-	Rifabutin[35]

Conclusion

Zoonotic bacterial meningitis in adults is uncommon. The suspicion should be raised in patients with bacterial meningitis who have recreational or professional contact with animals, and in patients living in regions endemic for specific zoonotic pathogens. An immunocompromised state is associated with a worse prognosis in zoonotic bacterial meningitis. Different types of zoonotic bacterial meningitis have been described in this review and present with specific clinical characteristics, complications and outcome. Identification of risk factors and underlying disease is necessary to improve treatment.

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Future research and perspectives

This is the first research project to describe zoonotic bacterial meningitis. Zoonotic bacterial meningitis is uncommon. However, this might change, since zoonotic infectious diseases are emerging. More knowledge and identification of risk factors and underlying disease is necessary to improve diagnostics and treatment.

As animal contact is the most important risk factor for zoonotic bacterial meningitis, physicians need to be aware of this and ask patients about animal contact if they are suspected of bacterial meningitis. Furthermore, it would be useful to start a nationwide prospective surveillance to identify patients with zoonotic diseases, since many zoonotic diseases may be underreported.

Diagnosing zoonotic bacterial meningitis may be difficult. Since several zoonotic pathogens are difficult to detect due to the absence of CSF abnormalities and negative cultures, new molecular methods should be developed to identify these pathogens.

The treatment for zoonotic bacterial meningitis is highly diverse and has not been standardized. Furthermore, adjunctive dexamethasone has not been studied well. To investigate the effect of dexamethasone on mortality and neurological sequelae, one could perform a cohort study in countries endemic for specific zoonotic pathogens, *e.g.* for the non-tuberculous mycobacteria.

The mortality of meningitis caused by some zoonotic pathogens, such as *S. equi* and *B. anthracis*, is high. In pigs, unfavourable outcome of *S. equi* infection has been associated with specific bacterial genetic factors; these may also influence disease severity in humans. These bacterial genetic factors could be investigated in other zoonotic pathogens as well, to improve the prognosis and prevent sequelae of zoonotic bacterial meningitis.

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SUMMARY

Zoonotic bacterial meningitis in adults: clinical characteristics, etiology, treatment and outcome

Since the early days of history, it has been known that diseases can be transmitted from animals to humans. More than 200 zoonotic diseases have been described, of which some have had a major impact on human civilization. Since the invention of modern sanitation and public health practice, the spread of infectious diseases has declined markedly. Nevertheless, more than 60% of the emerging infectious diseases are zoonotic and zoonotic diseases are thus an increasing public health problem. One of the possible clinical manifestations of a zoonotic bacterial infection is meningitis. Meningitis caused by pathogens originating from humans has been studied, but little is known about the clinical presentation, risk factors, complications and prognosis of meningitis caused by bacteria originating from animals. In this thesis, we describe several zoonotic causes of bacterial meningitis and give an overview on zoonotic bacterial meningitis in general.

In **Chapters 2-6**, we describe cases of zoonotic bacterial meningitis identified in a nationwide prospective cohort study of adult bacterial meningitis patients, and perform a literature review on each zoonotic pathogen.

In **Chapter 2**, we discuss *Streptococcus equi* meningitis. *S. equi* meningitis is associated with horse contact and the consumption of unpasteurized dairy products. Although rare, the associated mortality is high and many survivors suffer from neurological sequelae. Endocarditis should be considered in all patients with *S. equi* meningitis.

In **Chapters 3** and **4**, we describe cases of *Streptococcus suis* meningitis in the Netherlands and perform a systematic review and meta-analysis on *S. suis* meningitis. In the Netherlands, *S. suis* meningitis remains a rare disease which should be considered in patients with professional pig contact. In general, *S. suis* meningitis is predominantly seen in men after contact with pigs or pork and is endemic in pig rearing and pork consuming countries such as Vietnam, Thailand and China. The typical clinical presentation consists of hearing loss, fever, headache and neck stiffness, and skin injury in the presence of pig/pork contact is present in 20% of the cases. Although the mortality of *S. suis* meningitis is low compared with *S. suis* infection in general and other causes of bacterial meningitis, 53% of patients end up with hearing loss. Dexamethasone has shown to reduce hearing loss.

In **Chapter 5**, we discuss *Capnocytophaga canimorsus* meningitis. *C. canimorsus* meningitis has a clear association with dog bites and an immunocompromised status. Since CSF cultures may remain negative during the first days, molecular diagnostic tools based on 16S rRNA gene amplification of bacterial DNA in CSF following PCR is recommended in patients with meningitis after a dog bite and negative initial CSF cultures. When bacterial meningitis occurs after a dog bite, other pathogens originating from dogs as a cause of the bacterial meningitis, such as *Pasteurella multocida* and *Capnocytohaga cynodegmi*, should be kept in mind when the choice for empirical antibiotic treatment is made.

In **Chapter 6**, we discuss *Campylobacter fetus* meningitis. *C. fetus* is a rare cause of bacterial meningitis and is associated with an immunocompromised state. Recurrence of symptoms is often described and prolonged antibiotics treatment with meropenem or imipenem is recommended.

In **Chapter 7**, we discuss leptospiral meningitis. In the case of suspected meningitis and a history of visiting tropical areas or direct or indirect contact with animal urine, leptospiral meningitis should be considered. Cerebrospinal fluid examination is vital for the differential diagnosis of leptospirosis. Outcome is generally favourable in patients with leptospiral meningitis treated with antibiotics.

In **Chapter 8**, we describe cases of *Streptococcus gallolyticus* meningitis and perform a review of the literature. *S. gallolyticus* was first discovered in cattle, but cases of *S. gallolyticus* meningitis are not associated with animal contact. However, *S. gallolyticus* meningitis is associated with colon diseases and endocarditis, and therefore, consulting a gastroenterologist and cardiologist is important. Stool examinations for *Strongyloides stercoralis* should be performed in patients who have travelled to or originate from endemic areas.

Finally, an overview of zoonotic bacterial meningitis in adults in general is provided in **Chapter 9**. Zoonotic bacterial meningitis is uncommon and the suspicion should be raised in patients with bacterial meningitis who have recreational or professional contact with animals, and in patients living in regions endemic for specific zoonotic pathogens. An immunocompromised

state is associated with a worse prognosis in zoonotic bacterial meningitis. Different types of zoonotic bacterial meningitis are described and present with specific clinical characteristics, complications and outcome. Identification of risk factors and underlying disease is necessary to improve treatment.

SAMENVATTING

Zoönotische bacteriële meningitis bij volwassenen: klinische karakteristieken, etiologie, behandeling en uitkomst

Het is reeds lang bekend dat ziekten kunnen worden overgedragen van dier op mens. Wereldwijd zijn er meer dan 200 zogeheten zoönotische infectieziekten beschreven, waarvan sommigen een grote invloed hebben gehad op de beschaving. De verspreiding van infectieziekten is sterk afgenomen door hygiënische maatregelen en publieke gezondheidszorg. Meer dan 60% van de opkomende infectieziekten wordt echter veroorzaakt door zoönotische pathogenen en zoönotische infecties zijn dan ook een toenemend gezondheidsprobleem. Eén van de mogelijke uitingen van een zoönotische bacteriële infectie is hersenvliesontsteking (meningitis). Er is uitgebreid onderzoek gedaan naar meningitis veroorzaakt door humane pathogenen, maar er is weinig bekend over de klinische presentatie, risicofactoren, complicaties en prognose van meningitis veroorzaakt door van dieren afkomstige bacteriën. In dit proefschrift worden verschillende oorzaken van zoönotische bacteriële meningitis beschreven en geven we een overzicht van zoönotische bacteriële meningitis in het algemeen.

In **Hoofdstuk 2** tot en met **6** beschrijven we verschillende bacteriën die zoönotische meningitis veroorzaken. Deze bacteriën zijn geïdentificeerd in een nationale prospectieve cohort studie waarin volwassen patiënten met bacteriële meningitis in Nederland zijn geïncludeerd. Ook geven we per pathogeen een overzicht van de literatuur. In **Hoofdstuk 2** beschrijven we een casus van *Streptococcus equi* meningitis. *S. equi* meningitis is geassocieerd met contact met paarden en het consumeren van ongepasteuriseerde melkproducten. Hoewel het een zeldzame aandoening is, is de mortaliteit hoog en veel overlevende patiënten houden er restverschijnselen aan over. Bij alle patiënten met S. *equi* meningitis dient endocarditis in het achterhoofd gehouden te worden.

In **Hoofdstuk 3** en **4** beschrijven we casus van *Streptococcus suis* meningitis in Nederland en verrichten we een systematische review en meta-analyse van *S. suis* meningitis. In Nederland is *S. suis* meningitis een zeldzame ziekte waaraan gedacht moet worden bij patiënten met meningitis die

regelmatig in contact komen met varkens. *S. suis* meningitis wordt vooral gezien bij mannen die contact hebben met varkens of varkensvlees en is endemisch in landen waar varkens worden gehouden en veel varkensvlees wordt gegeten, zoals Vietnam, Thailand en China. Patiënten met *S. suis* meningitis presenteren zich meestal met gehoorverlies, hoofdpijn, koorts en nekstijfheid, en in 20% van de gevallen is er sprak van huidletsel bij patiënten die contact hebben gehad met (varkens)vlees. Hoewel de mortaliteit van *S. suis* meningitis laag is vergeleken met *S. suis* infectie in het algemeen en andere oorzaken van bacteriële meningitis, houdt 53% van de patiënten er gehoorverlies aan over. Er is aangetoond dat dexamethason in patiënten met *S. suis* meningitis gehoorverlies vermindert.

In **Hoofdstuk 5** gaan we in op *Capnocytophaga canimorsus* meningitis. *C. canimorsus* meningitis heeft een duidelijk verband met hondenbeten en een immuungecompromitteerde status. Aangezien liquorkweken de eerste dagen negatief kunnen zijn, wordt er aanbevolen om ook andere vormen van diagnostiek zoals 16S rRNA genetische amplificatie met PCR in te zetten om de bacterie te isoleren bij patiënten met meningitis die recent door een hond zijn gebeten. Als bacteriële meningitis optreedt na een hondenbeet, moet er ook gedacht worden aan andere pathogenen uit de natuurlijke flora van honden als oorzaak van de meningitis, zoals *Pasteurella multocida* en *Capnocytophaga cynodegmi*, waarop de antibiotische behandeling moet worden afgestemd.

In **Hoofdstuk 6** beschrijven we *Campylobacter fetus* meningitis. *C. fetus* is een zeldzame oorzaak van bacteriële meningitis en wordt geassocieerd met een immuungecompromitteerde status. Terugkeer van de symptomen na behandeling wordt vaak beschreven en langdurige antibiotische behandeling met meropenem of imipenem wordt aangeraden.

In **Hoofdstuk 7** beschrijven we meningitis veroorzaakt door *Leptospira*. Bij verdenking meningitis en een recent buitenlandbezoek of direct of indirect contact met dierlijke urine, dient er te worden gedacht aan leptospirose meningitis. Liquordiagnostiek is van belang voor de differentiaaldiagnose. De prognose is over het algemeen goed bij patiënten die worden behandeld met antibiotica.

In **Hoofdstuk 8** beschrijven we een aantal patiënten met *Streptococcus gallolyticus* meningitis en geven we een overzicht van de literatuur. *S. gallolyticus* werd voor het eerst geïdentificeerd in runderen, maar *S. gallolyticus* meningitis is niet geassocieerd met diercontact. *S. gallolyticus* meningitis wordt wel geassocieerd met aandoeningen aan de dikke darm en endocarditis. Het is daarom belangrijk om een gastro-enteroloog en cardioloog te consulteren, om de bovengenoemde aandoeningen uit te sluiten. Bij patiënten afkomstig uit gebieden komen die endemisch zijn voor *Strongyloides stercoralis*, is ontlastingsonderzoek geïndiceerd.

Tot slot geven we in **Hoofdstuk 9** een overzicht van zoönotische bacteriële meningitis in het algemeen. Zoönotische bacteriële meningitis komt niet vaak voor en er dient aan gedacht te worden bij patiënten met bacteriële meningitis die recreatief dan wel professioneel contact hebben met dieren, en bij patiënten die in gebieden wonen die endemisch zijn voor bepaalde zoönotische pathogenen. Een immuungecompromitteerde status wordt geassocieerd met een slechtere prognose. In Hoofdstuk 9 worden verschillende oorzaken van zoönotische bacteriële meningitis beschreven, die zich presenteren met specifieke klinische karakteristieken, complicaties en prognose. Identificatie van risicofactoren en onderliggende aandoeningen is essentieel om de therapie te verbeteren.

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Graag wil ik iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit proefschrift. Een aantal mensen wil ik in het bijzonder bedanken:

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PORTFOLIO

Curriculum vitae

Anusha van Samkar was born on January 19, 1992 in Leiden, the Netherlands. She graduated cum laude from grammar school (Gemeentelijk Gymnasium Hilversum) in July 2009. In September 2009, she started her medical education at the University of Amsterdam, which she completed cum laude in 6 years. During her medical education, she published an article on detecting vision disorders as co-author and an article on quality of life after endoscopic surgery on sinonasal inverted papillomas as first author.

In February 2015, Anusha started her scientific research internship on zoonotic bacterial meningitis at the Department of Neurology of the Academic Medical Centre, under supervision of prof. dr. D. van de Beek and dr. M.C. Brouwer. After four publications, the scientific research internship was continued as PhD project under supervision of prof. dr. D. van de Beek, dr. M.C. Brouwer and dr. A. van der Ende, and Anusha continued writing research articles, resulting in this thesis. From September 2015 to September 2016, she works as resident (ANIOS) in Neurology in Gelre ziekenhuizen Apeldoorn, while completing the PhD thesis. From October 2016 onwards, she will work as resident in Neurology in the Canisius Wilhelmina hospital in Nijmegen.

Publications

In this thesis

1. **van Samkar A**, Brouwer MC, van der Ende A, van de Beek D. Letter to the editor: *Streptococcus equi* meningitis. *Clin Microbiol Infect* 2016; 22: e3-4.
Author contributions: AvS, MCB and DvdB designed the study. AvS, MCB, AvdE and DvdB acquired the data. AvS, MCB and DvdB analysed and interpreted the data. AvS, MCB, AvdE and DvdB drafted the manuscript, revised it critically and gave final approval of this version of the manuscript. No conflicts of interests were declared.

2. **van Samkar A**, Brouwer MC, Schultsz C, van der Ende A, van de Beek D. *Streptococcus suis* meningitis in the Netherlands. *J Infect* 2015; 71: 602-4.
Author contributions: AvS, MCB and DvdB designed the study. AvS, MCB, CS, AvdE and DvdB acquired the data. AvS, MCB and DvdB analysed and interpreted the data. AvS, MCB, CS, AvdE and DvdB drafted the manuscript, revised it critically and gave final approval of this version of the manuscript. No conflicts of interests were declared.

3. **van Samkar A**, Brouwer MC, Schultsz C, van der Ende A, van de Beek D. *Streptococcus suis* Meningitis: A Systematic Review and Meta-analysis. *PLoS Negl Trop Dis* 2015; 9: e0004191.
Author contributions: AvS, MCB, CS, AvdE and DvdB designed the study and acquired the data. AvS, MCB, CS and DvdB analysed and interpreted the data. AvS, MCB, CS, AvdE and DvdB drafted the manuscript, revised it critically and gave final approval of this version of the manuscript. No conflicts of interests were declared.

4. **van Samkar A**, Brouwer MC, Schultsz C, van der Ende A, van de Beek D. *Capnocytophaga canimorsus* meningitis in adults: three cases and a review of the literature. *Zoonoses Public Health* 2016; 63: 442-8.
Author contributions: AvS, MCB and DvdB designed the study and acquired the data. AvS, MCB, CS, AvdE and DvdB analysed and interpreted the data. AvS, MCB, CS, AvdE and DvdB drafted the manuscript, revised it critically and gave final approval of this version of the manuscript. No conflicts of interests were declared.

5. **van Samkar A**, Brouwer MC, van der Ende A, van de Beek D. *Campylobacter fetus* meningitis in adults: report of two cases and review of the literature. *Medicine* 2016; 95: e2858.
Author contributions: AvS, MCB, and DvdB designed the study. AvS, MCB, AvdE and DvdB acquired the data. AvS, MCB and DvdB analysed and interpreted the data. AvS, MCB, AvdE and DvdB drafted the manuscript, revised it critically and gave final approval of this version of the manuscript. No conflicts of interests were declared.

6. **van Samkar A**, van de Beek D, Stijnis C, Goris M, Brouwer MC. Suspected leptospiral meningitis in adults: report of four cases and review of the literature. *Neth J Med* 2015; 73: 464-70.
Author contributions: AvS, DvdB, CS and MCB designed the study. AvS and CS acquired the clinical data. MG acquired the epidemiological data. AvS, DvdB, CS, MG and MCB analysed and interpreted the data. AvS, DvdB, CS, MG and MCB drafted the manuscript and revised it critically. All authors gave final approval of this version of the manuscript. No conflicts of interests were declared.

7. **van Samkar A**, Brouwer MC, Pannekoek Y, van der Ende A, van de Beek D. *Streptococcus gallolyticus* meningitis in adults: report of five cases and review of the literature. *Clin Microbiol Infect* 2015; 21: 1077-83.
Author contributions: AvS, MCB, YP, AvdE and DvdB designed the study and acquired the data. YP and AvdE developed the molecular biological technique for identifying the subspecies. AvS, MCB and DvdB analysed and interpreted the data. AvS, MCB, YP, AvdE and DvdB drafted the manuscript, revised it critically and gave final approval of this version of the manuscript. No conflicts of interests were declared.

8. **van Samkar A,** Brouwer MC, van der Ende A, van de Beek D. Zoonotic bacterial meningitis in human adults: clinical characteristics, etiology, treatment and outcome. *Neurology* 2016, *article published online*.
Author contributions: AvS, MCB, and DvdB designed the study. AvS, MCB, AvdE and DvdB acquired the data. AvS, MCB and DvdB analysed and interpreted the data. AvS, MCB, AvdE and DvdB drafted the manuscript and revised it critically. All authors gave final approval of this version of the manuscript. No conflicts of interests were declared.

Other publications

1. **van Samkar A**, Poulsen MNF, Bienfait HP, van Leeuwen RB. Acute cerebellitis in adults: case report and literature review. *Submitted for publication*

2. Iyer V, **van Samkar A**, Vlasblom E, Minderhoud E, van der Harst S. Effectiveness of standard Dutch vision screening: room for improvement. *Submitted for publication*

3. **van Samkar A**, Georgalas C. Long-term quality of life after endoscopic removal of sinonasal inverted papilomas: a 6-year cohort analysis in a tertiary academic hospital. *Eur Arch Otorhinolaryngol* 2016;273: 1433-7

4. Iyer V, **van Samkar A**, Saeed P. The Bruckner test variant (BTV): a promising instrument in detecting vision disorders. *Am Orthopt J* 2013;63: 97-102

PhD training

General courses

Course: Scientific writing in English	15 hours	0.5 ECTS
Course: Practical Biostatistics	28 hours,	1.0 ECTS

(Inter)national conferences

European Congress of Clinical Microbiology and Infectious Diseases 2016	32 hours	1.0 ECTS