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CASE REPORT

Capnocytophaga canimorsus Meningitis: Diagnosis Using Polymerase Chain Reaction Testing and Systematic Review of the Literature

Megan Hansen · Nancy F. Crum-Cianflone

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ABSTRACT

Introduction: *Capnocytophaga canimorsus* infections are associated with dog bites, especially in asplenic or immunocompromised patients, and typically manifest as sepsis and/or bacteremia. Meningitis has been rarely described, and its diagnosis may be delayed due to poor or slow growth using traditional culture techniques. We provide our experience using polymerase chain reaction (PCR) to establish the diagnosis and perform a comprehensive review of *C. canimorsus* meningitis cases to provide summary data on the clinical manifestations, diagnosis, and outcomes of this unusual infection.

Methods: A systematic review of the peer-reviewed English literature (PubMed, Embase, Ovid Medline) from January 1966 to March 2018 was conducted to identify cases of *C. canimorsus* meningitis. Data collected included demographics, risk factors, cerebrospinal fluid (CSF) findings, PCR results, treatments, and outcomes. Descriptive statistics are presented as numbers (percentages) and medians (ranges).

Results: A total of 37 patients were reviewed with a median age of 63 years (12 days to 83 years) with a male predominance (76%). A relatively low proportion had an immunocompromised state (16% splenectomy and 5% steroid use); the most common risk factor was alcoholism (19%). Fifty-nine percent reported a dog bite (all within $\leq$ 14 days prior to presentation), while 22% reported a non-bite dog exposure, 3% reported cat bite, and 3% reported both dog and cat exposures; 11% reported no animal contact. CSF parameters included a median white count of 1024 cells/mm^3, 81% had neutrophilic predominance, median protein of 190 mg/dl, and median glucose CSF/serum ratio 0.23. In 54% of cases, blood cultures were positive for *C. canimorsus* (median, 4 days) and 70% had positive CSF cultures (median, 5 days). PCR established the diagnosis in eight (22%) cases. Antibiotic therapy was given for a median of 15 days (range, 7 to 42 days). Prognosis was overall favorable with only one (3%) death reported and adverse neurologic and/or physical sequelae in 19% of the survivors.

Conclusion: *C. canimorsus* meningitis is a rare but increasingly important clinical entity occurring in patients of all ages, typically after dog exposure. While classically considered an infection among immunocompromised patients, most cases have occurred in previously healthy, immunocompetent persons. Diagnosis

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M. Hansen · N. F. Crum-Cianflone (✉)
Internal Medicine Department, Scripps Mercy Hospital, San Diego, CA, USA
e-mail: Nancy32red@yahoo.com

N. F. Crum-Cianflone
Infectious Disease Division, Scripps Mercy Hospital, San Diego, CA, USA

may be rapidly established by PCR, and this test should be considered in culture-negative cases with associated exposures. Outcome was generally favorable after a median antibiotic duration of 15 days.

Keywords: *Capnocytophaga canimorsus*; Meningitis; Review

INTRODUCTION

Capnocytophaga canimorsus, known formerly as "dysgonic fermenter-2", is part of the normal flora in the mouths of dogs and, less commonly, cats. Data suggest that nearly a quarter of dogs carry this organism in their mouths with a lower proportion among cats [1]. Transmission to humans may occur via bites, scratches, or licking; occasionally cases have been reported after non-contact-related exposures. Clinical infections caused by *C. canimorsus* include bacteremia, septic shock, arthritis, endocarditis, and rarely meningitis [2, 3]. While *Capnocytophaga* is thought to be pathogenic primarily among immunocompromised persons, especially those with a prior splenectomy, cases among immunocompetent persons have been described [3].

Capnocytophaga is a fastidious, gram-negative bacillus. Diagnosis can be made by culture; however, since the organism grows slowly (2–7 days) and requires blood or chocolate agar incubated with 10% carbon dioxide, the diagnosis can be missed. Polymerase chain reaction (PCR) can be a valuable tool in establishing the diagnosis in cases of suspected infection, especially in the setting of negative cultures and/or prior antibiotic exposure. While treatment is generally with beta-lactam antibiotics, including penicillins, there is a lack of clinical data on the optimal treatment type and duration especially for severe infections such as meningitis.

We report a case of *C. canimorsus* meningitis and provide a comprehensive review of the English literature reviewing 36 additional published cases. Given the rarity of this condition, we summarize the risk factors, exposure history, symptoms, cerebrospinal fluid (CSF) parameters, diagnosis, treatment, and outcomes of this condition.

METHODS

We report a case of *C. canimorsus* meningitis that was diagnosed using PCR technology. CSF was sent for cell counts and cultures and to the University of Washington for testing using a multiplex PCR. Informed consent was obtained from the individual participant reported on in this article.

In addition to our case, a comprehensive search of peer-reviewed English literature (1961–present) was performed to identify published cases of *Capnocytophaga* meningitis and compile relevant clinical data from these cases. The MEDLINE database was interrogated with the following MeSH terms: "*Capnocytophaga*" [MeSH], "Meningitis" [MeSH] and "Gram-Negative Bacterial Infections" [MeSH] with additional keyword searches with the terms "*Capnocytophaga*," "dysgonic fermenter-2," and "df-2." Additionally, a search of Embase was performed with the following Emtree Subject Headings: "*Capnocytophaga*," "Meningitis," and "Gram-Negative Infection."

Cases involving species other than *C. canimorsus* were excluded (e.g., *C. gingivalis* [5], *C. cynodegmi* [6]), as were cases not published in English literature or that did not include individual case data [7]. Additionally, *C. canimorsus* causing other types of central nervous infections (e.g., brain abscess) were excluded. Additional cases included in this review were identified through a review of articles on *Capnocytophaga canimorsus* meningitis as well as reviews of severe *Capnocytophaga canimorsus* infections.

Data collected included demographic and clinical information including age, sex, preexisting medical conditions, history of splenectomy, animal contact, symptoms, serum white cell count, time to positive blood cultures, results of head imaging, CSF counts and culture results, antibiotic selection and duration, and patient outcome. A total of 37 cases of *Capnocytophaga canimorsus* meningitis were identified including the current case.

RESULTS

Case Report

A 71-year-old Caucasian female was found altered at home and transferred to an outside hospital. On presentation, she complained of fevers and severe headaches; however, she was uncertain of the length of her illness. Vitals signs included a temperature of 38.8 °C, pulse of 100 beats per minute, respiration 20 breaths per minute, and blood pressure of 182/86 mmHg. She had an altered mental status and meningismus including neck stiffness. There were no focal neurologic deficits or other examination findings.

Past medical history was remarkable for recently diagnosed lung cancer status-post lobectomy; she did not require adjunctive chemoradiation therapy. She also had a history of hypertension and chronic subdural hematoma. She denied diabetes, alcohol abuse, or prior splenectomy. She lived in Southern California and reported no recent travel history. She owned a dog and frequented a dog park with contact with several canines on a regular basis; she reported no dog bites.

Laboratory data on presentation were notable for a white blood count of 19,900 cells/mm^3 (92% neutrophils), hemoglobin 13 g/dl, and platelets of $196 \times 10^3/mm^3$. Lactate level was 2.4 mmol/l, creatinine was 1.0 mg/dl, and glucose was 109 mg/dl. Liver function tests and urinalysis were within normal limits.

A magnetic resonance image (MRI) with and without gadolinium showed left occipital and parietal acute infarcts without mass effect and stable small bilateral frontal subdural hematomas. A lumbar puncture was performed during the first 24 h of admission and revealed neutrophilic pleocytosis (590 white cells/mm^3; 95% polymorphonuclear cells), red cell count of 2600 cells/mm^3, low glucose of 12 mg/dl (reference range, 40–70 mg/dl), and elevated protein level of 413 mg/dl (reference range, 15–59 mg/dl). Gram stain did not show any organisms.

The patient was started on empiric antibiotic therapy with intravenous vancomycin and piperacillin-tazobactam prior to the lumbar puncture, but antibiotics were changed after the lumbar puncture revealed meningitis to intravenous vancomycin 500 mg every 8 h, ampicillin 2 g every 4 h, and ceftriaxone 2 g every 12 h; no steroids were administered.

Blood cultures (two sets) were drawn on admission using BD Plus Aerobic/F and BD Lytic/10 Anaerobic/F media. The first set was positive at approximately 4 days (98 h) and the second set at 4.6 days (110 h), in both the BD Lytic/10 Anaerobic/F media. The gram stain was reported as gram-negative rods with bacterial growth on plates by day 6. Matrix Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF) was performed, but no identification was obtained. A Remel RapID ANA II test system was used for a biochemical identification, and *Capnocytophaga* was identified. The organism could not be successfully grown on culture for susceptibility testing.

Cerebrospinal fluid (CSF) cultures obtained on admission were sterile; however, antibiotics had been given prior to the lumbar puncture. Due to high suspicion of *Capnocytophaga canimorsus* as the causative organism given the patient's exposure to dogs, a CSF specimen was sent to the University of Washington for multiplex broad-range bacterial polymerase reaction (PCR) testing, which was positive for *C. canimorsus*.

Antibiotic therapy was modified to meropenem 2 g IV q8 h. A transthoracic echocardiogram did not show vegetations and a chest, abdominal, and pelvic CT scan was unremarkable except for post-surgical finding consistent with prior lung lobectomy. The spleen appeared within normal limits. Repeat blood cultures after the initiation of antibiotics showed no growth.

The patient's meningismus resolved during her hospital stay, and at the time of discharge her headache was significantly improved. She completed a 21-day total course of antibiotics and subsequently made a full recovery. She was educated on the potential infectious risks associated with dog ownership/exposure.

Review of the Literature

A total of 37 cases of *Capnocytophaga canimorsus* meningitis were identified including the current case (Table 1) [2, 4, 8–28]. Median age at presentation was 63 years (range, 12 days to 83 years) with a male predominance (28/37, 76%). While *C. canimorsus* meningitis has classically been characterized as a disease of immunocompromised patients, particularly patients who are asplenic, only 16% (6/37) of published cases occurred in patients with splenectomies. Five percent (2/37) had active steroid use. When summating all possible immunosuppressive states (e.g., medications or the presence of splenectomy or hematologic/autoimmune condition that impairs the immune system), 24% (9/37) of cases had one of these conditions: 5 splenectomy, 1 splenectomy and lymphoma, 2 steroid use, and 1 rheumatoid arthritis. Additionally, alcoholism was noted in 19% (7/37) and was the most common single medical condition identified.

Regarding animal exposure history, the majority of patients (59%; 22/37) reported a recent dog bite. The timing between the dog bite and presentation was a median of 6 days (range, 3 to 14 days). A smaller proportion reported non-bite dog exposures (22%; 8/37) and single cases of non-bite exposures to both dog and cat (3%, 1/37) and a cat bite (3%; 1/37). In addition, there was one reported case of indirect contact through two health providers who owned dogs. Overall, 11% (4/37) indicated no known animal contact prior to development of meningitis.

Presenting symptoms often included fever, headache, neck stiffness, altered mental status, and photophobia (Table 1). Other manifestations included rash in six cases, which was described as macular/papular in most cases; two cases had a rash that had a petechial/purpuric appearance. Other symptoms included seizures, myalgias, vomiting, fatigue, and hearing loss. Serum white blood cell (WBC) count was reported elevated in 11 (69%) of 16 cases that reported these data with a median WBC count of 13,500 cells/mm^3 (range, 8000–25,000 cells/mm^3).

CSF studies demonstrated a pattern consistent with bacterial meningitis with elevated CSF white counts of a median of 1024 cells/mm^3 (range, 0–15,630 cells/mm^3) with only one case with a normal white count. Most cases had neutrophilic predominance (81%, 26/32 cases with data). In addition, an elevated CSF protein was noted in 92% (22/24) of cases with a median value of (190 mg/dl) and low CSF/serum glucose ratio in all cases (median, 0.23). In cases that reported brain imaging, it was typically normal but in three cases (19%; 3/16 with imaging data), including the present case, acute infarcts were noted, and one additional case had cerebritis.

Blood cultures were found to be positive in 20 (54%) cases with a median growth time of 4 days (range, 2–9 days); 9 (24%) had negative blood cultures and 8 (22%) did not report results. CSF cultures were positive in 26 (70%) of cases with a median growth time of 5 days (range, 1–9 days). Due to the relatively long time for cultures to become positive, PCR is emerging as an important diagnostic technique. PCR was utilized to establish the diagnosis in the current case and overall in eight (22%) cases in this review.

Treatment involved extended courses of antibiotics with median treatment duration of 15 days (7–42 days). The most commonly utilized antibiotics were penicillin, ampicillin, and cephalosporins. Antibiotic susceptibilities were presented in eight cases in the literature with many cases lacking data, often because of insufficient growth of the bacteria on culture media. Overall, penicillins (including ampicillin), second- and third-generation cephalosporins, carbapenems (e.g., imipenem), and fluoroquinolones were susceptible in all cases reporting data for these antibiotics (Table 2).

Outcomes were generally favorable with only one (3%) death observed in the published cases; this death may have been unrelated to the infection as the patient died of a cardiac arrest 10 days after discharge and had known coronary artery disease. Overall, 19% of survivors (7/36) had chronic sequelae of the disease including four with hearing loss, one with chronic headaches/disorientation, one with extremity amputations and chronic neurologic

Table 1 Summary of *Capnocytophaga canimorsus* meningitis cases in the published literature, $n = 37$

Case no.	First author, year [reference]	Age/sex	Medical conditions	History of splenectomy, y/n	Animal contact	Symptoms	Serum WBC (cells/mm^3)	Blood cultures, positive y/n, time to result
1	Bobo, 1976 [8]	42/M	Alcoholism	N	Dog bites (two) 6 and 7 days before	Fevers, seizures, headache	8,900	Yes, 3 days
2	Butler, 1977 [2]	26/M	Splenectomy	Y	Dog bite 4 days prior	NR	NR	Yes; time not reported
3	Butler, 1977 [2]	25/M	Splenectomy	Y	Dog bite 3 days prior	NR	NR	Yes; time not reported
4	Butler, 1977 [2]	17/M	Splenectomy	Y	Dog bite several days prior	NR	NR	Yes; time not reported
5	Ofori-Adjei, 1982 [9]	66/F	None	N	Dog exposure but no history of bites	Fever, myalgias, headache, photophobia, vomiting, neck stiffness, macular rash confined to trunk	10,800	Negative
6	Chan, 1986 [10]	63/M	Hypertension	N	Dog bite, 14 days before	Fevers, rigors, arthralgia and erythematous rash on trunk	14,500	Yes, 2 days
7	Carpenter, 1987 [11]	26/M	Splenectomy, Hodgkin's lymphoma in remission	Y	Cat bite, scratches	Fevers, myalgias, malaise, photophobia, headache	13,400	Yes, 3 days
8	Westerink, 1989 [12]	26/M	None	N	Dog exposure	Fevers, headaches, myalgias, vomiting, erythematous and pruritic rash starting on back and spreading to extremities, confluent, blanching maculopapular rash over forehead, back and anterior dorsal aspects of upper and lower extremities, dorsum of hands and feet; petechial rash on lower extremities. Palms/soles spared.	11,500	Yes, 4 days
9	Imanse, 1989 [13]	39/F	None	N	Dog and cat exposure	Fever, malaise, headache, vomiting, dizziness, complete hearing loss, gait instability	11,300	Yes, 5 days

Table 1 continued

Case no.	First author, year [reference]	Age/sex	Medical conditions	History of splenectomy, y/n	Animal contact	Symptoms	Serum WBC (cells/mm^3)	Blood cultures, positive y/n, time to result
10	Herbst, 1989 [14]	47/F	Alcoholism	N	Dog exposure	Unresponsive, febrile, hypotensive, widespread purpuric rash; purple-red patches in reticulated pattern arms/abdomen/thighs/lower legs/feet with petechiae at periphery	20,700 w/significant left shift	Yes, time not reported
11	Krol-van Straaten, 1990 [15]	75/F	Splenectomy	Y	Dog bite 9 days earlier	Fevers, change of mental status	25,000	Negative
12	Blanche, 1994 [16]	57/M	None	N	Dog bite, 9 days earlier	Fevers	NR	Yes, 5 days
13	Kristensen, 1996 [17]	74/M	Heart failure	N	Dog bite, several days earlier	Fever, confusion	NR	Negative
14	Pers, 1996 [18]	74/M	CAD	N	Dog bite 7 days prior, received unknown abx prophylactically	Meningitis, symptoms not specified	NR	NR
15	Pers, 1996 [18]	80/M	CAD	N	Dog bite 3 days prior	Meningitis, symptoms not specified	NR	NR
16	Pers, 1996 [18]	83/M	Rheumatoid arthritis	N	No known animal exposure	Meningitis, symptoms not specified	NR	NR
17	Pers, 1996 [18]	42/M	None	N	No known animal exposure	Meningitis, symptoms not specified	NR	NR
18	Pers, 1996 [18]	74/M	None	N	Dog exposure with no history of bites	Meningitis, symptoms not specified	NR	NR
19	Lion, 1996 [3]	54/M	Alcoholism	N	Dog bite, 10 days earlier	NR	NR	Yes, 3 days

Table 1 continued

Case no.	First author, year [reference]	Age/sex	Medical conditions	History of splenectomy, y/n	Animal contact	Symptoms	Serum WBC (cells/mm^3)	Blood cultures, positive y/n, time to result
20	Risi, 2000 [19]	65/F	None	N	Possible second hand exposure → procedure performed by radiologist had 3 dogs and tech had 2 dogs	Chills, myalgias, fatigue, confusion	Not reported	NR
21	Le Moal, 2003 [20]	45/M	Alcoholism	N	Dog bite 9 days prior	Fevers, headache, confusion, photophobia, meningismus	15,700	Negative
22	Rosenman, 2003 [21]	12 days/F	Recent steroid use, gonadal dysgenesis	N	Abrasion from dog tooth	Fevers, poor feeding, irritability	23,900	Negative
23	Gottwein, 2006 [22]	56/M	Alcoholism	N	Dog bite, 10 days earlier	Headache, fever, chills diarrhea, vomiting, arthralgia	12,900	Yes, 7 days
24	Meybeck, 2006 [23]	65/M	Pulmonary embolism	N	Dog bite, 5 days earlier	Fever, headache, confusion	8,000	Yes, 2 days
25	de Boer, 2007 [24]	69/M	COPD on steroids	N	Dog bite, 4 days earlier	Fevers, chills, confusion	20,500	Yes, 9 days
26	de Boer, 2007 [24]	58/M	None	N	None	Headache, fever, malaise, nausea	13,700	Yes, 9 days
27	Gasch, 2009 [25]	64/M	None	N	Dog bite 7 days earlier	Fever, headache, severe hearing loss, dizziness	Normal (# not reported)	Negative
28	Monrad, 2012 [26]	66/M	Alcoholism	N	Recent dog bite	Confusion, tachycardia, fever; neck stiffness and bilateral hearing loss noted after 48 h	NR	Negative

Table 1 continued

Case no.	First author, year [reference]	Age/sex	Medical conditions	History of splenectomy, y/n	Animal contact	Symptoms	Serum WBC (cells/mm^3)	Blood cultures, positive y/n, time to result
29	Monrad, 2012 [26]	67/F	Splenectomy	Y	2 dogs in household; no bites	Fever, headache, confusion, transient right arm paresis	NR	Negative
30	Monrad, 2012 [26]	79/M	None	N	Dog bite 7 days prior	Unconscious at home	NR	NR
31	Beernink, 2016 [27]	52/M	None	N	Dog licked scratches on knee several days prior to admission	Headache, dizziness	12,000	NR
32	Van Samkar, 2016 [28]	78/M	None	N	Dog bite 4 days prior	Neck stiffness, altered mental status	NR	Positive, 3 days
33	Van Samkar, 2016 [28]	37/M	Alcoholism	N	Dog bite 4 days prior	Headache, fever, nausea, generalized rash	NR	Negative
34	Van Samkar, 2016 [28]	60/M	None	N	No known animal exposures	Headache, fever, altered mental status, generalized rash	NR	Positive, 5 days
35	Bertin, 2018 [4]	69/F	HTN	N	Dog bite 3 days prior	Fever, dyspnea, fatigue	NR	Positive, days to growth not reported PCR+
36	Bertin, 2018 [4]	65/M	HTN	N	Dog bite 3 days prior	Headache, nuchal rigidity	NR	Positive, 1 day

Table 1 continued

Case no.	First author, year [reference]	Age/sex	Medical conditions	History of splenectomy, y/n	Animal contact	Symptoms	Serum WBC (cells/mm^3)	Blood cultures, positive y/n, time to result
37	Current Case	71/F	Lung cancer s/p resection, HTN, hypothyroidism, chronic subdural hematomas	N	Dog exposure, ongoing; no reported bites	Altered mental status, fever, headache	19,900	Positive, 4 days

Case no.	Brain imaging	CSF white count (cells/mm^3)	CSF protein (mg/dl)	CSF glucose-to-serum ratio (value in mg/dl)	CSF gram stain and culture, time to result (days)	Antibiotics, type and duration (days)	Outcome
1	NR	2,300 (30% PMN)	722	0.17	Gram stain with GNRs, culture positive, 3 days	Ampicillin, gentamicin, chloramphenicol and carbenicillin → Ampicillin (14 days total)	Recovered
2	NR	NR	NR	NR	NR	NR	Recovered
3	NR	NR	NR	NR	NR	NR	Recovered
4	NR	NR	NR	NR	NR	NR	Recovered
5	NR	575 (90% PMN)	240	0.24	Gram stain GNR; culture positive 5 days	Penicillin (7), Chloramphenicol (10); (10 days total)	Recovered
6	NR	1,121 (80% PMN)	175	37.8; 0.45	Gram stain GNRS; culture positive, 2 days	Chloramphenicol, Ampicillin (7 days total)	Recovered
7	CT normal	520 (70% PMN)	143	0.2	Gram stain negative; culture positive; time NR	Penicillin G and cefotaxime (14 days total)	Recovered
8	NR	0	31	0.53	Gram stain negative; culture positive, 4 days	Chloramphenicol (4 d) → Pen (10 d); (14 days total)	Recovered

Table 1 continued

Case no.	Brain imaging	CSF white count (cells/mm^3)	CSF protein (mg/dl)	CSF glucose-to-serum ratio (value in mg/dl)	CSF gram stain and culture, time to result (days)	Antibiotics, type and duration (days)	Outcome
9	CT normal	480 (70% PMN)	32	NR	Culture negative	None	Survived with persistent deafness
10	CT with multiple brain infarctions	820 (74% PMN)	465	CSF 39.24 mg/dl; 0.08	NR	Imipenem/cilastatin → Penicillin (14 days total)	Survived; bilateral below-knee amputations, persistent neurologic deficits
11	NR	6000, *mainly PMN)	NR	NR	Culture positive, 4 days	Chloramphenicol IV for 5 days and po for 6 days (11 days total)	Recovered
12	NR	43 (74% lymph)	153	0.3	Culture positive, 5 days	Amoxicillin (21 days total)	Recovered
13	NR	240 (80% PMN)	NR	NR	Gram stain GNRs; culture positive, time NR	Penicillin (15 days total)	Recovered
14	NR	~ 240 (> 80% PMN)	NR, elevated	NR, low	Positive culture, time NR	Erythromycin → Penicillin	Died, cardiac arrest 10 days after discharge
15	NR	> 1700 (> 80% PMN)	NR, elevated	NR, low	Positive culture, time NR	Ampicillin	Recovered
16	NR	~ 245 (> 80% PMN)	NR, elevated	NR, low	Positive culture, time NR	Penicillin → Ampicillin, Gentamicin	Recovered
17	NR	> 1700 (> 80% PMN)	NR, elevated	NR, low	Gram stain GNRs, culture negative	Penicillin → Ceftazidime, Metronidazole	Recovered

Table 1 continued

Case no.	Brain imaging	CSF white count (cells/mm^3)	CSF protein (mg/dl)	CSF glucose-to-serum ratio (value in mg/dl)	CSF gram stain and culture, time to result (days)	Antibiotics, type and duration (days)	Outcome
18	NR	> 1700 (> 80% PMN)	NR, elevated	NR, low	Positive culture, time NR	Ceftriaxone, Ampicillin → Ampicillin, Netilmicin, Metronidazole → Penicillin	Recovered
19	NR	NR	NR	NR	Culture positive, 4 days	Cefotaxime, Amoxicillin	Recovered
20	CT normal	11,138 (99% PMN)	192	<0.01	Gram stain GNR, culture positive, time NR, also partial 16 s rRNA sequencing (PCR)	Cefepime, ampicillin, metronidazole (total duration not provided) → Ceftriaxone (14 days total)	Recovered
21	CT normal	1240 (65% PMN)	165	0.21	Gram stain GNRs; culture positive, 2 days	Cefotaxime (9 d) → Amoxicillin (12 d); (21 days total)	Recovered
22	CT normal	15,630 (92% PMN)	146	CSF glucose 20 → 0.14	Gram stain negative; culture positive, 5 days	Ampicillin, gentamicin, cefotaxime; (21 days total)	Recovered
23	NR	1001 (82% PMN)	169	0.3	Gram stain negative, culture positive, 5 days; PCR+	Ceftriaxone (13 days total)	Recovered
24	CT and MRI normal	1226 (96% PMN)	328	0.24	Gram stain GNRs; culture positive, time NR	Cefotaxime and gentamicin (1 d) → Cefotaxime and metronidazole → amoxicillin; (15 days total)	Recovered
25	NR	1024 (100% PMN)	173	0.43	Gram stain GNRs; culture positive, 9 days	Ceftriaxone	Recovered
26	CT normal	1566 (54% PMN)	130	0.5	Gram stain GNRs; culture negative	Ceftriaxone	Recovered

Table 1 continued

Case no.	Brain imaging	CSF white count (cells/mm^3)	CSF protein (mg/dl)	CSF glucose-to-serum ratio (value in mg/dl)	CSF gram stain and culture, time to result (days)	Antibiotics, type and duration (days)	Outcome
27	CT normal	730 (22% PMN)	1342	0.125	Gram stain negative, culture positive at 2 days	Ampicillin (14 days total)	Survived with near total deafness
28	CT normal	1814 (74% PMN)	276	0.03	Gram stain GNR; culture positive at 9 days; PCR+	Penicillin (48 h) → ceftriaxone and ampicillin (6 d) → ceftriaxone additional 14 d; (22 days total)	Survived with persistent bilateral sensorineural hearing loss
29	NR	2120 (81% PMN)	191	0.24	Gram stain GNR; culture positive at 5 days; PCR+	Ceftriaxone → meropenem (21 d); (21 days total)	Survived with persistent hearing loss
30	CT normal	234 (85% PMN)	221	0.02	Gram stain GNR; culture positive at 6 days; PCR+	Ampicillin, ceftriaxone, acyclovir → meropenem 3 days → ceftriaxone 21 days; (24 days total)	Recovered
31	No imaging	5,210	515	CSF glucose 0	GNR on gram stain, culture neg, PCR+	Ceftriaxone, amoxicillin × 2 days → penicillin × 12 days (14 days total)	Recovered
32	CT normal	901	346	CSF glucose 25.2 → 0.07	Culture positive, 3 days	Amoxicillin (10 d), ceftriaxone (14 days total)	Recovered
33	CT normal	2,376	261	CSF glucose 66.6 → 0.26	Culture positive, 5 days	Amoxicillin (3 d), ceftriaxone (20 d), acyclovir 3 d (23 days total)	Survived with headache, disorientation
34	No imaging	828	190	CSF glucose 54 → 0.28	Culture positive, 5 days	Amoxicillin (14 d), ceftriaxone (1 d), meropenem (12 d); (27 days total)	Recovered

Table 1 continued

Case no.	Brain imaging	CSF white count (cells/mm^3)	CSF protein (mg/dl)	CSF glucose-to-serum ratio (value in mg/dl)	CSF gram stain and culture, time to result (days)	Antibiotics, type and duration (days)	Outcome
35	CT with 3 ischemic lesions	NR	NR	NR	NR	Vancomycin, piperacillin-tazobactam (28 days total)	Survived; amputations of extremities of bilateral upper and lower limbs
36	CT normal on admission. MRI at 8 days with cerebritis	443	97	0.24	Gram stain GNR; culture positive, 1 day; PCR+	Ceftriaxone, ampicillin 2 weeks → ampicillin-sulbactam, moxifloxacin 4 weeks; (42 days total)	Recovered
37	MRI stable bifrontal subdural hematomas, acute occipital and parietal lobe infarcts	590 (95% PMN)	413	0.11	Gram stain and culture negative; PCR+	Vancomycin, ceftriaxone, ampicillin (4 d) → Meropenem (17d); (21 days total)	Recovered

CAD coronary artery disease, *COPD* chronic obstructive pulmonary disease, *CSF* cerebrospinal fluid, *CT* computed tomography, *D* days, *F* female, *GNR* gram-negative rod, *HTN* hypertension, *M* male, *MRI* magnetic resonance imaging, *N* no, *NR* not reported, *PCR* polymerase chain reaction, *PMN* polymorphonuclear cell, *WBC* white blood cell, *Y* yes

Table 2 Antibiotic susceptibilities for the *Capnocytophaga canimorsus* isolates among meningitis cases in the published literature

First author, year (references)	Susceptible	Intermediate	Resistant
Bobo, 1976, $n = 1$ [8]	"All tested abx" including ampicillin	NR	Gentamicin
Chan, 1986, $n = 1$ [10]	Penicillin, erythromycin, chloramphenicol, cefuroxime	NR	Gentamicin, trimethoprim, sulphafurazole, metronidazole
Krol-van Straaten, 1990, $n = 1$ [15]	Penicillin, amoxicillin, cephalothin, norfloxacin, rifampin, chloramphenicol	NR	Aminoglycosides
Risi, 2000, $n = 1$ [19]	Penicillin, third-generation cephalosporin and ciprofloxacin	NR	NR
Le Moel, 2003, $n = 1$ [20]	Ampicillin, cephalothin, cefotaxime, pefloxacin, and vancomycin	Erythromycin	gentamicin, colistin, trimethoprim-sulfamethoxazole
Meybeck, 2006, $n = 1$ [23]	Penicillin, amoxicillin, cefotaxime, cefixime, clindamycin, erythromycin, rifampin, pefloxacin, tetracycline, chloramphenicol	NR	Kanamycin, gentamicin, sulfamethoxazole, trimethoprim
Gasch, 2009, $n = 1$ [25]	Ampicillin, cefotaxime, imipenem and ciprofloxacin	NR	Aminoglycosides
Monrad, 2012, $n = 1$ [26]	Penicillin, cefuroxime, erythromycin, ciprofloxacin	NR	Gentamicin

NR not reported

abnormalities, and one with extremity amputations. Both patients who underwent amputations also had brain imaging showing acute infarcts. Of the seven patients with chronic sequelae, three had a history of alcohol abuse and one was asplenic. No clear relationship between antibiotic duration and adverse outcomes was noted.

DISCUSSION

Since the first reported case of *Capnocytophaga canimorsus* meningitis in 1976 [8], there have been 36 additional cases including the present case. We provide a comprehensive summary and provide a novel case of *Capnocytophaga canimorsus* meningitis to add to the existing literature. While this pathogen was previously reported to primarily cause severe disease in immunocompromised patients (e.g., history of splenectomy), our literature review revealed that most cases occurred among healthy, immunocompetent persons. As most cases had a recent dog exposure, *C. canimorsus* should be suspected in cases of bacterial meningitis with this exposure history.

Regarding underlying medical conditions, only 24% had an underlying immunosuppressive medical condition. While classically asplenia was deemed to be the characteristic condition associated with this pathogen, in our review only 16% (6 patients) with *C. canimorsus* meningitis were asplenic and 5% (2 patients) were receiving chronic steroids. The most common risk factor found in our review was

alcoholism present in 19% (7 patients). These data suggest that *Capnocytophaga* is pathogenic and can cause severe disease in all hosts of all ages regardless of underlying risk factors.

A history of exposure to dogs was common in our review and emphasizes the importance of this historical feature in the early suspicion and diagnosis of this pathogen. Dog exposure, mostly common via a dog bite, was present in 86% of cases. Cat exposure was less commonly (3%) reported; only 11% of cases reported no known animal exposure. The incubation period was relatively short between animal exposure and presentation (median 6 days between bite and presentation). Whether antibiotic exposure after dog or cat bites would have prevented the reported cases of *C. canimorsus* meningitis is unclear, but prophylactic antibiotics did not prevent its occurrence in one previously published case although erythromycin was used rather than a β-lactam [18]. Among cases reviewed, there was a notable male predominance (3:1) perhaps related to an increased risk of canine bites or exposures among men.

Patients with *C. canimorsus* meningitis commonly presented with classic meningismus symptoms. In several of the cases, the course was fulminant and mimicked that of meningococcal disease. Of note, some *C. canimorsus* cases had purpuric or petechial rashes at presentation and required subsequent extremity amputations similar to the clinical course of *Neisseria meningitidis* [14]. CSF analysis was consistent with bacterial meningitis with an elevated leukocyte count with neutrophil predominance, elevated protein, and low glucose values occurring in most cases. Given the lack of differentiating clinical or laboratory findings for *C. canimorsus meningitis* compared with other bacterial organisms, clinicians must have a high index of suspicion suspecting this pathogen among patients presenting with findings of bacterial meningitis along with recent animal exposure.

The identification of *Capnocytophaga sp.* is supported by its growth using specific culture conditions as well as its colony morphology and microscopic characteristics [29]. The organism grows best at 35–37 °C on 5% sheep's blood or chocolate agar (but not MacConkey's) using anaerobic or aerobic conditions with 5–10% CO_2. Even with ideal growing conditions, growth can take up to 7 days, and identification can be missed if culture plates are discarded at the traditional day 5 of incubation. The organism displays fingerlike projections on agar and gliding motility on microscopy, which may provide clues to its identification. A variety of biochemical identification systems and strips can be utilized for species determination. MALDI-TOF mass spectrometry using an enriched database may also aide in species level identification [30].

Capnocytophaga canimorsus is a relatively difficult organism to identify given its long incubation and specific culture requirements as noted above. In this review, only 54% of blood cultures and 70% of CSF cultures were positive with median growth times of 4 and 5 days, respectively. Two cases in the literature had gram stains showing gram-negative bacilli, but negative cultures. In cases where gram stains and/or cultures are negative, PCR can be helpful in definitively identifying the causative organism and improving the rapidity of the diagnosis [31], as was done in eight (22%) of the cases in our literature review. The value of PCR technology is particularly important in cases involving slow-growing or fastidious organisms (such as *Capnocytophaga sp.*) and in the setting of prior antibiotic exposure before cultures are obtained. Commercial PCR tests are becoming more widely available; however, *C. canimorsus* may not be included in all testing platforms (e.g., BioFire FilmArray Meningitis/Encephalitis Panel) [32] and hence may require broad-range PCR technology.

Regarding treatment, penicillin has been reported as the drug of choice in the past, although clinical comparative trials are lacking [12]. Since beta-lactamase activity has been reported among some *Capnocytophaga* species [33], clinical isolates should be tested for β-lactamase production to inform the optimal treatment regimen. Because the organism can be difficult to grow, susceptibilities may not be feasible. To provide further guidance on treatment options, we reviewed the published susceptibility data from *C. canimorsus* meningitis cases. These data suggest that *C. canimorsus* is

typically susceptible to penicillins (including ampicillin), third-generation cephalosporins, carbapenems such as imipenem, and fluoroquinolones. Despite being a gram-negative organism, aminoglycosides and aztreonam are typically inactive. Isolates were also typically resistant to trimethoprim-sulfamethoxazole. In our review, the median treatment time was 15 days although the optimal duration is unknown. The current Infectious Disease Society of America (IDSA) Meningitis Guidelines suggest 21 days for meningitis involving aerobic gram-negative organisms (other than *Haemophilus influenzae*) [34].

The outcome of *C. canimorsus* meningitis was overall favorable and had a lower overall mortality rate compared with both other bacterial causes of meningitis (~ 14–25%) [35] and *C. canimorsus* sepsis (~ 30%) [3, 18]. Only one patient in our review died, and this event was unlikely related to the infection. Adverse sequalae, however, were notable with 19% of patients suffering from a residual deficit, which was most commonly hearing loss. Additionally, 19% of those with *C. canimorsus* meningitis with reported brain imaging had evidence of acute infarcts. Cerebral infarctions are potential complications of bacterial meningitis and in a prior study were reported among 36% of patients with pneumococcal meningitis, 9% with meningococcal meningitis, and 28% due to other bacteria; patients with infarctions are often older and have an immunocompromised state [36].

Limitations of this review include the overall small number of *C. canimorsus* meningitis cases in the literature and the lack of complete individualized data for some cases. Additionally, our review only included cases in the English literature. Strengths include this being the largest and most comprehensive review to date. Given that animal exposures are increasingly common [29], understanding this disease entity is important. Unlike other bacteria pathogens associated with animal bites (e.g., *Pasteurella*, streptococci), this organism is not typically associated with local wound infections, but rather presents as severe, disseminated infections including bacteremia, sepsis, and meningitis.

CONCLUSION

Capnocytophaga canimorsus is a rare but important cause of bacterial meningitis and should be considered in cases following a recent dog bite or exposure. Given the increasing incidence of infections associated with animal exposures, knowledge regarding the clinical manifestations, diagnosis, and treatment of this clinical entity is important. This case and review provides the most up-to-date information about the clinical management of this important infection. Furthermore, it highlights the value of PCR technology to enhance the timely diagnosis of *C. canimorsus* meningitis.

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