Eur J Clin Microbiol Infect Dis (2015) 34:1271–1280
DOI 10.1007/s10096-015-2360-7

REVIEW

Capnocytophaga canimorsus: an emerging cause of sepsis, meningitis, and post-splenectomy infection after dog bites

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Received: 30 January 2015 / Accepted: 4 March 2015 / Published online: 1 April 2015

Abstract Newly named in 1989, *Capnocytophaga canimorsus* is a bacterial pathogen found in the saliva of healthy dogs and cats, and is transmitted to humans principally by dog bites. This review compiled all laboratory-confirmed cases, animal sources, and virulence attributes to describe its epidemiology, clinical features, and pathogenesis. An estimated 484 patients with a median age of 55 years were reported, two-thirds of which were male. The case-fatality rate was about 26 %. Its clinical presentations included severe sepsis and fatal septic shock, gangrene of the digits or extremities, high-grade bacteremia, meningitis, endocarditis, and eye infections. Predispositions were prior splenectomy in 59 patients and alcoholism in 58 patients. Dog bites before illness occurred in 60 %; additionally, in 27 %, there were scratches, licking, or other contact with dogs or cats. Patients with meningitis showed more advanced ages, higher male preponderance, lower mortality, and longer incubation periods after dog bites than patients with sepsis ($p<0.05$). Patients with prior splenectomy presented more frequently with high-grade bacteremia than patients with intact spleens ($p<0.05$). The organism possesses virulence attributes of catalase and sialidase production, gliding motility, cytotoxin production, and resistance to killing by serum complement due to its unique lipopolysaccharide. Penicillin is the drug of choice, but some practitioners prefer third-generation cephalosporins or beta-lactamase inhibitor combinations. *C. canimorsus* has emerged as a leading cause of sepsis, particularly post-splenectomy sepsis, and meningitis after dog bites.

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Introduction

The discovery of *Capnocytophaga canimorsus* is credited to the Special Bacteriology Section at the Centers for Disease Control (CDC) in Atlanta, Georgia, USA [1]. A blood culture isolate fitting this species was first received from a bacteremic patient in 1961 in California. The patient was a 17-year-old boy who had undergone splenectomy 3 years earlier for a football injury and had been bitten by a dog a few days before his illness. Between 1961 and 1975, 17 patients' blood culture isolates had been received that fit the same laboratory criteria: Gram-negative, bacillary, slow to grow during several days of incubation, microaerophilic, capnophilic, unable to grow on MacConkey agar, negative for indole, urease, and nitrate reduction, positive for oxidase and catalase, able to ferment glucose, maltose, and lactose but not sucrose and mannitol, and negative for motility in agar but showing gliding motility. These 17 patients were clinically described as having sepsis caused by an unidentified Gram-negative rod in 1977 [2]. Fifteen patients were males, of whom 11 were over 40 years old, five had prior splenectomy, and four were alcoholics. Ten gave histories of dog bites and four others had been in contact with dogs or other animals. The most common physical finding, in addition to fever, was cellulitis in seven patients, followed by meningitis in four, with growth of the organism in cerebrospinal fluid (CSF) as well as blood, and endocarditis in three. Bacteria were visible in Gram-stained specimens of blood buffy coats of two patients, and three died. The CDC classified this organism as DF-2 (dysgonic fermenter-2) until 1989, when it acquired the name of *Capnocytophaga*

canimorsus as a new species [1]. The genus *Capnocytophaga* had been proposed In 1979 and contained three other species that differed from *C. canimorsus* by being negative for oxidase and catalase and present in human oral flora. These were *C. ochracea*, *C. sputigena*, and *C. gingivalis*. Another organism in dogs' oral flora that was placed into this genus in 1989 was *C. cynodegmi*, formerly called DF-2-like and differed from *C. canimorsus* by fermenting sucrose, raffinose, inulin, and mellobiose, and by being cultured more often from bite wounds but not from blood [1].

Previous reviews reported 58 cases in 1990 [3], 106 cases in 1996 [4], and 125 cases in 2006 [5]. This review updates the clinical experience during 1990–2014, the first 25 years after its inaugural appearance, as well as recording earlier DF-2 cases. Culture-documented cases were found in published reports from PubMed listings between 1976 and 2014.

Incidence of reported cases with epidemiological features, underlying diseases, and animal exposures

The number of reported cases through 1989 was estimated at 192 patients, a number that was dominated by the 150 cultures identified in the CDC laboratory [1]. Although most of these cases were not individually described, 71 of the cases, including some from the CDC series, were characterized in a review [3] and case reports [6–19]. After 1990, 292 additional cases were reported [20–150], to make a grand total of 484 cases (Table 1). In both historic periods, patients over 50 years old were dominant, but the age range has widened from the youngest of 12 days, after a newborn was scratched in the face by the family dog [122], to the oldest of 99 years [77]. About two-thirds of the patients were males. Whereas most of the patients in the earlier period were from the USA, most of the cases after 1990 were reported from other countries. Countries that reported after 1990 at least three cases were the USA (84 cases), the Netherlands (49 cases), Denmark (47 cases), France (23 cases), Australia (18 cases), UK (13 cases), Japan (12 cases), Spain (five cases), Switzerland (five cases), Belgium (four cases), Canada (four cases), Finland (four cases), and Germany (three cases). In both periods, prior splenectomy was present as a prominent immunodeficiency in a total of 59 patients. Additionally, ten patients were identified as having other causes of hyposplenism, including functional asplenia in two cases [28, 123], infarction of the spleen in two cases [31, 112], one with asplenia due to irradiation [127], one with congenital asplenia [94], one with a hypoplastic spleen at autopsy [95], one with fibrosis of the spleen at autopsy [114], one with hemoglobin SC disease [3], and another with atrophy after bone marrow transplantation for acute myelocytic leukemia [138]. Alcoholism was reported in 58 patients, with fewer patients having diagnoses of other immunocompromising conditions. Most of the remaining patients were described as previously healthy or had no mention of an underlying disease. Dog bites occurring within a few days before illness were reported in about 60 % of the cases, with dog scratches, licking, or other contact in 24 % of patients. Cat exposures were much less frequent, occurring in 3 % of cases. Case-fatality rates of 30 % and 24 % were recorded in the two periods, respectively.

Table 1 Features of laboratory-documented cases of *Capnocytophaga canimorsus* infections during historical periods before 1990 and during the 25 years of the period 1990–2014. In parentheses are the percentages of cases with relevant information reported

	Before 1990 (1961–1989)	After 1990 (1990–2014)
Total numbers of documented cases	192	292
Median age, years	52	56
Males/females (% males)	50/71 (70)	180/276 (65)
No. of cases in USA/total cases (%)	43/71 (61)	84/292 (29)
No. of cases with prior splenectomy	23/71 (31)	36/283 (13)
No. of cases of hyposplenism*	1/71 (1)	9/283 (3)
No. of cases with alcoholism**	16/71 (23)	42/217 (19)
No. of cases with leukemia, myeloma, HIV, macroglobulinemia, other lymphoproliferative disease, diabetes, or corticosteroid use***	3/71 (4)	13/283 (5)
Dog bites before illness (%)	43/71 (60)	122/209 (58)
Other dog contact, such as scratches, licking, and owning pets, before illness (%)	17/71 (24)	51/209 (24)
Cat bites, scratches, or licking	2/71 (3)	7/209 (3)
Case-fatality rate (%)	21/71 (30)	60/251 (24)

*Other than splenectomy, including splenic infarction, splenic fibrosis, functional asplenia, and congenital asplenia

**Excluding any cases with splenectomy or hyposplenism

***Excluding any cases with splenectomy, hyposplenism, or alcoholism

Roles of the spleen and alcoholism

For the 59 patients with splenectomy, the interval between splenectomy and infection ranged from 8 months to 52 years, with a median of 8 years. The median age of the patients was 48.5 years, appreciably younger than other groups of patients (Table 2). Genders specified were 41 male and 15 female (73 % males). Specified outcomes were death in 16 patients (29 %), while in three surviving patients, there was necrosis of the digits or limbs, resulting in amputations of the legs and fingers [24, 44, 130].

Of the 58 patients with *C. canimorsus* sepsis who were alcoholics, their median age was 54 years, with males accounting for 85 % of reported cases. Their case-fatality rate was 29 %. Autopsies of four patients showed expected effects

of alcoholic hepatitis, hepatic steatosis, and fibrosis [14, 114, 140]. Another patient had cirrhosis [121].

When patients with *C. canimorsus* sepsis with intact spleens and without alcoholism were compared to patients with splenectomy or other causes of hyposplenism, the patients with intact spleens were significantly older, with a median age of 60 years versus 49.5 years ($p<0.05$). The median age of alcoholic patients of 54 years was intermediate between the other two groups. The age trends suggest that alcohol use needs time to exert its effect and that the residual function of an intact spleen helps to protect against illness due to *C. canimorsus* by deferring illness to more advanced ages. The median ages of fatal cases were about the same as for all infections in these groups in Table 2, suggesting that an aging effect on the immune system does not add to the deleterious effect of lost splenic function or to the effect of alcoholism on the liver.

Clinical features updated

In patients with *C. canimorsus* infections after 1990, the most common clinical presentation was sepsis with the organism identified in blood cultures (Table 3). Some patients with severe sepsis and shock demonstrated purpura or petechiae, disseminated intravascular coagulation (DIC), hemolytic uremic syndrome (HUS) [105, 136], or thrombotic thrombocytopenic purpura (TTP) [31, 57, 82, 92, 129]. Autopsies in 25 cases showed adrenal hemorrhage characteristic of the Waterhouse–Friderichsen syndrome in 8 cases (32 %) [39, 45, 95, 101, 114, 131, 145]. Gangrene of the extremities resulting in amputations of the digits and extremities continue to be part of the spectrum of *C. canimorsus* sepsis [24, 47, 57, 62, 72, 87, 91, 96, 109, 118, 134, 135, 142]. Other notable features were abdominal complaints, including pain, diarrhea, and unnecessary laparotomy [22, 29, 37, 46, 67, 128] and myocardial infarctions [53, 56, 102].

The second most common presentation was meningitis in 32 cases with cultures or polymerase chain reaction (PCR)-based testing of CSF showing *C. canimorsus*; blood cultures were positive in 41 % of these cases. They differed from sepsis cases by showing lower rates of splenectomy (only one) and a lower mortality rate. The one death was a 74-year-old male with atherosclerotic heart disease who died 10 days after hospital discharge rather than during acute illness [114]. They differed also demographically with older ages (median of 64 years) and 83 % were males. Additionally, the incubation period from dog bite or other exposure to illness was longer (median of 7 days) compared to sepsis patients (median of 3 days) (Table 4, $p<0.05$).

Endocarditis or mycotic aneurysms occurred less frequently, present in 12 patients, including one with a prosthetic aortic valve and hepatitis C infection [124]. Another patient had a ventricular assist device awaiting a heart transplant who developed bacteremia after a dog bite but recovered satisfactorily [54].

Although animal bites were reported in most patients, only five cases had prominent wound infections with the organism isolated from a wound culture. Some bite wounds, however, showed severe necrosis [72, 135, 143]. Eye infections were, likewise, rare, present in only six cases. Two were veterinarians who handled animal teeth [36, 48], one was a patient who had undergone cataract removal [115], one had endophthalmitis [111], one infection after a cat bite resulted in retinal detachment and permanent loss of vision [150], and one resulted in enucleation [141].

High-grade bacteremia

Another feature of the organism is that it causes, in most cases, minimal inflammation at the bite site, but has invasive properties to gain access to blood, where it sometimes proliferates to a high-grade bacteremia with organisms visible in blood smears, both inside polymorphonuclear leukocytes and extracellularly [3, 32, 35, 50, 52, 101, 106, 110, 134, 146, 149]. Images of blood smears showed multiple bacilli in

Table 2 Relation of spleen status and alcoholism to age and mortality in reported patients with sepsis, meningitis, and other intravascular infections due to *C. canimorsus*

Patient status	No. of cases	Median age, years	Case-fatality rate (%)	Median age of fatal cases
Splenectomy*	59	48.5	16/56 (29)	47
Hyposplenism**	10	52	3/10 (30)	36
Alcoholism	54	54	15/51 (29)	56
Intact spleen without alcoholism	129	60***	32/129 (25)	59

*Reasons for splenectomy were trauma (23 cases), not specified (12 cases), idiopathic thrombocytopenic purpura (ITP) (seven cases), Hodgkin's disease (six cases), incidental removal during surgery (five cases), leukemias (three cases), and one case each of Gaucher's disease, hemolytic anemia, and splenic vein thrombosis with pancreatitis

**Included congenital asplenia, functional asplenism, splenic infarction, splenic fibrosis, and hemoglobin SC disease

***Median age of 60 years greater than the median of 49.5 years for splenectomies and hyposplenism ($p<0.05$ by the Mann–Whitney *U*-test [151])

Table 3 Update of clinical presentations in documented *C. canimorsus* infections in 1990–2014. Numbers of reported cases*

Feature	No. of patients
Sepsis with positive blood culture	222
Purpura or petechiae	25
DIC	31
Shock	30
Gangrene or amputation of digits or extremities	18
Abdominal complaints with pain, distention, diarrhea, or need for laparotomy	28
Myocardial infarction	3
Meningitis with positive CSF findings	32
Endocarditis with positive culture of blood, artery, or aneurysm	12
Wound infection	5
Eye infection	6
Other sites**	5

*Patients with more than one of the features were entered more than once

**Includes joints [40, 88], pleura [34], peritoneum [67], and brain abscess [139]

polymorphonuclear neutrophils (PMN), suggesting that phagocytosis of *C. canimorsus* occurred without effective removal or rapid destruction of the organisms. Detection of high-grade bacteremia in 39 patients, of whom 23 had prior splenectomy or hyposplenism, indicated a greater incidence of this finding in patients lacking splenic function than in patients with alcoholism and others with *C. canimorsus* infections (Table 5, $p<0.05$).

Prevalence of *C. canimorsus* in dogs and cats

Examinations of dogs' oral flora for *C. canimorsus* was first done in 1978 by Bailie et al. [152] in the USA, with the finding that 4 of 50 healthy dogs (8 %) carried the pathogen. Krol-van Straaten et al.[3] subsequently reported isolation of *C. canimorsus* from the mouth of the same dog that had bitten a patient with sepsis due to the bacterium. *C. canimorsus* was detected in a gingival swab of the dog that had bitten a patient with meningitis in the Netherlands [78]. Subsequent surveys of healthy dogs in the USA [153], UK [154], the Netherlands [155, 156], France [157], Switzerland [158], and Japan [159] detected oral carriage with a wide range of prevalences, from 3 to 74 %. One explanation for the discrepancies in prevalence is methodology. Studies using culture methods showed lower prevalences, whereas methods employing DNA detection using PCR-based testing for the 16S rRNA gene showed higher prevalences [156, 159]. In the USA, dogs more likely to carry the organism were older than 6 months, males that had been neutered and spayed, and small breeds, including toy dogs [153]. In the oral flora of healthy cats, *C. canimorsus* was present in 57 % of Japanese cats [159], 15 % of French cats [157], 17 % of British cats [154], and 1 % of Dutch cats [155]. Sheep, cattle, horses, guinea pigs, and rabbits also harbor the organism in their mouths [154, 155].

Table 4 Comparison of patients with meningitis and sepsis. Values are given as medians or numbers of cases (percentage of cases) for whom clinical information was reported

Features	Meningitis (n=24)	Sepsis (n=135)	p-Value*
Age, in years	64	54	<0.05
Males/females (% males)	20/4 (83)	80/54 (60)	<0.05
Median number of days from dog bite or other animal exposure to illness	7	3	<0.05
Prior splenectomy	1 (4)	26 (19)	>0.05
Deaths	1 (4)	42 (31)	<0.05

*Mann–Whitney *U*-test for ages and time after dog bites; Fisher's exact test for males/females, prior splenectomy, and deaths [151]

Virulence factors

C. canimorsus has been described variously as having weak pathogenicity, with a requirement for immunodeficiency in its hosts and as having exceptionally strong pathogenicity that can produce fatal high-grade bacteremic disease, even in immunocompetent hosts. From the diversity of host factors in case reports, both features, respectively, apply in individual cases.

Several virulence attributes have been identified. The organism is positive for catalase, unlike most of the other species of *Capnocytophaga* that are catalase-negative. By degrading hydrogen peroxide in phagocytic vacuoles, this enzyme could allow the bacteria to survive within phagocytes. Unlike other

Table 5 Detection of high-grade bacteremia* related to risk categories in patients with sepsis and meningitis caused by *C. canimorsus***. Numbers of patients

Risk categories	High-grade bacteremia	
	Detected	Not detected
Splenectomy***	21	38
Hyposplenism	2	8
Alcoholism	5	51
Others with bacteremia or meningitis	11	143
Totals	39	238

*Presence of visible bacteria in stained smears of peripheral blood

**Patients with wound and eye infections excluded

***High-grade bacteremia detected more frequently in patients with splenectomy than in other patients with bacteremia or meningitis ($p<0.05$ by Fisher's exact test [151])

species of *Capnocytophaga*, *C. canimorsus* is resistant to killing by serum complement [160, 161]. *C. canimorsus* lacks flagella but shows gliding motility on solid agar [1], a feature that may enable it to traverse tissues to reach the bloodstream. The organism possesses sialidase, which permits it to obtain amino-sugars as nutrients from glycoproteins on the surfaces of host cells [158, 162, 163]. When *C. canimorsus* is placed into human blood or in cultured macrophages, it elicits lower quantities of proinflammatory cytokines and nitric oxide than other bacteria [164, 165], suggesting that it can escape immune surveillance by failing to stimulate an innate immune response. When cultured macrophages were exposed to *C. canimorsus*, cytotoxic effects were observed, and a cell-free cytotoxin could be detected in culture supernatants [166]. As a Gram-negative organism, it contains lipopolysaccharide (LPS), which has a unique penta-acylated lipid A that does not interact with the usual LPS receptor, Toll-like receptor 4, unless the lipid A is attached to its core oligosaccharide [167].

Discussion

With an estimated 484 confirmed cases in the literature, *C. canimorsus* should no longer be regarded as a rare infection. It has taken on an importance as a prominent cause of infection after dog bites just behind *Pasteurella multocida* in frequency and as a cause of post-splenectomy sepsis just behind *Streptococcus pneumoniae* in frequency. In patients with *C. canimorsus* infection reported between 1990 and 2014, their features were remarkably similar to patients reported earlier when the organism was known as DF-2 [2]. Most were males over 50 years of age who had been bitten by dogs a few days before their illnesses and had the bacteria identified in blood cultures. The male preponderance of cases can be correlated with alcoholism occurring twice as often in males [168], as well as males more likely to undergo splenectomy due to motor vehicle accidents or sports injuries [169]. Males are more prone to dog bites [170, 171], which are probably also provoked sometimes by persons who neglect or provoke their animals during periods of drunkenness. Elderly persons were at higher risk for infections probably because of aging of the immune system and perhaps because older persons frequently own pets.

The most common presentation was sepsis, often with DIC, shock, organisms visible in blood smears, and peripheral gangrene, resulting in a mortality rate of approximately 26 %. Other presentations included meningitis, endocarditis, wound infections, and eye infections. About half the patients were immunocompromised due to prior splenectomy, alcoholism, malignancies, and other conditions. Patients with immune defects involving primarily T cell function, such as human immunodeficiency virus (HIV) infection, seem not to be at increased risk of *C. canimorsus* sepsis because only one reported patient had HIV infection [124]. When patients with sepsis were compared to patients with meningitis, sepsis cases were younger, more often splenectomized, and showed a higher case-fatality rate. Furthermore, the incubation period from dog bite or other animal exposure to onset of symptoms in meningitis patients, with a median of 7 days, was longer than the 3 days for sepsis, explaining how additional time for the evolution of an immune response in meningitis perhaps reduced mortality. The longer incubation period for meningitis is consistent with a requirement for bacteremia to be established to seed the meninges, after which growth occurs in spinal fluid, with each step requiring about 3 days. Additionally, several meningitis cases were described as subacute or resembling viral meningitis with a predominance of lymphocytes in CSF [42, 63].

Among sepsis pathogens, *C. canimorsus* is distinctive for being isolated from blood or CSF almost exclusively. Rarely have isolations been accomplished from bite-site wound cultures and eye cultures. Only 3 out of 150 isolates at the CDC in 1987 were from wounds [1] and only five patients after 1990 had the bacterium isolated from wounds. The reasons for wounds rarely yielding the organism are that wounds have often been described as minor with no care sought for them [81, 98, 107, 109, 127, 131, 135], and that wounds are contaminated by skin flora that easily overgrow this slow-growing fastidious organism. Besides, this organism is susceptible to penicillin and other antibiotics routinely given as prophylaxis after animal bites, so many infections are prevented or cannot be diagnosed by obtaining cultures. In reports of antibiotic susceptibilities, the majority of strains were susceptible to beta-lactams as well as to tetracyclines, erythromycin, clindamycin, fluoroquinolones, carbapenems, vancomycin, chloramphenicol, and rifampin, with only two strains showing resistance to penicillin [18, 73]. Most strains showed resistance or variable sensitivity to aminoglycosides, trimethoprim–sulfamethoxazole, aztreonam, colistin, and metronidazole.

Risk factors of splenectomy, other causes of hyposplenism, and alcoholism implicate the spleen and liver as key organs for protection against *C. canimorsus* infection. Splenic macrophages in the red pulp and Kupffer cells in the liver sinusoids are important cells of the innate immune system for removing bacteria from the blood. When *Escherichia coli* bacteria were injected into rats, bacteria localized within minutes to the spleen and liver [172]; injected LPS was excreted into the bile of mice [173]. In *C. canimorsus* sepsis, which can develop as fast as one day after a dog bite [62, 74, 98, 104, 107, 109, 136, 142], it is clearly the early phagocytosis of the innate immune system that has failed because antibody production would require several days to unfold. Splenectomies are carried out in about 25,000 patients per year in the USA [169], often because of trauma or hematologic conditions or hepatitis C [174]. For patients with spleens, splenic function may be

depressed by immunosuppressive therapies, irradiation, alcoholism, or by other diseases [175]. Of the 54 patients with *C. canimorsus* sepsis who were alcoholics, some of their livers developed cirrhosis with an indirect effect through portal vein hypertension to cause splenic dysfunction [176].

In patients with septicemia due to *P. multocida*, a high mortality of 30 % occurs with cirrhosis as the underlying disease [177], but apparently not an association with splenectomy. Further comparison of these bacteria indicates that *P. multocida* is more likely to be isolated from wounds but less likely from blood or CSF. Both organisms have LPS and are serum-resistant, but only *P. multocida* has been shown to possess an antiphagocytic capsule [177]. *C. canimorsus* is one of the most lethal of sepsis pathogens ever described, with its estimated case-fatality rate of 26 %. The reasons for this high mortality include its ability to overwhelm patients with a high-grade bacteremia and shock that represents explosive growth of bacteria during a few days after a dog bite. The only other bacteria capable of this unchecked growth in blood are a few notorious killers such as *Neisseria meningitidis* and *S. pneumoniae*, which are prominent causes of post-splenectomy sepsis attributable to their possession of antiphagocytic capsules [174]. On the other hand, *C. canimorsus* is not known to be encapsulated, but its LPS blocks complement at the bacterial surface, thus preventing lysis [161] and perhaps also opsonization.

The recognition of *C. canimorsus* as an important cause of sepsis and meningitis after animal bites and other pet exposures depended on improved laboratory methods for the identification of fastidious bacteria in blood cultures developed at the CDC in the 1960s. *C. canimorsus* was slow-growing as well as capnophilic and required serum for growth on agar plates. Its identification has been aided more recently by the use of PCR to detect rRNA sequences. Other reasons for the emergence of the infection include a rising incidence of splenectomy due to sports injuries and motor vehicle accidents and gunshot wounds, a high prevalence of alcoholism, popularity of pet ownership due to a public perception of their safety, and aging of human populations.

Conflict of interest The author declares that he has no conflict of interest.

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