

The Characteristics of *Capnocytophaga* Infection: 10 Years of Experience

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Background. *Capnocytophaga* is a gram-negative, facultative anaerobe. Human infection is rare but can lead to devastating outcomes. *Capnocytophaga canimorsus* can cause sepsis following an animal bite, whereas human-oral-associated *Capnocytophaga* infections were reported in immunocompromised patients. Current data on these infections are not robust. Our goal is to provide a contemporary description of a unique characteristic of *Capnocytophaga* infections.

Methods. We performed a retrospective review of all patients with *Capnocytophaga* infection from January 2010 to August 2020 at 3 main hospitals of Mayo Clinic in Rochester, Minnesota; Scottsdale, Arizona; and Jacksonville, Florida. We collected baseline demographic data, clinical characteristics, microbiological data, and outcomes of *C. canimorsus* and human-oral-associated *Capnocytophaga* infection.

Results. Among 82 patients with *Capnocytophaga* infection, 46 patients (56.0%) had bacteremia. The most common species identified in this group was *C. sputigena* (57.9%), followed by *C. canimorsus* (34.8%). Patients with human-oral-associated *Capnocytophaga* bacteremia were often immunocompromised, presented with neutropenic fever, and had worse 6-month all-cause mortality compared to *C. canimorsus* bacteremia (36.4% vs 6.2%, $P = .03$). They also had a higher β -lactamase production rate (36.4% vs 0.0%, $P = .02$). Among patients without bacteremia, the main clinical syndrome was polymicrobial head and neck infections (47.2%).

Conclusions. Human-oral-associated *Capnocytophaga* bacteremia occurs primarily in immunocompromised patients, particularly those with hematologic malignancy. In contrast, *C. canimorsus* bacteremia is more likely to present with community-onset infection related to zoonotic exposure. Human-oral-associated *Capnocytophaga* infection without bacteremia is frequently isolated in polymicrobial infection; this phenomenon's significance is yet to be fully understood.

Keywords. *Capnocytophaga*; bacteremia; mortality; zoonosis.

Capnocytophaga species are a slow-growing, facultative anaerobic, gram-negative bacilli that can cause various clinical syndromes in humans [1]. There are 9 species of *Capnocytophaga*, which can be classified into 2 main categories: human-oral associated and zoonosis associated. The species *C. gingivalis*, *C. granulosa*, *C. haemolytica*, *C. leadbetteri*, *C. ochracea*, and *C. sputigena* are a part of human oral microbiota, whereas *C. canimorsus*, *C. canis*, and *C. cynodegmi* are commensal organisms in the mouths of dogs or cats [1–3].

Capnocytophaga infection in humans is rare. Previous studies were focused on *C. canimorsus*, as it is the most common among the genus to cause human disease [4]. According to 1 population-based study, incidence of infection

was approximately 0.67 infections per million population [5]. Bacteremia can occur with both zoonotic and human-oral-associated *Capnocytophaga* [5, 6]. Other previously reported clinical manifestations of *C. canimorsus* infection include fever of unknown origin, meningitis, brain abscess, endocarditis, mycotic aneurysm, respiratory tract infection, and orthopedic infections such as septic arthritis and soft tissue infections [7–11].

In contrast to *C. canimorsus*, clinical syndromes from human-oral-associated *Capnocytophaga* infection other than bacteremia are sporadic and have not been well studied. Sepsis is common in immunocompromised populations, especially in patients with hematologic malignancies [12]. Some studies reported human-oral-associated *Capnocytophaga* as a rare cause of pleural empyema, chorioamnionitis, and neonatal sepsis [13–15].

Our study aims to highlight the key differences in clinical characteristics of *C. canimorsus* and human-oral-associated *Capnocytophaga* bloodstream infections, as well as to outline the clinical manifestations and outcomes of such infections.

METHODS

Study Design and Participants

We conducted a retrospective review of all patients diagnosed with *Capnocytophaga* infection from 1 January 2010 to 31

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August 2020, at 3 main hospitals of Mayo Clinic in Rochester, Minnesota; Scottsdale, Arizona; and Jacksonville, Florida. We used Mayo Clinic Advance Text Explorer software and the Division of Clinical Microbiology laboratory database to identify all adult patients (age 18 years or older) who had *Capnocytophaga* isolated from their clinical specimens.

We manually reviewed all the medical records to determine the clinical significance of each positive culture. We deemed that the culture was clinically significant if the patient developed a clinical syndrome consistent with *Capnocytophaga* infection and was documented as such by the treating providers. All clinical data were collected and managed using REDCap electronic data capture tools hosted at Mayo Clinic [16, 17].

We gathered patient characteristics such as age, sex, reported animal bite/scratch, and comorbidities. Comorbidities of interest included host immune status in addition to known risk factors for *Capnocytophaga* infections [13, 18, 19]. Hospitalization data including an initial clinical syndrome, length of hospital stay, intensive care unit (ICU) admission, type and duration of antimicrobial therapy, and surgical management were also included. Additionally, we collected all-cause mortality at the time of hospital discharge and 6 months for bacteremia patients.

Patient Consent Statement

The study was reviewed and approved by the Mayo Clinic Institutional Review Board. The study was granted an exemption from patient consent, as it does not include factors necessitating patient consent.

Microbiological Data

Matrix-assisted laser desorption/ionization–time of flight mass spectrometry (MALDI-TOF MS) was used for species

identification after subculturing. β -lactamase testing was done using Cefinase (Becton Dickinson, catalog number 231650). Cefinase disks are impregnated with a cephalosporin nitrocefin solution, which is normally yellow but changes color to red when a β -lactamase hydrolyses the β -lactam ring.

Statistical Analysis

We used Fisher exact or χ^2 test for categorical data and Wilcoxon-Mann-Whitney test for nonparametric quantitative data. All analyses were performed using BlueSky Statistics version 7.10 software (BlueSky Statistics LLC, Chicago, Illinois).

RESULTS

Clinical Characteristics

We identified 110 patients who had positive cultures for *Capnocytophaga* species. Of those, 82 patients had clinically significant culture results and were included in the study (Figure 1). Forty-six patients (56.1%) had positive cultures from the blood (bacteremia group), and 36 patients (43.9%) had positive cultures from non-blood clinical specimens (nonbacteremia group). The median age was 59 years (interquartile range [IQR], 49.3–68.8 years), and the majority of patients were male. Thirteen patients (15.9%) reported a history of an animal bite or scratch, while it was not documented in the rest of the cases. The median Charlson comorbidity index was 3 (IQR, 2–5). Forty-seven patients (57.3%) had at least 1 comorbidity. Twenty-eight patients (34.1%) actively received immunosuppressive medications.

Overall, 79 patients required hospitalization (96.3%), with 23 patients (29.1%) admitted to the ICU. The median length of stay was 7 days (IQR, 3.5–13.0 days). Surgical management was needed in 32 patients (39%). The most common antimicrobial

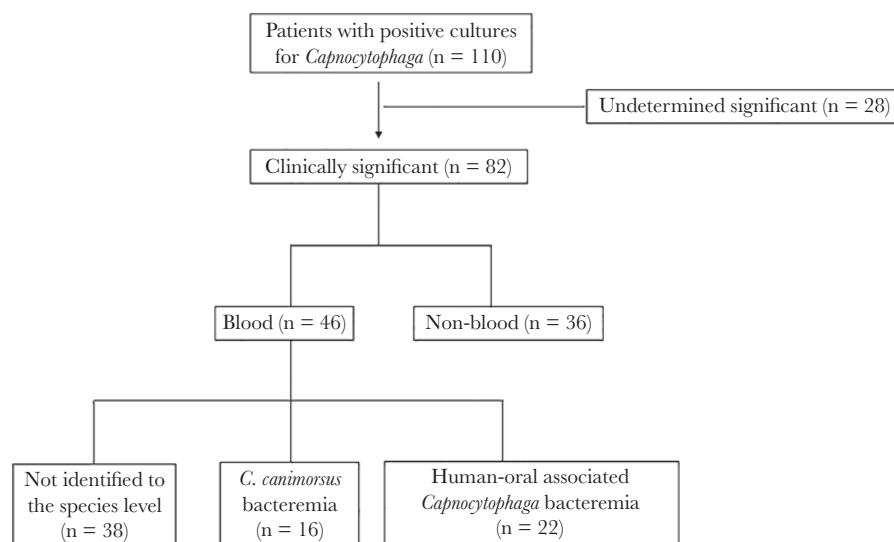


Figure 1. Study design and participants.

regimens involved combination β -lactam/ β -lactamase inhibitors (n = 25 [30.5%]), third/fourth-generation cephalosporins (n = 25 [30.5%]), and carbapenems (n = 25 [30.5%]). The median duration of antimicrobial therapy was 14 days (IQR, 10–28 days). Other detailed clinical characteristics were summarized in [Table 1](#).

Bacteremia Group

Forty-three patients (93.5%) had a monomicrobial bloodstream infection. The clinical syndromes associated with bacteremia were neutropenic fever (n = 19 [41.3%]), sepsis/septic shock in nonneutropenia (n = 16 [34.8%]), skin and soft tissue infection

(n = 8 [17.4%]), septic joint (n = 1 [2.2%]), postoperative respiratory failure (n = 1 [2.2%]), and meningitis (n = 1 [2.2%]). Identification to the species level was done in 38 isolates (82.6%). *Capnocytophaga canimorsus* bacteremia comprised 42.1% of cases (n = 16), while 57.9% (n = 22) had human-oral-associated *Capnocytophaga* bacteremia (*C. sputigena*, *C. ochracea*, and *C. gingivalis*). The median time to blood culture positivity was 70 hours (IQR, 57–96 hours). Nine isolates (24.3%) produced β -lactamase, which was found only in the human-oral-associated *Capnocytophaga* group. The detail of antibiotic therapy based on β -lactamase production can be found in [Supplementary Table 1](#).

There were no differences in age or sex between *C. canimorsus* and human-oral-associated *Capnocytophaga* groups. Hematopoietic stem cell transplantation was more common in the human-oral-associated *Capnocytophaga* group ($P < .001$). Sixteen patients (72.7%) in the human-oral-associated *Capnocytophaga* group were taking immunosuppressive medications compared with 2 patients (12.5%) in the *C. canimorsus* group ($P < .001$). Unsurprisingly, all patients with a reported history of animal bite/scratch were in the *C. canimorsus* group. Detailed clinical syndromes of each group and sources of bacteremia were described in [Table 2](#).

The median length of stay was 8 days (IQR, 5.0–16.0 days) in the human-oral-associated *Capnocytophaga* group and 4.5 days (IQR, 2.8–8.0 days) in the *C. canimorsus* group ($P = .025$). There was no difference in the rates of ICU admission between the groups. All-cause mortality at discharge was not different between the 2 groups. However, 6-month all-cause mortality was higher in the human-oral-associated *Capnocytophaga* group (36.4% vs 6.2%, $P = .03$).

Nonbacteremia Group

Capnocytophaga was isolated from 33 of 36 patients (91.7%) as part of a polymicrobial infection. Twenty-four isolates (66.7%) were identified to the species level; all were human-oral-associated *Capnocytophaga* species. Seven isolates (33.3%) produced β -lactamase ([Supplementary Table 1](#)). The most common clinical syndrome was head and neck infections (n = 17 [47.2%]), such as neck abscess, facial cellulitis, facial abscess, osteomyelitis of mandible/maxilla, retropharyngeal abscess, and dental root infection. This was followed by osteomyelitis of extremities (n = 4 [11.1%]), thoracic empyema (n = 4 [11.1%]), respiratory tract infection (n = 4 [11.1%]), and intra-abdominal abscess (n = 2 [5.6%]). Other rare clinical syndromes included surgical site infection, skin abscess, breast abscess, brain abscess, and vascular graft infection (1 patient each).

DISCUSSION

Our study illustrated the clinical characteristics of *Capnocytophaga* infection at 3 main hospitals of Mayo

Table 1. Characteristics of Patients With *Capnocytophaga* Infection

Characteristic	No. (%)
Age, y, median (IQR)	59 (49.3–68.8)
Male sex	45 (54.9)
Charlson comorbidity index, median (IQR)	3 (2.0–5.0)
Comorbidities	
Active immunosuppressive medications ^a	28 (34.1)
Diabetes	15 (18.3)
Hematopoietic stem cell transplantation	13 (15.9)
Active hematologic malignancy	12 (14.6)
Active solid organ malignancy	7 (8.5)
End-stage renal disease	4 (4.9)
Alcohol use disorder	3 (3.7)
Splenectomy	3 (3.7)
Solid organ transplantation	3 (3.7)
Reported history of animal bite or scratch	
Dog	9 (11)
Cat	4 (4.9)
Hospitalization	
Requiring hospitalization	79 (96.3)
Length of stay, d, median (IQR)	7 (3.5–13.0)
Requiring ICU admission	23 (29.1)
Specific antibiotic therapy	
β -lactam/ β -lactamase inhibitor ^b	25 (30.5)
Cephalosporin ^c	25 (30.5)
Carbapenem ^d	25 (30.5)
Other antibiotics ^e	6 (7.3)
No antibiotic due to hospice care	1 (1.2)
<i>Capnocytophaga</i> species (n = 62)	
<i>C. sputigena</i>	28 (45.2)
<i>C. canimorsus</i>	16 (25.8)
<i>C. ochracea</i>	10 (16.1)
<i>C. gingivalis</i>	5 (8.1)
<i>C. cynodegmi</i>	1 (1.6)
<i>C. granulosa</i>	1 (1.6)
<i>C. leadbetteri</i>	1 (1.6)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

^aActive immunosuppressive medications included daily steroid >20 mg of prednisone equivalence for >1 month; active chemotherapy within 3 months; calcineurin inhibitor; other biologic agent; cytostatic agent other than chemotherapy.

^b β -lactam/ β -lactamase inhibitor included amoxicillin/clavulanate, ampicillin/sulbactam, and piperacillin/tazobactam.

^cCephalosporin included ceftriaxone and cefepime.

^dCarbapenem included ertapenem and meropenem.

^eOther antibiotics included levofloxacin, moxifloxacin, and clindamycin.

Table 2. Comparison of *Capnocytophaga canimorsus* and Human-Oral-Associated *Capnocytophaga* Bacteremia

Characteristic	<i>Capnocytophaga canimorsus</i> Bacteremia (n = 16)	Human-Oral-Associated <i>Capnocytophaga</i> Bacteremia (n = 22)	P Value
Baseline characteristic			
Age, y, median (IQR)	57 (48.0–74.3)	59.5 (47.3–68.5)	.69
Male sex	10 (62.5)	13 (59.1)	.832
Risk factors			
Alcohol use disorder	2 (12.5)	0 (0.0)	.171
Splenectomy	2 (12.5)	0 (0.0)	.171
Diabetes	3 (18.8)	4 (18.2)	1
End-stage renal disease	1 (6.2)	1 (4.5)	1
Solid organ transplantation	1 (6.2)	1 (4.5)	1
Hematopoietic stem cell transplantation	0 (0.0)	12 (54.5)	<.001
Active solid organ malignancy	0 (0.0)	2 (9.1)	.499
Active hematologic malignancy	1 (6.2)	9 (40.9)	.025
Active immunosuppressive	2 (12.5)	16 (72.7)	<.001
At least 1 risk factor presence	8 (50)	22 (100)	<.001
Reported animal bite/scratch	11 (68.8)	0 (0.0)	<.001
Clinical syndromes			
<.001			
Neutropenic fever	0 (0.0)	17 (77.3)	
Sepsis/septic shock without neutropenia	8 (50.0)	3 (13.6)	
Skin and soft tissue infection of extremities	6 (37.5)	1 (4.5)	
Septic joint	1 (6.2)	0 (0.0)	
Postoperative respiratory failure	0 (0.0)	1 (4.5)	
Meningitis	1 (6.2)	0 (0.0)	
Source of bacteremia			
.001			
Unable to identify the source of bacteremia	6 (37.5)	6 (27.3)	
Central catheter associated	0	10 (45.5)	
Skin and soft tissue infection of extremities	8 (50.0)	0 (0.0)	
Neutropenic colitis/mucositis	0 (0.0)	4 (18.2)	
Jaw osteomyelitis	0 (0.0)	1 (4.5)	
Septic arthritis	1 (6.2)	0 (0.0)	
Upper/lower respiratory tract infection	0 (0.0)	1 (4.5)	
Meningitis	1 (6.2)	0 (0.0)	
Outcome			
Mortality on hospital discharge	0 (0.0)	2 (9.1)	.306
All-cause mortality at 6 mo	1 (6.2)	8 (36.4)	.03

Data are presented as No. (%) unless otherwise indicated. Abbreviation: IQR, interquartile range.

Clinic in Rochester, Minnesota; Scottsdale, Arizona; and Jacksonville, Florida during the past 10 years. More than half of all *Capnocytophaga* infections in our study were bloodstream infections. We found that *C. sputigena* was the most prevalent species among all *Capnocytophaga* infections, followed by *C. canimorsus*. One previous study revealed that >70% of *C. canimorsus* infection presented with bacteremia [20]. However, the actual incidence of bacteremia in other *Capnocytophaga* infections is unknown.

Traditional risk factors associated with severe *C. canimorsus* infections are a history of dog bite, asplenia, cirrhosis, and alcohol use disorder [19–21]. Risk factors for human-oral-associated *Capnocytophaga* infections are less well studied. Our study found that not all patients with *C. canimorsus* bloodstream infection had classical risk factors; overall, the numbers of patients with asplenia, cirrhosis, and alcohol use disorder were approximately only 4%. Additionally, only 68% of our *C. canimorsus* bacteremia patients were linked to animal bites or scratches. These findings are consistent with a nationwide survey from the Netherlands. They found that only half of the patients reported a history of animal contact and a low prevalence of splenectomy and alcohol use disorder [5]. In the clinical setting, the decision to obtain blood cultures in patients presenting with animal bite skin and soft tissue infection is often determined based on the severity of presentation, the presence of systemic features of sepsis, and specific host risk factors.

In contrast, human-oral-associated *Capnocytophaga* bacteremia was implicated in immunocompromised patients, especially with neutropenia secondary to chemotherapy for hematologic malignancy and hematopoietic stem cell transplantation. This finding was observed in previous case reports and small case series [12, 18, 22]. Blood cultures were obtained as part of routine investigations for febrile episodes in neutropenic patients; approximately 27% of these episodes were without a clear source, whereas the rest were attributed to translocation through the oral or gastrointestinal mucosa or labeled as central venous catheter-associated bloodstream infections. Consequently, the growth of small gram-negative bacilli in anaerobic blood culture bottles after 48 hours in a neutropenic patient should raise the suspicion for human-oral-associated *Capnocytophaga*, and empiric antibiotic coverage should be reviewed to ensure appropriate coverage. Once identified, a close evaluation of the oral mucosa, assessment for differential time to positivity to detect line-related infection, and abdominal imaging may be indicated.

According to the literature, mortality from *C. canimorsus* ranged from 10% to 30% [5, 6, 11, 20]. Our study found that 6-month all-cause mortality was higher in the human-oral-associated *Capnocytophaga* group. This could be from poorer baseline clinical status in the human-oral-associated *Capnocytophaga* group. We found that patients with

C. canimorsus bacteremia had fewer comorbidities compared to human-oral-associated *Capnocytophaga* bacteremia.

Polymicrobial infections involving *Capnocytophaga* species are less defined in the literature. Recent advancements in the microbiology field, especially in the era of MALDI-TOF MS [23], may explain the increased detection of *Capnocytophaga* in various other clinical specimens, often as part of polymicrobial infection. Their exact role in the disease process is difficult to interpret as many other virulent bacteria were isolated. As normal commensal microbiota of the human-oral cavity, it is not surprising that they are implicated in head and neck infections or respiratory tract infections. As we have found, almost all of the nonbacteremia group had polymicrobial infection. The treatment and choice of antibiotic regimens are also unlikely to be affected by *Capnocytophaga* species' presence.

Currently, there is no standard antimicrobial susceptibility guide for *Capnocytophaga* species. Previous in vitro susceptibility is based on the breakpoint for anaerobes, which is not widely available [24]. β -lactamase detection is an alternative way to help guide antimicrobial therapy. However, this result may take days to become available due to the slow-growing nature of *Capnocytophaga*. Our rate of β -lactamase production is almost 30% and it was solely found in the human-oral-associated *Capnocytophaga* group. These findings were previously described in past studies [25–27]. Previous exposure to antibiotics could contribute to this finding, especially among patients with hematologic malignancies and other immunocompromising conditions.

Owing to the higher prevalence of β -lactamase production among the human-oral *Capnocytophaga* group, stable agents against β -lactamases should be utilized for definitive therapy. This includes a combination of β -lactam/ β -lactamase inhibitors, advanced-generation cephalosporins (third or fourth generation), or carbapenems. We have not noted treatment failure with advanced-generation cephalosporins in our cohort. On the contrary, β -lactamase production was rare among *C. canimorsus*, making penicillin a viable choice for *C. canimorsus* monomicrobial infections. The duration of therapy in both bacteremia and nonbacteremia is often dictated by the primary syndrome.

To our knowledge, this is the largest cohort evaluating clinical characteristics of *Capnocytophaga* infection. However, there are some limitations. First, not all patients in the nonbacteremia group had blood culture collection at the time of diagnosis; therefore, it is possible that some patients in this group had bacteremia. Second, the nature of cross-sectional study limited the ability to define the association and causation of the variables. Third, not all isolates were identified to the species level, limiting the accuracy of the conclusions regarding the significance of species identification and association between particular species and specific syndromes or populations at risk. Finally,

there may be reporting bias. Most of our patients had multiple comorbidities; therefore, these findings may not be generalizable to *Capnocytophaga* infection in other populations.

In conclusion, our study provides contemporary data on the host factors, clinical presentations, and management trends of *Capnocytophaga* infection. We also described the difference between human-oral-associated vs zoonosis-associated *Capnocytophaga* infection.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts of interest.

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