The Characteristics of \textit{Capnocytophaga} Infection: 10 Years of Experience

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**Background.** \textit{Capnocytophaga} is a gram-negative, facultative anaerobe. Human infection is rare but can lead to devastating outcomes. \textit{Capnocytophaga canimorsus} can cause sepsis following an animal bite, whereas human–oral–associated \textit{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 \textit{Capnocytophaga} infections.

**Methods.** We performed a retrospective review of all patients with \textit{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 \textit{C. canimorsus} and human–oral–associated \textit{Capnocytophaga} infection.

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

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

**Keywords.** \textit{Capnocytophaga}; bacteremia; mortality; zoonosis.
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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 χ² 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.](image-url)
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 = 62 [30.5%]), and carbapenems (n = 25 [30.5%]). 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 abscesses (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 2. Comparison of Capnocytophaga canimorsus and Human-Oral–Associated Capnocytophaga Bacteremia

| Characteristic                              | Capnocytophaga canimorsus Bacteremia (n = 16) | Human-Oral–Associated Capnocytophaga 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              |                                             |                                                        | <.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.

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 among 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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