Le syndrome de Bobo-Newton : un cadeau malvenu du meilleur ami de l’homme

Le Capnocytophaga canimorsus est un bacille Gram négatif facultatif qui fait généralement partie de la flore buccale des chiens et des chats. C’est Bobo et Newton qui l’ont isolé pour la première fois en 1976, chez un homme souffrant d’une méningite après avoir été mordu par un chien. La transmission aux humains est secondaire à plusieurs blessures liées aux animaux, qui peuvent être évidentes ou discrètes. Le C canimorsus peut causer une série de syndromes, de l’infection de la peau et des tissus mous à une maladie invasive comme la méningite ou l’endocardite. Le présent article rend compte d’un cas de méningite à Capnocytophaga chez un patient ayant les facteurs de risque classiques de cirrhose hépatique alcoolique. La présomption clinique a été confirmée par culture et identification génétique de l’isolat sanguin. Dans le présent article, on trouve une analyse du gène Capnocytophaga, des syndromes cliniques les plus associés à cet organisme zoonotique, de son identification en laboratoire et de son traitement.


Capnocytophaga canimorsus est un bacille facultatif Gram-négatif bacille qui est typiquement un constituant de la flore buccale de chiens et de chats. Il a été isolé par Bobo et Newton en 1976 au cours d’un cas présentant avec une méningite suivi d’une morsure par un chien. La transmission à l’homme peut se faire par divers moyens, parfois subtile. C. canimorsus peut causer une gamme de symptômes allant de l’infection cutanée à une infection invasive comme la méningite ou l’endocardite.

Le présent article rapporte un cas de C. canimorsus chez un patient avec le classicisme de la cirrhose hépatique alcoolique. Cliniquement, la présomption a été confirmée par culture et identification génétique de l’isolat sanguin. Le présent article revient sur le Capnocytophaga, un genre de germes zoonotiques, et comment un simple traumatisme cutané peut entraîner une infection invasive.

Key Words: Capnocytophaga canimorsus; Dog bite; Gram-negative bacillus; Meningitis

Leir 1976, Bobo et Newton (1) décrit un syndrome qui permettrait de modifier les relations de l’homme avec les chiens. Un germes méconnu, fastidieux bacille Gram-négatif bacille était isolé de la flore de la peau et du liquide céphalorachidien d’un homme qui avait développé une septiciémie et une méningite d’une semaine après avoir été mordu par un chien. En effet, ces organismes avaient été signalés pour la première fois aux États-Unis en 1961, formant le ‘dysgonique fermenter type 2’ (DF-2) collection (2). Bientôt, Butler et al (3) ont révisé les informations cliniques et épidémiologiques pour 17 patients, démontrant que cet organisme était le plus fréquemment isolé. Le présent article revient sur le Capnocytophaga, un genre de germes zoonotiques, et comment un simple traumatisme cutané peut entraîner une infection invasive.

CASE PRESENTATION

A 56-year-old man initially presented to a peripheral hospital with a four-day history of fever, headache and arthralgias, with nausea and retching. His medical history was significant for mixed connective tissue disease with associated Raynaud’s phenomenon, which had caused several previous episodes of patchy, self-limited digital necrosis; he was never treated with immunosuppressants. He was also hypertensive and had benign prostatic hypertrophy. A few years previously, he was found to have a progressive mild thrombocytopenia (100×10^9/L) associated with mild hepatosplenomegaly; however, he was not compliant with further investigations. He regularly consumed alcohol, estimated by his wife to be six beers per day.

Soon after arrival to the hospital, the patient developed progressive obtundation requiring intubation. In the context of an altered mental status and concurrent fever, a meningitic and/or encephalitic process was suspected. A computed tomography scan of the head revealed no mass lesion or hemorrhage. Ampicillin, ceftriaxone, vancomycin and acyclovir were initiated before lumbar puncture. Dexamethasone was not administered. Cerebrospinal fluid was turbid, with 855 leukocytes/mL (97% neutrophils), 210 red blood cells/mL, elevated protein (2.7 g/dL) and low glucose (0.2 mmol/L); concurrent blood glucose was 7.04 mmol/L. No organisms were observed on Gram stain.

Because of profound neurological impairment, the patient was transferred to a tertiary care hospital. Within approximately 24 h, blood cultures from the initial hospital revealed a Gram-negative filamentous bacillus, also isolated from two sets of blood cultures at the referral centre. On careful examination, a small eschar at the base of the left index finger was noted (Figure 1). According to the patient’s wife and daughter, the recently acquired family dog had bitten the patient one week previously.

The constellation of a Gram-negative bacillary meningitis in an individual with probable cirrhosis and a dog-bite injury raised suspicion for Capnocytophaga meningitis. Other than thrombocytopenia, there was no evidence of disseminated intravascular coagulation (DIC). Antibiotics were eventually de-escalated to meropenem at a dose of 2 g every 8 h, pending speciation of the Gram-negative bacillus.

Despite significant disease revealed by magnetic resonance imaging of the brain, which demonstrated fluid levels in both ventricles with...
diffusion restriction suggestive of ventriculitis, likely due to proteinaceous necrotic debris such as pus (Figure 2), repeat lumbar puncture after three days of antibiotic treatment revealed resolving pleocytosis, protein and glucose concentrations, with no organism observed on Gram stain nor isolated in culture. Over the next few days, the patient’s mental and neurological status gradually improved, allowing extubation and eventual transfer to the original hospital, where he completed a total of three weeks of inpatient antibiotic therapy with meropenem.

Microbiological identification of the Gram-negative bacillus was hampered by its fastidious nature. Although the organism was detected using BACTEC blood culture bottles (Becton Dickinson, USA) after approximately two days, primary subculture onto solid media revealed only poor growth in anaerobically incubated blood agar plates. Subculture onto chocolate agar incubated in CO2 permitted sufficient growth for subsequent identification by the provincial reference laboratory (Laboratoire de Santé Publique du Québec, Sainte-Anne-de-Bellevue, Quebec) via 16S ribosomal RNA gene sequencing, which confirmed the isolate to be C canimorsus.

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DISCUSSION

The genus Capnocytophaga, proposed by Leadbetter et al (5) in 1979, includes capnophilic, facultatively anaerobic, non-spore-forming Gram-negative bacteria of the family Flavobacteriaceae. The genus is infamous for two species, C canimorsus (previously termed Centers for Disease Control and Prevention DF-2) and Capnocytophaga cynodegmi (DF-2-like). Their previous designation, ‘dysgonic fermenter’, referred to the phenotypic characteristics (ie, slow and relatively poorly fermenting carbohydrates); their current species designation reflects the fastidiousness of the organism and, thus, challenges regarding its isolation and identification in routine microbiology laboratories.

The number of cases of human infections due to C canimorsus was estimated to be 0.5 to 0.7 per one million inhabitants per year in large studies performed in Denmark and the Netherlands (11,12). This rate likely varies with different social, cultural and economic habits. These estimates are also skewed on the one hand by the frequent use of empirical antibiotics in the clinical management of animal bites and, on the other, by the fastidiousness of the organism and, thus, challenges regarding its isolation and identification in routine microbiology laboratories.

Historically, infections due to C canimorsus more commonly affect men (male:female ratio ranging from 2.7:1 to 3.75:1), with the mean age varying between 50 and 60 years of age (10,12-14), likely reflecting both the demographics of exposure and, importantly, the corresponding underlying risk factors. Since its first description, hyposplenism (typically from splenectomy) and alcohol-induced liver disease have emerged as significant risk factors for severe, noncellulitis C canimorsus infection (ie, septicemia, meningitis) (1,3,10,13,15,16). Although hematological malignancy and steroid use are often cited as risk factors for Capnocytophaga species infections, these predisposing conditions are, in reality, more commonly observed with invasive infections with species endogenous to humans, rather than the zoonotic ones. Of note, up to 40% of severe C canimorsus infections have occurred in subjects in whom no underlying predisposing condition is apparent (13). Although complicated septicemia (eg, with DIC, organ failure and/or shock) tends to be more often reported in individuals with hyposplenism or alcoholic liver disease, there are cases in which neither of these conditions is present. In such cases, C canimorsus septicemia may reflect a sentinel manifestation of an acquired or congenital defect in host defenses.

Overall mortality rates for severe C canimorsus infections range from 13% to 33% (11,12,17); notably, and perhaps paradoxically, meningitis portends a lower mortality rate of 5% (13).

Laboratory identification

Capnocytophaga species appear as long, slender Gram-negative bacilli with tapered ends, typically measuring 3 µm to 6 µm in length (18),...
In C. canimorsus meningitis, other than a possible bite wound on examination (as in the present case), the clinical picture and cerebrospinal fluid findings are distinguishable from bacterial meningitis caused by typical organisms. There is the suggestion that, compared with typical bacterial meningitides, some cases of C. canimorsus meningitis may demonstrate a lesser degree of pleocytosis (<1000 white blood cells/mL) along with a high percentage (≥30%) of lymphocytes (31). These cases may be confused with meningitis due to Listeria monocytogenes or, perhaps, viruses; confusion with the latter may lead to premature cessation of antibiotics, which may be disastrous. An interesting sequela of C. canimorsus meningitis appears to be permanent sensorineural hearing loss, which has even been described as a primary complaint (31-33). Whether C. canimorsus meningitis causes deafness more frequently than other causes of meningitis remains to be demonstrated. Radiological findings are rarely reported in the literature. Generally, computed tomography scanning of the head in affected patients has been denoted as being unchanged from baseline. In the present case, diffusion-weighted magnetic resonance imaging enabled us to appreciate the gravity and devastating pathogenicity of C. canimorsus. To our knowledge, there are no reports of purulent ventriculitis or cerebritis caused by this organism described to date.

C. canimorsus can also cause endocarditis. One-third of cases occur in individuals with pre-existing cardiac lesions (34). Given its fastidious nature, C. canimorsus may be difficult to isolate as the causative organism, prompting one author to suggest it be added to the list of HACEK (Haemophilus species, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens and Kingella kingae) group organisms (35). Although aortic and tricuspid valve replacements have been commonly involved in reported cases (34), there are no distinguishing clinical or echocardiographic features specific to C. canimorsus. Similar to other infectious endocarditides, C. canimorsus endocarditis may be complicated by paravalvular abscesses (36), fistula (34), mycotic aneurysms (11) and myocardial infarction (37,38). Surgical intervention was required in up to 47% of cases (34).

Pathogenesis
The pathogenetic mechanisms underlying C. canimorspha infections are not well understood but appear to segregate with the 'dysongenic fermenter' group. Infections due to DF-1 and related endogenous C. canimorspha species are primarily reported in patients following mucosal injury (eg, from mucositis and neutropenia associated with cytoreductive chemotherapy [39-41], periodontitis [42] or chorioamnionitis [43,44]). In such cases, an intact mucosal epithelium appears to be a critical factor in host defense.

Infections due to zoonotic C. canimorspha appear to occur by a different process. The classical risk factors for severe infection with C. canimorsus are hypoplasmin and liver disease/cirrhosis, typically from alcohol use (as in the present case). Hypoplasmin may confer susceptibility to C. canimorsus because of impaired antibody-mediated opsonophagocytosis; this hypothesis is supported by increased phagocytosis and killing of the bacteria, at least by murine macrophages following opsonization with specific antibody, but not with complement (45). The basis for susceptibility in cirrhotic patients may involve the unique enzyme complex of C. canimorsus that enables it to harvest amino sugars of glycan chains from host glycoproteins; in particular, this complex targets N-acetylglucosamine residues (46). In liver disease/cirrhosis, there are alterations in the glycosylation of numerous serum glycoproteins, including liver-derived proteins as well as immunoglobulins. Interestingly, as liver disease progresses, an increase in N-acetylglucosamine-containing glycoproteins is measurable (47). It is attractive to speculate, therefore, that the selective susceptibility to C. canimorsus in liver disease may reflect the unique opportunism of this species to feed on exactly those substrates that become more readily available.

Treatment
The fastidious nature of C. canimorspha species, the lack of validated susceptibility testing methods and the lack of interpretive criteria makes
standardized data on the in vitro antimicrobial susceptibility patterns of this genus difficult to collect. However, a general pattern describing *Capnocytophaga* species antimicrobial susceptibility proposed by Jolivet-Gougéon et al (17) is as follows: they are typically considered to be susceptible to penicillins, third-generation cephalosporins, carbapenems, clindamycin, doxycycline and chloramphenicol. Most isolates are also susceptible to macrolides, rifampin and fluoroquinolones. Susceptibility to vancomycin, metronidazole and aminoglycosides demonstrates significant variability among studies, likely reflecting differences in methodology. Most isolates are considered to be resistant to aminoglycosides, fosfomycin and amoxicillin.

Despite *Capnocytophaga* species being increasingly recognized to produce β-lactamase, detectable by the routine chromogenic nitrocefin test, review of the literature reveals that this resistance is observed more commonly in human endogenous *Capnocytophaga* species isolates (40,48-51) rather than zoonotic ones (34,52). Fortunately, β-lactamase-producing isolates remain susceptible to β-lactamase-resistant β-lactams or β-lactam/β-lactamase inhibitor combinations. Given the unclear correlation between in vitro antimicrobial susceptibility testing and clinical outcome, no firm recommendations can be given regarding antimicrobial selection for the various *C canimorsus* syndromes, particularly for patients demonstrating type I (immunoglobulin E-mediated) allergic reactions to β-lactams. Nonetheless, recommendations for targeted therapy of the different *Capnocytophaga* species syndromes, once the organism has been isolated, are proposed in Table 1.

For penetrating dog or cat bites, the polymicrobial nature of the wound necessitates proper wound management, including copious irrigation of the wound and application of an appropriate duration of antimicrobial therapy. For patients with β-lactam allergy, desensitization may have to be treated to prevent one infection (48).

TABLE 1

<table>
<thead>
<tr>
<th>Infection</th>
<th>Recommended first-line therapy</th>
<th>Alternative therapies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog/cat bite-related injury</td>
<td>Amoxicillin/clavulanic acid,</td>
<td>For patients with non-type I (immunoglobulin E-mediated) penicillin allergies, consider second- or third-generation cephalosporin + anti-anaerobic agent (metronidazole or clindamycin)</td>
<td>Dog bites include crush, lacerating and puncture wounds. Only 15% to 20% of dog bite wounds become infected. Crush injuries, puncture wounds and hand wounds are more likely to become infected than scratches. Licks of pre-existing wounds may also become infected. Although antibiotics reduce the incidence of infection, 14 patients may have to be treated to prevent one infection (48). Note that dog and cat bite-related infections are polymicrobial. Treatment should be directed toward canine/feline oral anaerobes/facultative anaerobes (eg, <em>Pasteurella</em>, <em>Capnocytophaga</em>), <em>Staphylococcus aureus</em>, <em>Streptococcus</em> species. Proper management includes (mnemonic: WATeR): • Wound care (eg, thorough cleansing; surgical intervention as clinically indicated); • Consideration of Antibiotics, especially if: <em>hyposplenism; alcoholic liver disease; systemic corticosteroid; diabetes mellitus</em>; • Tetanus prophylaxis; • Rabies prophylaxis</td>
</tr>
<tr>
<td>Brain abscess/meningitis</td>
<td>If no β-lactamase is detected, consider penicillins (high dose)</td>
<td>No clinical reports in the literature to guide alternative treatment options</td>
<td>Treatment duration: 14 to 21 days</td>
</tr>
<tr>
<td>Bacteremia, including endocarditis</td>
<td>If β-lactamase-producing isolate, consider third-generation cephalosporin or carbapenem</td>
<td>For patients with β-lactam allergy, consider desensitization</td>
<td>Rare (&lt;20 cases), with no distinguishing features on patient history, physical examination or echocardiography</td>
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<tr>
<td>Postsplenectomy β-lactam/β-lactamase inhibitor or carbapenem</td>
<td>Respiratory fluoroquinolone + vancomycin</td>
<td>For patients with β-lactam allergy, consider desensitization, or perhaps the use of one or more of the following agents (note: these are bacteriostatic): • Clindamycin • Linezolid • Tetracycline • Chloramphenicol • Fluoroquinolone • Rifampin</td>
<td>As with other endocarditides, monitor for need for surgical intervention</td>
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<td></td>
<td></td>
<td>Organisms that typically cause postsplenectomy sepsis: <em>Streptococcus pneumoniae</em>, <em>Neisseria meningitidis</em> and <em>Haemophilus influenzae</em>; therefore, empirical antimicrobial therapy should include coverage of these organisms</td>
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</table>

As with other endocarditides, monitor for need for surgical intervention. Wound care (eg, thorough cleansing; surgical intervention as clinically indicated). Rare (<20 cases), with no distinguishing features on patient history, physical examination or echocardiography. Because of its fastidious nature, may be a cause of 'culture-negative' endocarditis.

**Comments**

Patient history, physical examination or echocardiography. Valve involvement: aortic > tricuspid > mitral (29). Because of its fastidious nature, may be a cause of 'culture-negative' endocarditis.

**Postsplenectomy β-lactam/β-lactamase inhibitor or carbapenem**

**Recommended first-line therapy**

- Amoxicillin/clavulanic acid, 875 mg/125 mg orally twice per day or 500 mg/125 mg orally three times per day (10).
- for 3–5 days if no evidence of infection (prophylactic approach; see comment)
- for 10 to 14 days if signs of skin or soft tissue infection

Although many cases may be managed as outpatients, consider hospitalization if skin or soft tissue infection:

- is severe;
- has progressed beyond one joint;
- is rapidly spreading;
- has not responded to oral or outpatient therapy;
- involves a bone, joint, tendon or nerve

**Alternative therapies**

For patients with type I (immunoglobulin E-mediated) penicillin allergy, consider either doxycycline 100 mg orally twice per day or fluoroquinolone + anti-anaerobic agent (metronidazole or clindamycin)

**Comments**

Dog bites include crush, lacerating and puncture wounds. Only 15% to 20% of dog bite wounds become infected. Crush injuries, puncture wounds and hand wounds are more likely to become infected than scratches. Licks of pre-existing wounds may also become infected. Although antibiotics reduce the incidence of infection, 14 patients may have to be treated to prevent one infection (48). Note that dog and cat bite-related infections are polymicrobial. Treatment should be directed toward canine/feline oral anaerobes/facultative anaerobes (eg, *Pasteurella*, *Capnocytophaga*), *Staphylococcus aureus*, *Streptococcus* species. Proper management includes (mnemonic: WATeR): • Wound care (eg, thorough cleansing; surgical intervention as clinically indicated); • Consideration of Antibiotics, especially if: *hyposplenism; alcoholic liver disease; systemic corticosteroid; diabetes mellitus*; • Tetanus prophylaxis; • Rabies prophylaxis. Treatment duration: 14 to 21 days.
For the different Capnocytophaga species synergists, targeted therapy ultimately depends on whether they also produce β-lactamase. For isolates that do not, penicillins and amoxicillin-clavulanate are appropriate. For those that produce a β-lactamase, therapeutic options include a β-lactam/β-lactamase inhibitor combination, a β-lactamase-resistant β-lactam or a carbapenem. Clindamycin, a respiratory fluoroquinolone or doxycycline may be appropriate alternatives, although reports of clinical efficacy in the literature are scant. Combination therapy may be theoretically advantageous, but again, the absolute benefit has not been investigated.

The duration of antimicrobial therapy for treatment of Capnocytophaga species infections is hampered by the absence of randomized studies. As such, extrapolations from other similar infections provide the basis for clinical management. For C. canimorsus meningitis, the recommended length of treatment varies between 14 and 21 days or longer, as for other Gram-negative meningitis infections (13). For endocarditis, the duration of treatment is at least four to six weeks, with monitoring need for surgical intervention, while at least six to eight weeks may be required for bone/joint involvement.

CONCLUSION

C. canimorsus can cause a variety of syndromes. Hyposplenism and alcoholic liver disease are the main risk factors for severe infection; these conditions should raise suspicion for this organism. Its fastidious nature may delay or prevent isolation and appropriate speciation. Antimicrobial susceptibility testing is not standardized. However, clues to its presence should be sought by thorough review of history and physical examination. With appropriate, duly initiated therapy, C. canimorsus meningitis, a potentially fatal infection, has a relatively favourable prognosis compared with other more common bacterial meningitides.

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REFERENCES


