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Capnocytophaga - a dangerous infection in humans associated with canines

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Many kinds of bacteria are found in the mouths of dogs and cats. One common group of bacteria are called *Capnocytophaga*. These bacteria sometimes cause opportunistic infections, which means under the right conditions they can cause an infection, such as in a person with a weakened immune system. Most people who have contact with a dog or cat do not become sick. People with weakened immune systems who have difficulty fighting off infections are at greater risk of becoming sick if they're bitten. *Capnocytophaga* germs can make people sick if they're bitten or the dog or cat's saliva (spit) gets into an open wound or sore. *Capnocytophaga* infection can cause serious complications, including sepsis, heart attack, kidney failure, and gangrene. Some people may need to have fingers, toes, or limbs amputated.

Capnocytophaga spp. are fusiform Gram-negative bacilli. Normally found in the oropharyngeal tract of mammals and canines, they are involved in the pathogenesis of some animal bite wounds and periodontal diseases (Jolivet Gougeon *et. al.,* 2007). Microscopic observation revealed a high degree of polymorphism with a variation in the size and appearance depending on the strain and culture conditions. This polymorphism is also reflected in the observation of colonies (orange-pigmented colonies, spreading on agar, etc.). *Capnocytophaga spp.* are capnophilic bacteria; they can live only in environments where the concentration of carbon dioxide is greater than that of the atmosphere (at least 5% CO_2). They can also grow anaerobically. They require enriched media, type blood agar, incubated at 37 °C. The isolation of strains of *Capnocytophaga* from polymicrobial samples is also possible on selective media containing antibiotics (Ehrmann *et. al.,* 2013).

The name *Capnocytophaga* is derived from the Greek word *kapnos*, meaning "smoke", and given here because of its dependence on carbon dioxide for growth. It was added to distinguish this genus from the Cytophaga genus, originating from the Greek words of *kytos* (meaning "cell"), and *phagein* (meaning "eat"). The species name of *canimorsus* comes from the Latin words *canis* and *morsus*, meaning "dog" and "bite" respectively (Henry & Ronnie, 2018). It belongs to the family Flavobacteriaceae, order Flavobacteriales. This genus includes eight different species: *C. ochracea*, *C. gingivalis*, *C. granulosa*, *C. haemolytica*, *C. sputigena*, *C. leadbetteri* (isolated oral cavity of humans), *C. canimorsus*, and *C. cynodegmi* (isolated from the oral cavity of animals). Many strains have also been described whose classification remains uncertain.

There are nine species of *Capnocytophaga*, which can be classified into two main categories:

Human-oral associated, seen more commonly in immunocompromised patients: *C. gingivalis*, *C. granulosa*, *C. haemolytica*, *C. leadbetteri*, *C. ochracea*, and *C. Sputigena.* Most reported human-oral associated *Capnocytophaga* infections cause:

- Periodontal infections
- Respiratory tract infections
- Ocular infections

Zoonosis associated, seen more commonly in asplenic patients or those with immunocompromising conditions: *C. canimorsus*, *C. canis*, and *C. cynodegmi.* Symptoms from zoonosis

associated *Capnocytophaga* infections typically begin about 3 to 5 days after a dog or cat bite.

Capnocytophaga canimorsus was first observed in 1976 by Bobo and Newton. The pair isolated a previously unknown Gram-negative bacterium from a patient presenting with meningitis in addition to sepsis. *C. canimorsus* is a fastidious, Gram-negative, fermentative, encapsulated, nonspore-forming rod. (Renzi Francesco *et. al.,* 2016). Bacilli are usually 1-3 µm in length. After growth on agar plates, longer rods tend to have a curved shape. The bacteria do not have flagella, but move with a gliding motion, although this can be difficult to see. *C. canimorsus* requires the right medium for growth. The bacterium grows well on blood agar plates (heart infusion agar with 5% sheep or rabbit blood) and chocolate agar plates (Pers *et. al.,* 1996). Colonies may not be visible for up to 48 hours due to slow growth. At 18 hours, colonies are usually less than 0.5 mm in diameter, and are spotty and convex. At 24 hours, colonies may be up to 1 mm in diameter. After 48 hours, colonies are narrow, flat, and smooth, with spreading edges. At this time, colonies may appear to be purple, pink, or yellow, but once they are scraped from the agar plate, they are always yellow in appearance. (Brenner *et. al.,* 1989)

Pathogenicity:

Who's at risk: Most dog or cat bites do not lead to a *Capnocytophaga* infection or any illness. But you should take precautions if you have contact with animals, especially if you have a condition that puts you at higher risk of infection. These conditions include:

- Having a weakened immune system (immunocompromise) from conditions like cancer, diabetes, or HIV, among others
- Taking certain medicines that weaken your immune system, such as chemotherapy
- Not having a spleen (asplenic) / Splenectomies
- Alcohol use disorders
- Liver cirrhosis

Most Capnocytophaga infections occur in adults over 40 years of age. Asplenic patients have a 30 to 60 times greater risk of death from Capnocytophaga infections. These patients can advance to organ failure and death within 24 to 72 hours of onset.

In all *Capnocytophaga* infections the bacteria can enter the blood stream, which can lead to infection in various parts of the body (sepsis). Infection can also cause the following:

- Inflammation of the lining of the heart (endocarditis)
- Collections of pus, redness, and swelling in various body tissues (abscesses)
- Inflammation of the eyes, face, lymph nodes, or brain membranes (meningitis)

The disease can progress rapidly from mild, localized infection to systemic infection, sepsis, and death. Mortality is usually due to complications from shock, disseminated intravascular coagulation (DIC), and organ failure. *Capnocytophaga*-associated morbidity can include sepsis, myocardial infarction, renal failure, and amputation due to DIC.

Disease rates

Capnocytophaga infections are not nationally notifiable, and therefore there is no national estimate of incidence. Cases are rarely reported in the literature.

Signs and symptoms:

Signs and symptoms of a *Capnocytophaga* infection include:

- Blisters at the bite or scratch wound
- Redness, swelling, draining pus, or pain at the wound
- Fever
- Diarrhea and/or stomach pain
- Vomiting
- Headache and/or confusion

Diagnosis:

The identification is carried out through various biochemical tests, used for the identification of Gram-negative bacterial species, and rapid determination of enzymatic reactions. The diagnosis is delayed because of the slow and difficult growth of Capnocytophaga (48 to 72 hours). The molecular techniques (16S rDNA PCR and sequencing), and mass spectrometry appear as attractive methods for reliable identification to the genus. The identification at the species level remains difficult when a single method is used.

Capnocytophaga species are slow-growing, Gram-negative bacteria that are difficult to grow in a laboratory setting. Blood samples are usually used to identify the bacteria in culture, but identification can be difficult. In a California study, only approximately

1/3 of *Capnocytophaga* samples were correctly identified by the state public health laboratories that submitted them. Automated blood culture systems may not identify *Capnocytophaga* growth because of its slow-growing nature. Some other bacteria species are very similar to *Capnocytophaga*, and biochemical analysis used to identify bacteria species may not be able to tell the difference.

Other more reliable methods for identifying *Capnocytophaga* include:

- PCR
- 16S rRNA gene amplification
- Matrix Assisted Laser Desorption/Ionization Time of Flight (MALDI TOF) mass spectrometry

Prevention:

Preventing *Capnocytophaga* infection starts with preventing bites from dogs and cats, especially if you have a condition that puts you at higher risk of getting sick.

Treatment:

If you do get *Capnocytophaga* from a bite, your doctor can prescribe specific kinds of antibiotics to help you recover. You may need to take more than one type of antibiotic to find the one that works best.

Patient management

Capnocytophaga is typically sensitive to routinely used antibiotics. Healthcare providers can determine the most appropriate course of treatment based on patient's history and clinical presentation. Patients with severe *Capnocytophaga* infection should be treated initially with a beta-lactam-beta-lactamase combination (such as piperacillin-tazobactam) or a carbapenem (such as imipenem), pending susceptibility testing. If antibiotic susceptibilities are performed, the regimen can be adjusted accordingly. Patients with non-severe infection may be treated with oral therapy such as amoxicillin-clavulanate or clindamycin.

Resistance to antibiotics

Capnocytophaga spp. are usually susceptible to antibiotics, but the emergence of beta-lactam-resistant strains has been observed as early as 1980. Genes for antibiotic resistance have gradually spread among other pathogenic bacterial species by horizontal gene transfer. Susceptibility to various beta-lactam antibiotics has been described as variable depending on the strain of *Capnocytophaga*. This resistance is often linked to the production of beta- lactamases. Most beta-lactamases identified in *Bacteroides*, *Prevotella*, and *Capnocytophaga* belong to the Ambler class A. Several beta-lactamases encoded by the chromosome or a plasmid and associated with mobile genetic elements have been described in *Capnocytophaga* spp. The most common are: *CfxA, CfxA2, CepA, CblA*, and/or *CSP-1*. (Jolivet-Gougeon *et al.,* 2004).

The *CfxA* group of beta-lactamases: *Capnocytophaga* spp. can be resistant to third-generation cephalosporins, but remain susceptible to imipenem, cefoxitin, and amoxicillin combined with clavulanic acid. Although resistant strains are most frequently isolated in oral cavities, their prevalence is worrying (Jolivet-Gougeon *et al.,* 2008; Sixou *et al.,* 2006).

The CSP-1 beta- lactamase: In 2005, Handal *et al.* (2005) identified a novel Ambler class A beta-lactamase called CSP-1 from a NOR *C. sputigena* strain, resistant to amoxicillin and first and second generation cephalosporins.

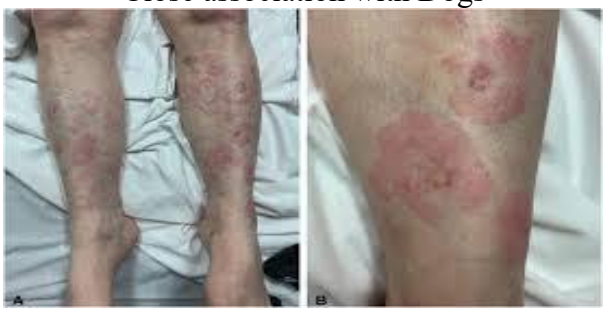
The beta- lactamases CepA/CblA: CepA (Chromosomal cephalosporinase from *Bacteroides fragilis* belonging to Ambler class A) is an endogenous cephalosporinase A described in *Bacteroides fragilis*. This beta- lactamase is ubiquitous, but frequently inactive. CepA is encoded by the cepA gene, most frequently vertically transferred. CblA (Chromosomal beta-lactamase from *Bacteroides uniformis* belonging to Ambler class A) is a specific endogenous cephalosporinase described in B. uniformis, susceptible to clavulanic acid. The homology is 43% between protein sequences CepA and CblA and 51% between nucleotide sequences. A comparison with protein sequence alignment by cepA with other beta-lactamases reveals the conservation of at least four common elements of Ambler class A (Jolivet-Gougeon *et. al.,* 2004).

Other acquired resistance: According to studies, different sensitivities were reported for macrolides, rifampin, quinolones, metronidazole, vancomycin, and aminoglycosides, but the mechanism involved is not precisely described (Ma A, Goetz MB, 2013).

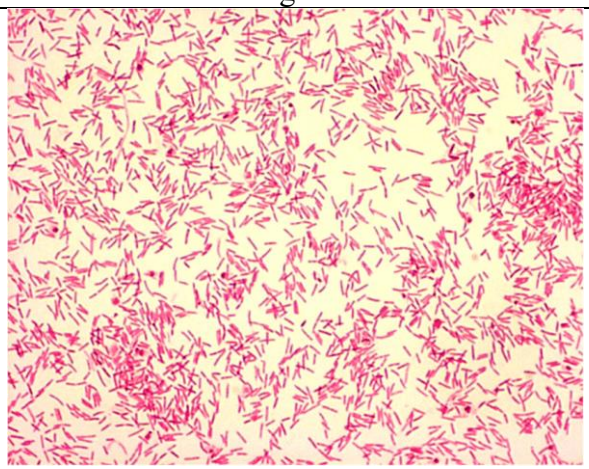
Close association with Dogs

Close association with Dogs

Dog bite

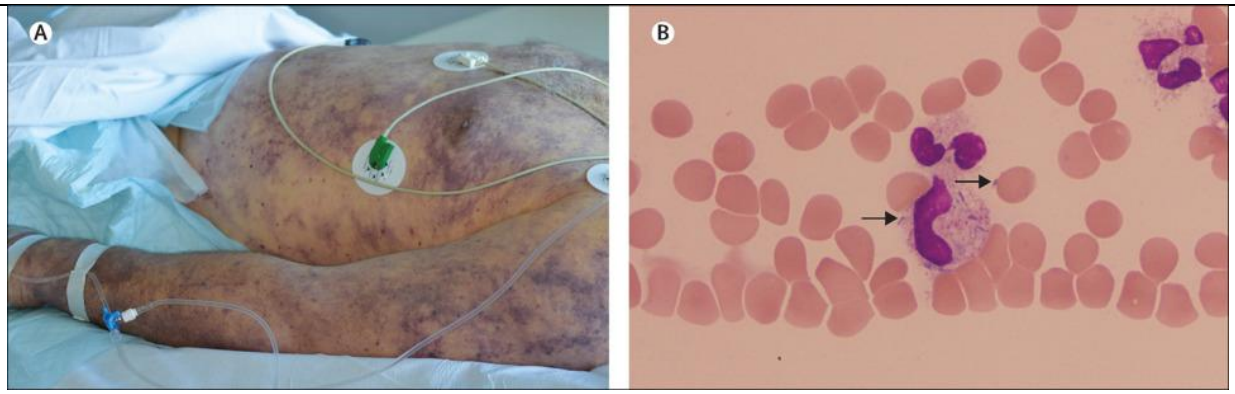


Numerous well-circumscribed, erythematous, arcuate plaques on the bilateral lower extremities (A) demonstrating central clearing with petechiae and purpura in *Capnocytophaga.*

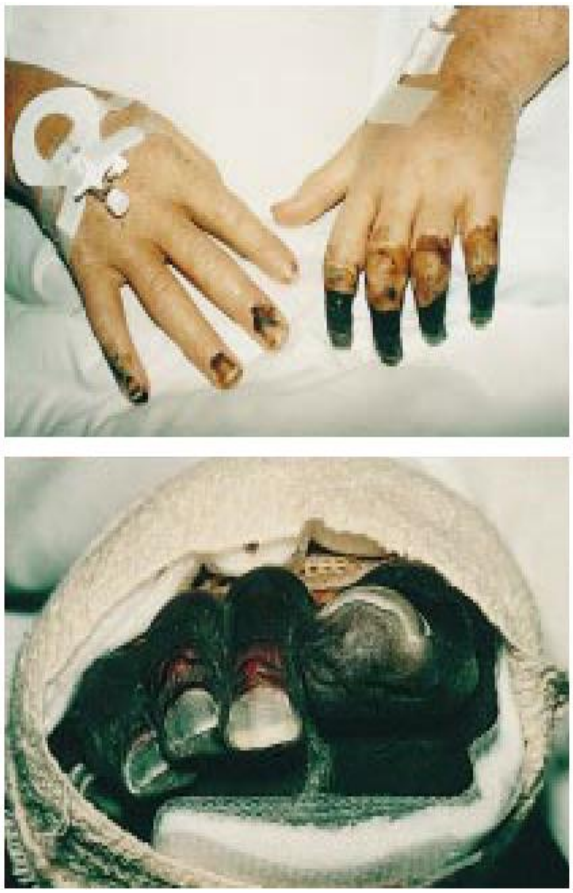


Capnocytophaga canimorsus Gram stain image. Gram negative rods, fusiform cells generally 1–3 µm in length.

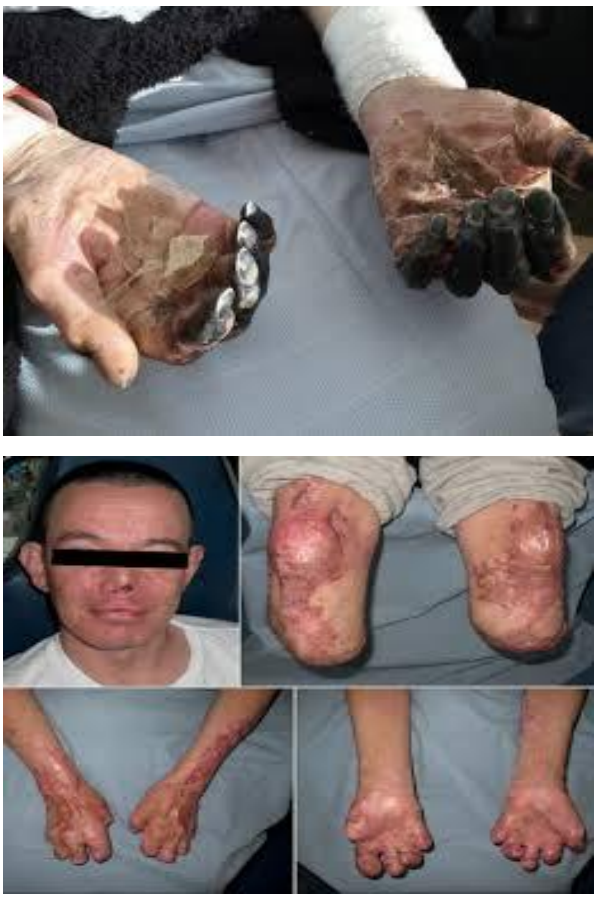
Capnocytophaga colonies on blood agar showing gliding motility



Fatal septicemic infection caused by *Capnocytophaga canimorsus*



Peripheral ischaemic gangrene secondary to *capnocytophaga*



Capnocytophaga bacteria, and hands & feet amputation in extreme conditions especially in asplenic persons

References:

Brenner, D J; Hollis, D G; Fanning, G R; Weaver, R E (1989). "Capnocytophaga canimorsus sp. nov. (formerly CDC group DF-2), a cause of septicemia following dog bite, and C. cynodegmi sp. nov., a cause of localized wound infection following dog bite". Journal of Clinical Microbiology. **27** (2): 231–235.

Ehrmann E, Jolivet-Gougeon A, Bonnaure-Mallet M, Fosse T (2013). "Antibiotic content of selective culture media for isolation of Capnocytophaga species from oral polymicrobial samples". Letters in Applied Microbiology. **57** (4): 303–

9. doi:10.1111/lam.12112. PMID 23725093. S2CID 206168867.

Handal T, Olsen I, Walker CB, Caugant DA (2005). "Detection and characterization of beta-lactamase genes in subgingival bacteria from patients with refractory periodontitis". FEMS Microbiology Letters. 242 (2): 319-24. doi:10.1016/j.femsle.2004.11.023. PMID 15621454.

Henry, Ronnie (2018). "Etymologia: Capnocytophaga canimorsus". Emerging Infectious Diseases. **24** (12): 2201. doi:10.3201/eid2412.ET2412. ISSN 1080-6040. PMC 6256413.

Jolivet-Gougeon A, Guérin J, Tamanai-Shacoori Z, Gandemer V, Sixou JL, Bonnaure-Mallet M (2008). "Influence of previous antimicrobial therapy on oral carriage of beta-lactamase producing Capnocytophaga isolates". Acta Paediatrica. 97 (7). Oslo, Norway: 964–7. doi:10.1111/j.1651-2227.2008.00824.x. PMID 18532936. S2CID 12600819.

Jolivet-Gougeon A, Sixou JL, Tamanai-Shacoori Z, Bonnaure-Mallet M (2007). "Antimicrobial treatment of Capnocytophaga infections". International Journal of Antimicrobial Agents. **29** (4): 367-73. doi:10.1016/j.ijantimicag.2006.10.005. PMID 17250994.

Jolivet-Gougeon A, Tamanai-Shacoori Z, Desbordes L, Burggraeve N, Cormier M, Bonnaure-Mallet M (2004). "Genetic analysis of an ambler class A extended-spectrum beta-lactamase from Capnocytophaga ochracea". Journal of Clinical Microbiology. 42 (2): 888–90. doi:10.1128/jcm.42.2.888-890.2004. PMC 344468. PMID 14766881.

Ma A, Goetz MB (2013). "Capnocytophaga canimorsus sepsis with associated thrombotic thrombocytopenic purpura". The American Journal of the Medical Sciences. 345 (1): 78–80. doi:10.1097/MAJ.0b013e318262db1a. PMID 22990045.

Pers, C.; Gahrn-Hansen, B.; Frederiksen, W. (1996). "Capnocytophaga canimorsus Septicemia in Denmark, 1982-1995: Review of 39 Cases". Clinical Infectious Diseases. **23** (1): 71–75.

Renzi, Francesco; Ittig, Simon J.; Sadovskaya, Irina; Hess, Estelle; Lauber, Frederic; Dol, Melanie; Shin, Hwain; Mally, Manuela; Fiechter, Chantal; Sauder, Ursula; Chami, Mohamed; Cornelis, Guy R. (2016). "Evidence for a LOS and a capsular polysaccharide in Capnocytophaga canimorsus". Scientifi cReports. **6** 38914. Bibcode:2016NatSR...638914R. doi:10.1038/srep38914. PMC 5156936. PMID 27974829.

Sixou JL, Aubry-Leuliette A, De Medeiros-Battista O, Lejeune S, Jolivet-Gougeon A, Solhi-Pinsard H, Gandemer V, Barbosa-Rogier M, Bonnaure-Mallet M (2006). "Capnocytophaga in the dental plaque of immunocompromised children with cancer". International Journal of Paediatric Dentistry. 16 (2): 75–80. doi:10.1111/j.1365-263X.2006.00697.x. PMID 16430520.