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Capnocytophaga canimorsus

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Abstract

Capnocytophaga canimorsus is a commensal bacterium in the oral flora of dogs and cats. The bacterium is a zoonotic agent and has been isolated from humans, infected by dog or cat bites, scratches, licks or simply exposure to dogs or cats. Here the infectious agent, its pathogenicity and potential virulence factors, infection in animals and humans, diagnostic methods, prevalence, therapy and prevention are described. Suggestions for future research are given.

Keywords: *Capnocytophaga canimorsus*, zoonosis, sepsis, virulence, risk factors, therapy.

Introduction

Worldwide millions of people are bitten by animals each year. It is estimated that 50% of all Americans will be bitten at least once in their lifetime. Ninety percent of these bites are caused by dogs and cats. The majority of dog and cat bite wounds is minor and no medical attention is sought by the victim. Occasionally a dog or cat bite is complicated and an overwhelming systemic infection occurs. In the USA the annual mortality rate due to dog and cat bites is 6.7 per 10^8 persons, albeit that not all these fatalities are caused by infections (Griego et al., 1995).

The genus *Capnocytophaga* consists of seven species which inhabit the oral cavity of humans or domestic animals. *Capnocytophaga gingivalis, Capnocytophaga ochracea, Capnocytophaga sputigena, Capnocytophaga granulosa and Capnocytophaga haemolytica* are inhabitants of the human oral cavity and have been associated with peridontitis. *Capnocytophaga cynodegmi* and *Capnocytophaga canimorsus* (latin canis = dog and latin morsus = bite) are part of the oral microbiota of canines and more rarely of cats. Eight percent of 50 dogs tested positive for *C. canimorsus* in the first report on the prevalence of *C. canimorsus* (Bailie et al., 1978). In a later report *C. canimorsus* could be cultured from 26% of the dogs tested and from 18% of the tested cats. The agent could not be cultured from hamsters and humans (Blanche et al., 1998). In our laboratory, a PCR test with primers for the 16S rRNA gene of *C. canimorsus* was positive for 41% of the dogs (de Poel et al.,unpublished results). An even higher percentage was observed with a similar PCR by van Dam et al (manuscript submitted for publication). In a single report, the isolation of *C. canimorsus* (DF-2) from sheep and

cattle (25-30% of the animals tested) but not from pigs was reported (Westwell et al., 1989). To our knowledge no attempt to confirm this observation has ever been made. *C. canimorsus* can cause zoonotic infections ranging from very mild flu like symptoms to fatal sepsis (de Boer et al., 2007, Pers et al., 1996). *C. canimorsus* infections are associated with dog and cat bites (54% of cases), dog and cat scratches (8.5% of cases) or close animal contact (27% of cases), such as licking of human wounds (Lion et al., 1996:). Consequently human to human transmission of *C. canimorsus* has not been reported apart from one case where it could not be excluded 100% (Risi and Sprangler 2006). Studies on *C. canimorsus* and *C. cynodegmi* infections have mainly been initiated from an interest in human medicine for rapid diagnosis and antibiotic treatment, prompted by the often dramatic outcome of an infection with *C. canimorsus.* Since its first description in 1976 approximately 200 human cases of *C. canimorsus* infection have been reported worldwide (Macrea et al., 2008). Surprisingly little research on this zoonotic agent has been performed from a veterinary background. Regarding the millennia old bond between men and dog, this infection is probably not new, but only now it can be recognized due to the advances in modern medicine over the last four decades.

The Infectious Agent

Historical perspective

In 1976 a patient with meningitis and sepsis, caused by an unidentified Gram-negative bacillus, after a recent dog bite was first described (Bobo and Newton, 1976). At that time, the phenotypic as well as the biochemical characteristics of the agent also became known. We now know that this Gram-negative bacillus probably was a member of the *Capnocytophaga* family, very likely *C. canimorsus*-(CDC group DF-2 or dysgonic fermentor 2, dysgonic = slow and relatively poor growth of a bacterial culture). One year later, 17 cases of infection after recent dog bites , the majority caused by an unidentified Gram-negative rod were described (Butler et al., 1977). The nature of the infection varied from cellulitis to meningitis , endocarditis to organ failure and fatal sepsis. The organism was given its current name in 1989, based on its CO_2 requirement and usual mode of transmission (Brenner et al., 1989). Since then, *C. canimorsus* infections were found to occur worldwide and have been reported from the United States, Canada, Europe, Australia and South Africa.

Phenotypic and Genotypic Characteristics

Capnocytophaga canimorsus are capnophilic (greek:carbon dioxide loving) facultative anaerobic, fastidious Gram-negative rods (1-4µm long, Fig.1). They are fusiform or filamentous gliding bacteria and closely related to *Fusobacterium* and *Bacteroides* species (Andersen and Pedersen, 1992, Deshmukh et al., 2004). However, the gliding motility is not always apparent. The G+C content of *C. canimorsus* DNA is 35% (Speck et al., 1987; Brenner et al., 1989).

Cultural properties

Classically, the organism was regarded difficult to culture because of its specific requirements for nutrients and thus may have easily escaped detection. *C. canimorsus* has been shown to require large amounts of exogenous iron for growth (Brenner et al., 1989). It grows slowly on blood (5% sheep blood in Columbia agar) or chocolate agar in 10% CO_2 (Ciantar et al., 2001). Media had to be incubated at 37˚C for at least 5 days. Colonies could be not visible for 2-7 days, on blood agar. Initially they are pin point in size and later become larger, convex and smooth. Colonies are non hemolytic with the characteristic shiny spreading edge and finger-like projections of bacteria with gliding motility (Andersen and Pedersen, 1992, Desmukh et al., 2004). Although the color of colonies may vary from pink to yellow, the colonial mass of all isolates is yellow when scraped from the agar plate (Forlenza, 1991). Horse blood agar plates were found to be superior to sheep blood but do not seem to be used often (Westwell et al., 1989; Pers et al., 1996). The organism does not grow on MacConkey agar. Recently, the growth medium was optimized (Heart Infusion agar Difco with 5% sheep blood) and the bacteria were shown to grow in 2 days at 37˚C in 5 % CO_2 (Shin et al., 2007, Mally et al., 2008). To our knowledge, these growth conditions have only been used under experimental conditions and not yet in a clinical setting. It is to be expected that faster growth of *C. canimorsus* will be reflected in the speed with which diagnostics can be performed and therefore lead to less fatalities due to this organism.

Biochemical Characteristics

Biochemical tests are difficult to perform due to the slow growth of the organism. It is catalase, oxidase, ONPG (*O*-nitrophenyl-β-D-galactoside) and arginine dihydrolase positive and negative for urease, nitrate, indole, DNase, gelatin, lysine and ornithine (Hicklin et al., 1987; Brenner et al., 1989). Members of the genus *Capnocytophaga* can use various carbohydrates like glucose, dextran, glycogen, inulin or starch as fermentable substrates and energy source. For a comparison of the biochemical characteristics of *C. ochracea, sputigena*, *gingivalis, canimorsus* and *cynodegmi* see Forlenza (1991). Gas-liquid chromatography of cellular fatty acids provides an additional rapid test for differentiation of Gram-negative bacteria associated with dog-bite infections, including *C. canimorsus* (Dees et al., 1981).

Pathogenicity and Virulence Factors

Little is known about the pathogenesis of *C. canimorsus* infection. The bacterium was reported to multiply in mouse macrophages and to be cytotoxic probably because it produces a toxin (Fisher et al., 1995). In vitro, a very low level of cytokine production i.e. in comparison to *N. meningitidis* was observed (Frieling, et al., 1997). Cytotoxicity could not be demonstrated by Shin et al., (2007) in ten strains of *C. canimorsus* tested, including the same strain as in the original study. These strains also did not affect the viability of macrophages from different origin (mouse and human). The clinical course of *C. canimorsus* infection strongly indicates that the organism is able to avoid the immune system (at least in the early stages of infection). The absence of a proinflammatory response is due to the fact that *C. canimorsus* does not interact with human Toll-like receptor 4 (TLR4). The effector for TLR4 is the lipid A moiety of LPS, which indicates that lipid A of *C. canimorsus* is different from that of other pathogens. *Capnocytophaga canimorsus* is able to down regulate TLR4 and the proinflammatory signaling cascade (Shin et al., 2007). Not only is *C. canimorsus* resistant against phagocytosis and killing, it also blocks the killing of unrelated bacteria by macrophages (Meyer et al., 2008). Despite being classified as a fastidious grower, *C. canimorsus* exhibits robust growth when it is in direct contact with mammalian cells, including phagocytes (Mally et al., 2008). This is dependent on a surface located sialidase, which allows the bacterium to use internal amino-sugars from glycan chains of host cell glycoproteins (Mally et al., 2008). The

molecular biology of *C. canimorsus* is still in its infancy, but promising genetic tools for this bacterium have recently been developed using a naturally occurring plasmid found in one of eight strains tested (Mally and Cornelis, 2008).

Infection in Animals

The clinical syndrome in rabbits after experimental infection with *C. canimorsus* was characterized by disseminated intravascular coagulation, cellular necrosis in organs like kidneys and adrenal glands, cutaneous gangrene, thrombocytopenia, hypotension, hemorrhagic diathesis with purpuric lesions and petachiae and renal failure and is similar to that observed in man (Piccininno et al., 1984).

Only two reports have appeared in species other than humans that suffered from a dog inflicted *C. canimorsus* infection. In one case the bacterium was cultured from an infected, bite wound in a pet rabbit (van Duijkeren et al., 2006) (Fig.2). In the other *C. canimorsus* was isolated from an infected bite wound in a dog (Meyers et al., 2008).The dog did not have bacteremia, but *C. canimorsus* could still be isolated from the wound two days after the primary isolation (J. Picard, personal communication). Curiously both bite wounds were on the head. No *C. canimorsus* infections of cats after a bite incidence have been reported, but there is a case report of a cat with chronic sinusitis and rhinitis due to a *Capnocytophaga* infection. The organism was identified by a 97% identity with *C. canimorsus* of its 16S rDNA sequence (Frey et al., 2003). The incidence of bite wounds inflicted in dogs and cats by dogs or cats is not well known. It is estimated that they comprise between 10-15% of all trauma related emergencies (Kolata et al., 1974). Like with human bite wounds many wounds are not reported and owners do not seek veterinary attention. In the mobile, elastic skin of dogs and cats, bite injuries may be less noticeable or may migrate through deeper tissues and escape detection. Dogs and cats may also be less prone to *C. canimorsus* infection, which might explain the very low number of reported *C. canimorsus* infection in animals.

Human Infections and Clinical Symptoms

157 The incubation period from the dog bite to the onset of systemic symptoms is about 5 days. On
158 average seven days pass between the time of the bite and hospitalization (range 1-14 days) (LeMoal et
159 al., 2003). Patients who arrive at the emergency room within 8-12 hour after a dog bite may show
160 local lesions without significant signs of inflammation. At later stages, the infection may have
161 symptoms as: localized cellulitis, pain at the site of injury, a purulent discharge, lymphangitis and
162 regional lymphadenopathy. The initial symptoms of septicemia are fever (78% of patients), chills
163 (46%), myalgia (31%), vomiting (31%), diarrhea (26%), abdominal pain (26%), malaise (26%),
164 dyspnea (23%), mental confusion (23%) and headache (18%) (Pers et al., 1996). A fulminant and
165 severe course of the infection may occur in immuno-compromised persons, characterized by sepsis,
166 meningitis, osteomylitis, peritonitis, endocarditis, pneumonia, purulent arthritis, disseminated
167 intravascular coagulation (DIC) and fulminant purpura but has also been observed in previously
168 healthy persons (Hantson et al., 1991). DIC can lead to peripheral gangrene of the upper and lower
169 extremities, lips nose and ears (often resulting in amputation). Purpura is a group of blood disorders
170 that cause bleeding in the tissue from the small blood vessels, shock and multi organ failure. They are
171 often under or in the skin as tiny pinpoint petechiae (point-shaped skin bleedings or larger blue spots
172 (ecchymosis). Hemolytic uremic syndrome and Waterhouse-Friderichsen syndrome have also been
173 reported (Tobé et al., 1999; Mirza et al., 2000; Mulder et al., 2001; Macrea, et al., 2008). *C.*
174 *canimorsus* septicemia has been associated with up to 30% mortality (Lion et al., 1996) and significant
175 morbidity, including amputation secondary to gangrene, myocardial infarction and renal failure.
176 Curiously, Lion et al. (1996) report 22% mortality in asplenic individuals, 28% in individuals with
177 other predisposing conditions (alcohol abuse, immunosuppression) and 32% in individuals with no
178 risk factor. The mortality rate from *C. canimorsus* meningitis is low (5%) compared to that from *C.*
179 *canimorsus* septicemia (LeMoal et al., 2003; Janda et al., 2006). In a review of 12 cases of *C.*
180 *canimorsus* endocarditis a mortality rate of 25% was noted (Sandoe, 2004). A fatal outcome of the
181 infection in non-immunocompromised individuals occurs with lower frequency than in
182 immunocompromised persons. Four of these cases were reported until 1991 and several others
183 between 1991 and 2008 (Hicklin et al., 1987, Hantson et al., 1991, Deshmukh et al.,2004). Ocular

184 infections associated with cat scratches or cat bites have been reported several times (Glasser, 1986,
185 Zimmer-Galler et al., 1996, Papadaki et al., 2008).
186
187 **Risk groups**
188 At special risk are animal keepers, veterinarians, breeders and pet owners. A survey of
189 veterinarians in the US showed that 65% sustained a major animal related injury of which animal bites
190 and scratches accounted for 38% of the traumas. Dogs and cats were involved in 24% and 10% of the
191 injuries. In their entire careers, 92% of the veterinarians was bitten by a dog, 81% by a cat and 72%
192 was scratched by a cat (Landercasper et al., 1988). Yet only few reports of persons in this risk group
193 infected with *C. canimorsus* are available: an employee in an animal shelter (Deshmukh et al., 2004), a
194 pet shop worker (Hantson et al., 1991), three veterinarians (Job et al., 1988; de Smet et al., 1990;
195 Chodosh, 2001), a kennel operator (Tison and Latimer, 1986.) and a veterinary worker (Bobo and
196 Newton, 1976) , which is much lower than for rat bite fever, for which the same group is also at risk
197 (Gaastra et al., 2009). Two cases in veterinarians were not caused by bites or scratches, but by fracture
198 of a tooth during manual extraction which struck the veterinarians in the eye (de Smet et al., 1990;
199 Chodosh, 2001). In one case it was the tooth of a cat, in the other of a dog. *C. canimorsus* is primarily
200 an opportunistic pathogen that infects individuals weakened by a compromised immunity. Most
201 infections in humans occur among people older than 40 years, but infections have been reported in a 4-
202 month-old and 83 year-old patient, the ratio male to female is 3:1 (Danker et al., 1987; Pers et al.,
203 1996, Deshmukh et al., 2004; Sandoe, 2004; Janda et al., 2006). Sixty percent of the people that get an
204 infection with this organism have predisposing conditions. Those who have had a splenectomy (33%
205 of cases) comprise a high-risk group with a 30-60 times increased risk of fatal septicemia (Singer,
206 1973, Deprés-Brummer et al., 2001). Often, already within 24 hours of symptom onset, overwhelming
207 postsplenectomy infections (OPSI) can result in a rapidly deteriorating clinical course that progresses
208 to multiple organ system failure and death (Band et al., 2008; Sawmiller et al., 2008). In the United
209 States each year 25.000 splenectomies are performed (Sumaruju et al., 2001). Together with the
210 thousands of functionally hyposplenic or asplenic patients a significant number of people is therefore
211 at marked risk for OPSI, which has an estimated mortality rate of 70% (Brigden and Pattullo, 1999).

Asplenic individuals suffer deficient IgM and IgG production and delayed macrophage mobilization. They also produce less tuftsin, a protein derived from IgG that stimulates phagocytosis (August, 1988). Liver disease caused by alcohol abuse (24% of cases) and the use of cortisone (3% of cases) are other predisposing factors for the infection (Lion et al., 1996). Hematologic malignancy, neutropenia and chronic lung disease were also considered as predisposing conditions (Dire et al., 1994). Up to 40% of cases however occur in previously healthy adults (LeMoal,et al., 2003). Alcohol abuse, asplenia, hemochromatosis, β-thalassemia major and tobacco smoking lead to absorption of twice the amount of alimentary iron as in normal persons. In two cases of immune-competent persons with *C. canimorsus* infection, both women, heavy smoking was explicitly mentioned (Finn et al., 1996; Aslam, 1999). An alternative explanation for why these conditions form a risk for *C. canimorsus* infection might be that this two-fold increase in serum iron values much better supports the growth of the poor iron scavenger *C. canimorsus* (Weinberg, 2000). It was suggested that the presence of detectable amounts of *C. canimorsus* in only one quarter of dogs and cats might be due to the fact that positive animals have insufficient amounts of lactoferrin and other iron binding factors in their oral cavity (Weinberg, 2000). Since the 25% is likely to be an underestimation based on data with improved selective cultivation conditions (see above) and PCR (see above), the suggested lack of lactoferrin in *C. canimorsus* positive animals is unlikely. However, iron overload was suggested as a risk factor in a case of *C. canimorsus* infection in a patient receiving numerous blood transfusions over a two year period (Pletschette et al., 1992).

Diagnostics

The diagnosis *C. canimorsus* infection is usually made based on the bacterial culture of blood (88% of cases), other body fluids (cerebrospinal fluid, 7% of cases) or less frequently from the bite wound or tissue from the bitten individual (Janda et al., 2006). Polyanethole-sulphonate, an anticoagulant frequently present in automatic blood culture systems, inhibits the growth of *C. canimorsus* (Sowden et al., 1995). Swabs of the mouth of the dog that bit the patients have been taken in a number of cases, but growth of *C. canimorsus* was only obtained in half of them (Martone et al., 1980; Howell and Woodward, 1990; Hantson et al., 1991; Valtonen et al., 1995; Finn et al., 1996;

Phipps et al., 2002; van de Ven et al., 2004). An indication of a *C. canimorsus* infection can already be obtained when a Gram stain of the buffy coat of peripheral blood shows many extracellular Gram-negative rods and several intracellular copies of the same rods in almost all neutrophils (Pedersen et al., 1993; Sawmiller et al., 1998; Mirza et al., 2000). In cases of overwhelming *C. canimorsus* septicemia, whole blood smears have also been reported positive for Gram-negative rods in the Gram stain (Holmes and Kozinn, 1986; Ndon et al., 1992; Newton, 2006, Kleijnen-Grebien et al., 2008). Examination of the buffy coat by Gram stain in splenectomized patients is particularly useful when *C. canimorsus* infection is suspected, since several days may pass before the organism is identified in the laboratory (Hicklin et al., 1987). The slow growth of *C. canimorsus* may lead to diagnostic problems since culture plates are routinely discarded after five days and some strains do not grow at all. A Gram stain of the cerebrospinal fluid showed Gram-negative bacilli in 65% of 20 cases of *C. canimorsus* meningitis (de Boer et al., 2007).

The diagnosis of *C. canimorsus* infection was evaluated by Janda et al., (2006) with isolates collected over a 30 year period. It was concluded that many laboratories are unable to identify *C. canimorsus* isolates and report them as (fastidious) Gram-negative rods. In their identification procedure the authors use a combination of biochemical tests, fatty acid methyl ester analysis and 16S rDNA sequencing (Janda et al., 2006). The number of cases in which broad range PCR followed by DNA sequencing is used for diagnostic purposes is increasing (Ciantar et al., 2005; Gotwein et al., 2006; Janda et al., 2006; Meybeck et al., 2006; Wareham et al., 2007; Le Meur et al., 2008; Kleijnen-Grebien et al., 2008; Papadaki et al., 2008). It should be noted that in one case, amplification of *C. canimorsus* DNA from an infected valve was obtained while attempts to amplify the DNA from the positive blood culture of the same patient was unsuccessful, probably due to the presence of polyanethylsulphonate which inhibits the PCR reaction (Wareham et al., 2007).

Therapy and Prevention

The first choice antibiotic for infection with *C. canimorsus* is penicillin G, although resistance of isolates has been mentioned (Meybeck et al., 2006). After investigation of the available literature we came to the same conclusion as LeMoal et al. (2003), that no β-lactamase producing *C. canimorsus*

strain has been reported yet. There are however, several reports on β-lactamase producing *Capnocytophaga* species (Arlet et al., 1987; Roscoe et al., 1992; Jolivet-Gougeon et al., 2007). With broth or agar dilution techniques, susceptibility for penicillins, imipenem, clindamycin, chloramphenicol, third generation cephalosporins, fluoroquinolones, erythromycin, doxycycline and metranidazole has been demonstrated. Aztronam, polymyxin, fosfomycin, trimethoprim / sulfamethoxazole and aminoglycosides are not effective against this bacterium (Verghese et al., 1988; Bremmelgaard et al., 1989; Desmukh et al., 2004). However, in the literature disagreement on the results for trimethoprim / sulfamethoxazole, aminoglycosides and vancomycin can be found, which seem to depend on the method used. Routine prophylaxis with amoxicillin-clavulanic acid has been proposed for all immunocompromised patients and in cases seen within 8 hours after moderate to severe crush injuries or when the bones and joints are involved (Goldstein, 2005). Immediate cleaning of the wound and disposal of scrap fabric filler are important during the antibiotic therapy. Although systemic administration of antimicrobial agents is controversial for healthy persons, those from whom the spleen was removed should be given prophylactic antibiotics against this organism after a dog bite or in the case of an open wound which has been in contact with the saliva of a dog. In several countries systemic antibiotic treatment is recommended for all persons (not only immuno-compromised patients) after a dog bite. The clinical course of a patient with *C. canimorsus* sepsis, which presented as an acute abdomen described by Sawmiller et al., (1998) clearly demonstrates the importance of early diagnosis and treatment of an overwhelming postsplenectomy infection. One may wonder whether there is an indication to test healthy pets for *C. canimorsus*, in households with high-risk individuals and if there is an indication to treat colonized pets in these households. Given the high prevalence of dogs when tested by PCR for *C. canimorsus*, it is very likely that dogs in high risk households will test positive. It is unclear what the advance of treating the dogs in these households will be since a treated "*C. canimorsus* free" dog can readily be colonized again after contact with other dogs. There are no reports on dogs that have been tested several times over a period of time. So it is not known whether a negative dog will stay negative during its whole life or whether a positive dog will always test positive a next time. Furthermore, since a PCR test for *C. canimorsus* has not been

validated it is not clear what the value of a negative PCR is with respect to that particular dog being colonized or not

Prevalence

Worldwide millions of people are bitten by animals each year (one out of every two persons will be bitten by an animal at some point in his lifetime (Greene and Goldstein, 2006). Ninety percent of the bites are by dogs and cats (Griego et al., 1995, Matter and Sentinella, 1998). Less than half of the bites are reported and 18% of these persons seek medical attention (Overall and Love, 2001). Most bites are minor and occur (in descending order of incidence) on the extremities (hands and feet), head and neck and the fuselage. Although 80% of dog bite wounds inflicted on people culture positive for bacteria, the chance that a dog bite gets infected is between 3 and 20 % (Underman, 1987, Goldstein, 1992). For cat bites, this is between 20 and 50% (Talan et al., 1999). Usually the infection is caused by a combination of aerobic and anaerobic bacteria. In the Netherlands yearly between 50.000 and 100.000 people get bitten by a pet animal. The number of registered bite incidents by dogs or cats in children under the age of ten in The Netherlands is about 4800 per year (Deprés-Brummer et al., 2001). Since 1976, worldwide approximately 200 cases of septicemia, meningitis or gangrene caused by *C. canimorsus* have been reported in humans bitten, scratched or licked by a dog or cat (Brenner et al., 1989, Blanche et al., 1998, Tierney et al., 2006). Even though almost equal percentages of dogs and cats (24% vs. 18%)(Blanche et al., 1998) carry *C. canimorsus* in the oral cavity, the majority of cases is caused by dog bites or dog contact. Cat bites, scratches or contact with cats has been reported in less than 10 % of the cases. The deep, sharp, needle like punctures with relatively little tissue damage through cat bites are probably creating less favorable conditions for the growth of the bacterium than the larger superficial wounds with a lot of tissue damage caused by dog bites.(Carpenter et al., 1987; Scarlett et al., 1991; Mahrer and Raik, 1992; Valtonen et al., 1995; Zimmer-Gallen et al., 1996; McLean et al., 2004; Le Meur, et al., 2008). The risk of infection depends on adequate wound treatment and host factors like age, health status.

Infection with *C. canimorsus* is not a notifiable disease. The number of reports on *C. canimorsus* infection is increasing, but it is still a relatively rarely reported disease. The frequency of

C. canimorsus infection is very likely underestimated (Janda et al., 2006). Presently, not even all severe and lethal infections are reported but only those cases where the clinical picture has not been seen before. Additionally, patients who are supplied with antibiotics in time do not develop a *C. canimorsus* infection. This may also influence the infection rate. The bacteria may be transmitted in various ways by close contact between pets and their owners. Transmission is not necessarily followed by multiplication of the bacteria in the human body (infection). Infection does not necessarily lead to serious clinical symptoms and humans with subclinical infections will not report to the physician. If the incubation period extends to several weeks and clinical symptoms are aspecific, *C. canimorsus* infection is probably not considered when bites by dogs or cats or contact with these animals are not explicitly mentioned in the anamnesis.

Patients suspected of *C. canimorsus* infection will often be treated with antibiotics most of which will be active against the causative bacteria. The number of cases in which laboratory diagnostic examinations are carried out is therefore limited to very severe cases or when antibiotic therapy fails.

C. canimorsus may be difficult to grow in primary culture after antibiotic therapy and detection by broad range PCR and nucleotide sequence determination is operational in a limited number of diagnostic laboratories only. *C. canimorsus* strains may be misidentified despite the fact that the bacteriologic characteristics are rather typical.

Conclusions

C. canimorsus is a commensal in the oral cavity of dogs ands cats and is considered to be of low virulence under normal circumstances. The bacterium can cause severe illness in predisposed patients (i.e. those who have had a splenectomy, who are alcohol abusers, suffer from chronic lung or liver diseases or are on immunosuppressive medication). However, 40% of the reported cases occurred in previously healthy people.

The true number of *C. canimorsus* infections each year probably is largely underestimated due to the fastidious growth of the organism. The isolation from animal saliva is difficult and the organism is seldom isolated from bite wounds. The relatively more successful growth from blood culture can

explain why the bacterium is only detected in cases of septicemia. Penicillin is considered the drug of choice in the case of *C. canimorsus* infection. The length of the treatment varies between reports (14-21 days). (Le Moal et al., 2002).

In the past, diagnosis and identification have been difficult due to the fastidious growth of the organism, which has lead to fatal outcomes in cases where the patient probably could have survived since the bacterium is susceptible to a whole range of commonly used antibiotics. With the introduction of optimized growth conditions on selective media and PCR as a diagnostic tool this type of fatalities is expected to decrease. Because of the seriousness of *C. canimorsus* infection, taking this bacterium into account in the management of animal bites, is necessary. Moreover, high risk patients should be informed about the risks of keeping of pets. Not only do bites and scratches pose a risk to these patients but other scenario's one not normally thinks of are possible. This can be illustrated by a case report where an 18 year old person on automated peritoneal dialysis developed *C. canimorsus* peritonitis following the puncture of his dialysis tubing by a domestic cat that slept in his bed (Chada and Warady, 1999).

Administration of antimicrobial agents is controversial for healthy persons, but it is justifiable for the following groups of bite victims: those with deep wounds, particularly to the face or hands and those at high risk for *C. canimorsus* infection e.g. immuno-compromised patients.

Future research

More insight in the genetic properties and the molecular biology of *C. canimorsus* is a prerequisite for understanding the overwhelming sepsis, this organism can cause. In this respect whole genome sequencing of strains from different origin seems relevant. Questions to be answered are: are isolates from humans and dogs different? Or are the former a more virulent subset of the latter? Is there a difference between dog and cat isolates? Once the whole genome of *C. canimorsus* has been sequenced this might allow the identification of the genetic basis of virulence factors and the reason for the low virulence normally seen in immunocompetent bite victims. To improve diagnostics, media should be developed that allow rapid growth of the organism. For the following rapid identification the development of a species specific PCR is needed. This can eventually be followed by sequencing of

the amplicon for confirmation. A systematic search for the presence of *C. canimorsus* in the oral cavity of other animals than cats and dogs is also needed to determine the potential risk with bites from these animals. So far there are no indications that point to a host specificity that is limited to dogs and cats.

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Conflict of interest:

None of the authors (Wim Gaastra, Len J. A. Lipman) has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the paper entitled ”Capnocytophaga canimorsus”.

References:

Andersen, H.K., Pedersen, M. 1992. Infective endocarditis with involvement of the tricuspid valve due to *Capnocytophaga canimorsus*. Eur. J. Clin Microbiol. Infect. Dis. 11, 831-832.

Arlet, G., Sanson-Le Port, M.J., Casin, I.M., Ortenberg, M., Perol, Y. 1987. In vitro susceptibility of 96 *Capnocytophaga* strains, including a β-lactamase producer, to new β-lactam antibiotics and six quinolones. Antimicrob. Agents. Chemother. 31, 1283-1284.

Aslam, A. 1999. Life-threatening *Capnocytophaga canimorsus* infection after dog bite. J. R. Soc. Med. 92, 140-141.

August, J.R., 1988. Dysgonic fermentor-2 infections. J. Am. Vet. Med. Assoc. 193, 1506-1508.

Bailie, W.E., Stowe, E.C., Schmitt, A.M. 1978. Aerobic bacterial flora of oral and nasal fluids of canines with reference to bacteria associated with bites. J. Clin. Microbiol. 7, 223-231.

405 Band, R.A., Gaieski, D.F., Goyal, M., Perrone, J. 2009. A 52-year-old man with malaise and petechial
406 rash. J. Emerg. Med. In press.
407 Blanche, P., Bloch, E., Sicard, D. 1998. *Capnocytophaga canimorsus* in the oral flora of dogs and cats.
408 J. Infect. 36, 134.
409 de Boer, M.G.J., Lambregts, P.C.L.A., van Dam, A.P., van 't Wout, J.W. 2007. Meningitis caused by
410 *Capnocytophaga canimorsus*: when to expect the unexpected. Clin. Neurol. Neurosurg. 109,
411 393-398.
412 Bobo, R.A., Newton, E.J. 1976. A previously undescribed Gram-negative bacillus causing septicemia
413 and meningitis. Am. J. Clin. Pathol. 65, 564-569.
414 Bremmelgaard, A., Pers, C., Kristiansen, J.E., Korner, B., Heltberg, O., Frederiksen, W. 1989.
415 Susceptibility testing of Danish isolates of *Capnocytophaga* and CDC group DF2 bacteria.
416 Acta Pathol. Microbiol. Immunol. Scand. 97, 43-48.
417 Brenner, D.J., Hollis, D.G., Fanning, G.R., Weaver, R.E. 1989. *Capnocytophaga canimorsus* sp. Nov.
418 (formerly CDC group DF-2), a cause of septicaemia following dog bite, and *C. Cynodegmi* sp.
419 Nov., a cause of localized wound infection following dog bite. J. Clin. Microbiol. 27, 231-235.
420 Brigden, M.L., Pattullo, A.L. 1999. Prevention and management of overwhelming postsplenectomy
421 infection-an update. Crit. Care Med. 27, 836-842.
422 Butler, T., Weaver, R.E., Ramani, T.K.V., Uyeda, C.T., Bobo, R.A., Ruy, J.S., Kohler, R.B. 1977.
423 Unidentified gram-negative rod infection. Ann. Intern. Med. 86, 1-5.
424 Carpenter, P.D., Heppner, B.T., Gnann, J.W. 1987. DF-2 bacteremia following cat bites, report of two
425 cases. Am. J. Med. 82, 621-623.
426 Chadha, V., Warady, B.A. 1999. *Capnocytophaga* canimorsus peritonitis in a pediatric peritoneal
427 dialysis patient. Pediatr. Nephro. 13, 646-648.
428 Chodosh, J. 2001. Cat's tooth keratitis: Human corneal infection with *Capnocytophaga canimorsus*.
429 Cornea 20, 661-663.
430 Ciantar, M., Spratt, D.A., Newman, H.N., Wilson, M. 2001. Assessment of five culture media for the
431 growth and isolation of *Capnocytophaga* spp. Clin. Microbiol. Infect. 7, 158-160.

Ciantar, M., Newman, H.N., Wilson, M., Spratt, D.A. 2005. Molecular identification of *Capnocytophaga* spp. Via 16S rRNA PCR-restriction fragment length polymorphism analysis. L. Clin. Microbiol. 43, 1894-1901.

Danker, W.M., Davis, C.E., Thompson, M.A. 1987. DF-2 bacteremia following dog bite in a 4 month old child. Pediatr. Infect. Dis. J. 6, 695-696.

Dees, S.B., Powell, J., Moss, C.W., Hollis, D.G., Weaver, R.E. 1981. Cellular fatty acid composition of organisms frequently associated with human infections resulting from dog bites: *Pasteurella multocida* and groups EF-4, IIj, M-5 and DF-2. J. Clin. Microbiol. 14, 612-616.

Deprés-Brummer, P., Buijs, J., van Engelenburg, K.C.A., Oosten, H.R. 2008. *Capnocytophaga canimorsus* sepsis presenting as an acute abdomen in an aplenic patient. Neth. J. Med. 59, 213-217.

Deshmukh, P.M., Camp, C.J., Rose, F.B., Narayanan, S. 2004. *Capnocytophaga canimorsus* sepsis with purpura fulminans and symmetrical gangrene following a dog bite in a shelter employee. Am. J. Med. Sci. 327, 369-372.

Dire, D.J., Hogan, D.E., Riggs, M.W. 1994. A prospective evaluation of risk factors for infections from dog wounds. Acad. Emerg. Med. 1, 258-266.

van Duijkeren E., van Mourik, C., Broekhuizen, M., Leuven, M., Gaastra, W., Houwers, D. 2006. First documented *Capnocytophaga canimorsus* infection in a species other than humans. Vet. Microbiol. 118, 148-150.

Finn, M., Dale, B., Isles, C. 1996. Beware of the dog! A syndrome resembling throbotic thrombocytopenic purpura associated with *Capnocytophaga canimorsus* septicaemia. Nephrol. Dial. Transplant. 11, 1839-1840.

Fischer, L.J., Weyant, R.S., White, E.H., Quinn, F.D. 1995. Intracellular multiplication and toxic destruction of cultured macrophages by *Capnocytophaga canimorsus*. Infect. Immun. 63, 3484-3490.

Forlenza, S.W. 1991. *Capnocytophaga*: an update. Clin. Microbiol. Newsett. 13, 89-91.

Frey, E., Pressler, B., Guy, J., Pitulle, C., Breitschwerdt, E.l 2003. *Capnocytophaga* sp. Isolated from a cat with chronic sinusitis and rhinitis. J. Clin. Microbiol. 41, 5321-5324.

460 Frieling, J.T.M., Mulder, J.A., Hendriks, T., Curfs, J.H.A.J., van der Linden, C.J., Sauerwein, R.W.
461 1997. Differential induction of pro- and anti-inflammatory cytokines in whole blood by
462 bacteria: effects of antibiotic treatment. Antimicrob. Agents Chemother. 41, 1439-1443.
463 Gaastra, W., Boot, R., Ho, H.T.K., Lipman. L.J.A. 2009. Rat bite fever. Veterinary Microbiology. 133,
464 211-228..
465 Glasser, D.B. 1986. Angular blepharitis by gram-negative bacillus DF-2. Am. J. Ophtalmol. 102, 119-
466 120.
467 Goldstein, E.J.C. 1992. Bite wounds and infection. Clin. Infect. Dis. 14, 633-638.
468 Goldstein, E.F.C. 2005. Bites. In: Mandell, G.L., Bennett, J.E., Dolin, R. (eds). Principles of Infectious
469 Diseases, 6th edition, Churcill Livingstone, New York. pp. 3552-3556.
470 Gottwein, J., Zbinden, R., Maibach, R.C., Herren, T. 2006. Etiologic diagnosis of *Capnocytophaga*
471 *canimorsus* meningitis by broad ranfe PCR. Eur. J. Microbiol. Infect. Dis. 25, 132-134.
472 Greene, C.E., Goldstein, E.J.C. 2006. Bite wound infections. In: Greene, C.E. (ed). Infectious Diseases
473 of the dog and cat, 3th edition, Saunders, St. Louis. pp. 495-510.
474 Griego, R.D., Rosen, T., Orengo, I.F., Wolf, J.E. 1995. Dog, cat and human bites: a review. J. Am.
475 Acad. Dermatol. 33, 1019-1029.
476 Hantson, P., Gautier, P.E., Vekemans, M-E., Fievez, P., Evrard, P., Wauters, G., Mahieu, P. 1991.
477 Fatal *Capnocytophaga canimorsus* septicemia in a previously healthy woman. Ann. Emerg.
478 Med. 20, 93-94.
479 Hicklin, H., Verghese, A., Alvarez, S. 1987. Dysgonic Fermentor 2 septicemia. Rev. Infect. Dis. 9,
480 884-890.
481 Holmes, R.L., Kozinn, W.P. 1986. DF-2 septicemia following whirlpool spa immersion. J. Clin.
482 Microbiol. 23, 627-628.
483 Howell, J.M., Woodward, G.R. 1990. Precipitous hypotension in the emergency department caused by
484 *Capnocytophaga canimorsus* sp. Nov. sepsis. Am. J. Emerg. Med. 8, 312-314.
485 Janda, M.J., Graves, M.H., Lindquist, D.,Probert, W.S., 2006. Diagnosing *Capnocytophaga*
486 *canimorsus* infections. Emerging Infect. Dis., 12, 340-342.

487 Job, L., Horman, J.T., Grigor, J.K., Israel, E. 1988. Dysgonic fermenter-2: A clinico-epidemiologic
488 review. J. Emergency Med. 7, 185-192.
489 Jolivet-Gougeon, A., Sixou, J-L.,Tamanai-Shacoori, Z., Bonnaure-Mallet, M. 2007. Antimicrobial
490 treatment of *Capnocytophaga* infections. Int. J. Antimicrob. Agents 29, 367-373.
491 Kolata, R.J., Kraut, N.H., Johnston, D.E. 1974. Patterns of trauma in urban dogs and cats: a study of
492 1000 cases. J. Am. Vet. Med. Assoc. 164, 499-502.
493 Kleijnen-Grebien, B., Boorsma, S., Stals, F.S., van Schelven, R. 2008. Fatale afloop van een sepsis
494 met *Capnocytophaga canimorsus* na een triviale hondebeet. Ned. Tijdschr. Geneeskd. 152,
495 1882-1885.(in Dutch).
496 Landercasper, J., Cogbill, T.H., Strutt, P.J., Landercasper, B.O. 1988. Trauma and the veterinarian. J
497 Trauma 28, 1255-1258.
498 Le Meur, A., Albert, J-D., Gautier, P., Ropars, M., Perdriger, A., Gando, N., , Minet, J., Cormier, M.,
499 Bonnaure-Mallet, M., Jolivet-Gougeon, A. Acute tenosynovitus of the ankle due to
500 *Capnocytophaga cynodegmi/canimorsus* as identified bt 16S rRNA gene sequencing. Joint
501 Bone Spine, doi:10.1016/j.jbspin.2008.04.007.
502 LeMoal, G., Landron, C., Grollier, G., Robert, R., Burucoa, C. 2003. Meningitis due to
503 *Capnocytophaga canimorsis* after receipt of a dog bite: case report and review of the
504 literature. Clin. Infect. Dis. 36, e42-e46.
505 Lion, C., Escande, F., Burdin, J.C. 1996. *Capnocytophaga canimorsus* infections in human: Review of
506 the literature and cases report. Eur. J. Epidemiol. 12, 521-533.
507 Macrea, M.M., McNamee, M., Martin, T.J. 2008. Acute onset of fever, chills and lethargy in a 36-
508 year-old woman. Chest. 133, 1505-1507.
509 Mahrer, S., Raik, E. 1992. *Capnocytophaga canimorsus* septicemia associated with cat scratch.
510 Pathology 24, 194-196.
511 Mally, M., Cornelis, G.R. 2008. Genetic tools for *Capnocytophaga canimorsus*. Appl. Environ.
512 Microbiol. 74, 6369-6377.

513 Mally, M., Shin, H., Paroz, C., Landmann, R., Cornelis, G.R. 2008. *Capnocytophaga canimorsus*: A
514 human pathogen feeding at the surface of epithelial cells and phagocytes. PLoS Pathogens 4,
515 1-11.
516 Martone, M.J., Zuehl, R.W., Minson, G.E., Scheld, W.M. 1980. Post-splenectomy sepsis with DF-2:
517 report of a case with isolation of the organism from the patient's dog. Ann. Int. Med. 93, 457-
518 458.
519 Matter, H.C., Sentinella, A. 1998. The epidemiology of bite and scratch injuries by vertebrate animals
520 in Switzerland. Eur J Epidemiol 14:483-490.26.
521 McLean, C.R., Hargrove, R., Behn, E. 2004. The first fatal case of *Capnocytophaga canimorsus* sepsis
522 caused by a cat scratch. J. R. Nav. Serv. 90, 13-15.
523 Meybeck, A., Aoun, N., Granados, D., Pease, S., Yeni, P. 2006. Meningitis due to *Capnocytophaga*
524 *canimorsus*: contribution of 16S RNA ribosomal sequencing for species identification. Scand.
525 J. Infect. Dis. 38, 375-399.
526 Meyer, S., Shin, H., Cornelis, G.R. 2008. *Capnocytophaga canimorsus* resists phagocytosis by
527 macrophages and blocks the ability of macrophages to kill other bacteria. Immunobiol. 213,
528 805-814.
529 Meyers, B., Schoeman, J.P., Goddard, A., Picard, J. 2008. The bacteriology and antimicrobial
530 susceptibility of infected and non-infected dog bite wounds: Fifty cases. Vet. Microbiol., 127,
531 360-368.
532 Mirza, I., Wolk, J., Toth, L., Rostenburg, P., Kranwinkel, R., Sieber, S.C. 2000. Waterhouse-
533 Friderichsen syndrome secondary to *Capnocytophaga canimorsus* septicemia and
534 demonstration of bacteria by peripheral blood smear. Arch. Pathol. Lab. Med. 124, 859-863.
535 Mulder, A.H., Gerlag, P.G., Verhoef, L.H., van den Wall Bake, A.W. 2001. Hemolytic uremic
536 syndrome after *Capnocytophaga canimorsus* (DF-2) septicemia. Clin. Nephrol. 44, 167-170.
537 Newton, L. 2006. An unusual case of septicaemia. N. Z. J. Med. Lab. Sci. 60, 59-60.
538 Ndon, J., 1992. *Capnocytophaga canimorsus* septicaemia caused by a dog bite in a hairy cell leukemia
539 patient. J. Clin. Microbiol. 30, 211-213.

Overall, K.L., Love, M. 2001. Dog bites to humans—demography, epidemiology, injury, and risk. J. Am. Vet. Med. Assoc. 218, 1923-1934.

Papadaki, T.G., el Moussaoui, R., van Ketel, R.J., Verbraak, F.D., Tan, H.S. 2008. *Capnocytophaga canimorsus* endogenous endophtalmitis in an immunocompetent host. Br. J. Ophtalmol. 92, 1566-1567.

Pedersen, G., Schønheyder, H.C., Nielsen, L.C.. 1993. *Capnocytophaga canimorsus* bacteraemia demonstrated by appositive blood sear: A case report. Acta Pathol. Microbiol. Immunol. Scand. 101, 572-574..

Pers, C., Gahrn-Hansen, B., Frederiksen, W. 1996. *Capnocytophaga canimorsus* septicemia in Denmark, 1982-1995: review of 39 cases. Clin. Infect. Dis. 23, 71-75.

Phipps, S.E., Tamblyn, D.M., Badenoch, P.R. 2002. *Capnocytophaga canimorsus* endophthalmitis following cataract surgery. Clin. Experiment. Ophtal., 30, 375-377.

Piccininno, G., Palliola, E., Sala, V. 1984. Clinical and anatomohistological features of experimental infection by DF-2 in rabbits. Path. Res. Pract. 179, 95-100.

Pletschette, M., Kőhl, J., Kuipers, J., Schmidt, R.E. 1992. Opportunistic *Capnocytophaga canimorsus* infection. Lancet, 339, 308.

Risi, G.F.,Spangler, C.A. 2006. *Capnocytophaga canimorsus* meningitis after routine myelography: A sentinel event identifies multiple opportunities for improvement of standard practices in radiology. Am. J. Infect. Control 34, 540-542.

Roscoe, D.L., Zemcov, S.J.V., Thornber, D., Wise, R., Clarke, A.M. 1992. Antimicrobial susceptibilities and β-lactamase characterization of *Capnocytophaga* species. Antimicrob. Agents Chemother. 36, 2197-2200.

Sandoe, J.A.T. 2004. *Capnocytophaga canimorsus* endocarditis. J. Med. Microbiol. 53, 245-248.

Sawmiller, C., Dudrick, S.J., Hamzi, M. 1998. Postsplenectomy *Capnocytophaga canimorsus* sepsis presenting as an acute abdomen. Arch. Surg. 133, 1362-1365.

Scarlett, J.D., Williamson, H.G., Dadson, P.J., Fassett, R., Peel, M. 1991. A syndrome resembling thrombotic thrombocytopenic purpura associated with *Capnocytophaga canimorsus* septisemia. Am. J. Med. 90, 127-128.

568 Shin, H., Mally, M., Kuhn, M., Paroz, C., Cornelis, G.R. 2007. Escape from immune surveillance by
569 *Capnocytophaga canimorsus*. J. Infect. Dis. 195, 375-386.
570 Singer, D.B. 1973. Post-splenectomy sepsis. In: Rosenberg, H.S., Bolande, R.P. (eds). Perspectives in
571 Pediatric Pathology. Vol. I Chicago, Ill., Year Book Medical Publishers, pp. 549-563.
572 de Smet, M.D., Chan, C.C., Nussenblatt, R.B., Palestine, A.G. 1990. *Capnocytophaga canimorsus* as
573 the cause of a chronic corneal infection. Am. J. Ophtalmol. 109, 240-242.
574 Sowden, D., Allworth, A., Davis, L.B. 1995. *Capnocytophaga canimorsus* sepsis: poor growth using
575 an automated blood culture system. Clin. Microbiol. Newslett. 17, 94-96.
576 Speck, H., Kroppenstedt, R.M., Mannheim, W., 1987. Genomic relationships and species
577 differentiation in the genus *Capnocytophaga*. Zentralbl. Bakteriol. Mikrobiol. Hyg. (A). 266,
578 390-402.
579 Sumaruju, V., Smith, L.G., Smith, S.M. 2001. Infectious complications in asplenic hosts. Infect. Dis.
580 Clin. North Am. 15, 551-565.
581 Talan, D.A., Citron, D.M., Abrahamian, F.M., Gregory, D.M., Moran, J., Goldstein, E.J.C. 1999.
582 Bacteriologic analysis of infected dog and cat bites. N. Engl. J. Med. 340, 85-92.
583 Tierney, D.M., Strauss, L.P., Sanchez, J.L. 2006. *Capnocytophaga canimorsus* mycotic abdominal
584 aortic aneurysm: why the mailman is afraid of dogs. J. Clin. Microbiol. 44, 649-651.
585 Tison, D.L., Latimer, J.M. 1986. Lysis-centrifugation-Direct plating technique for isolation of Group
586 DF-2 from the blood of adog bite victim. J. Infect. Dis. 153, 1001-1002.
587 Tobé, T.J., Franssen, C.F., Zijlstra, J.G., de Jong, P.E., Stegeman, C.A. 199. Hemolytic uremic
588 syndrome due to *Capnocytophaga canimorsus* bacteremia after a dog bite. Am. J. Kidney Dis.
589 33, e5.
590 Underman, A.E. 1987. Bite wounds inflicted by dogs and cats. Vet. Clin. North Am. 17, 195-207.
591 Valtonen, M., Lauhio, A., Carlson, P., Multanen, J., Sivonen, A., Vaara, M., Lähdevirta.J. 1995.
592 *Capnocytophaga canimorsus* septicemia: fifth report of a cat-associated infection and five
593 other cases. Eur. J. Clin. Microbiol. Infect. Dis. 14, 520-523.
594 van de Ven, A. R.T., van Vliet, A.C.M., Maraha, B., Ponssen, H.H. 2004. Fibrinolytic therapy in
595 *Capnocytophaga canimorsus* sepsis after dog bite. Intensive Care Med. 30, 1980.

596 Verghese, A., Hamati, F., Berk, S., Franzus, B., Berk, S., Smith, J.K. 1988. Susceptibility of dysgonic
597 fermenter 2 to antimicrobial agents in vitro. Antimicrob. Agents Chemother. 32, 78-80.
598 Wareham, D.W., Michael, J.S., Warwick, S., Whitlock, P., Wood, A., Das, S.S. 2007. The dangers of
599 dog bites. J. Clin. Pathol. 60, 328-329.
600 Weinberg, E.D. 2000. Microbial pathogens with impaired ability to acquire host iron. BioMetals 13,
601 85-89.
602 Westwell, A.J., Kerr, K., Spencer, M.B., Hutchinson, D.N. 1989. DF-2 infection. Brit. Med. J. 298,
603 116-117.
604 Zimmer-Gallen, I.E., Pach, J.M. 1996. *Capnocytophaga canimorsus* endophthalmitis. Retina 16, 163-
605 164.
606

Figure Legends

Fig.1. Gram stain of *C .canimorsus* isolate from a rabbit bitten by a dog.

Fig.2. Rabbit with *C. canimorsus* infection after a dog bite in the head.

Fig.1

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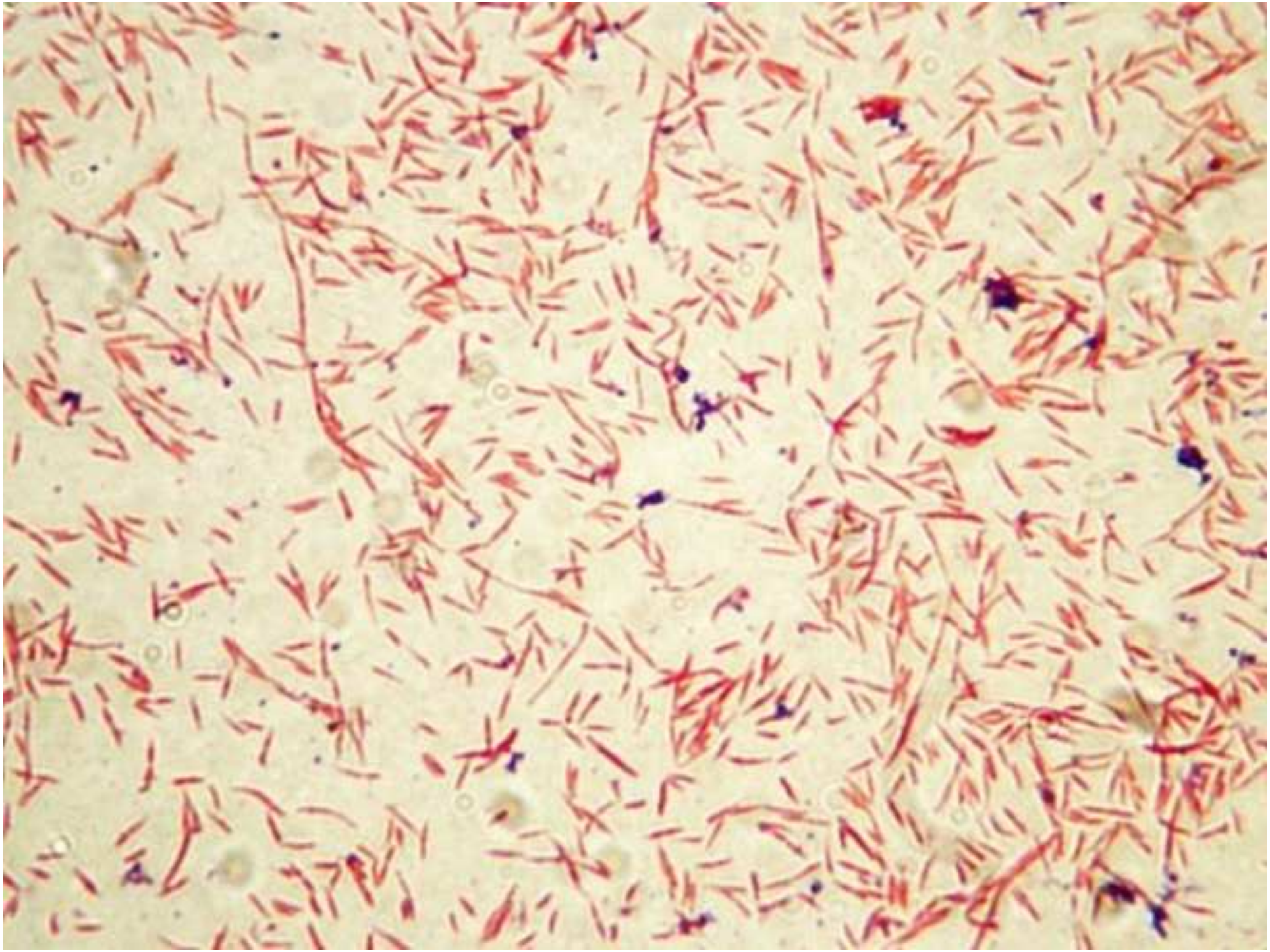

Fig.2

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