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Capnocytophaga canimorsus

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19 **Abstract**

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

25

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

27

28 **Introduction**

29 Worldwide millions of people are bitten by animals each year. It is estimated that 50% of all
30 Americans will be bitten at least once in their lifetime. Ninety percent of these bites are caused by
31 dogs and cats. The majority of dog and cat bite wounds is minor and no medical attention is sought by
32 the victim. Occasionally a dog or cat bite is complicated and an overwhelming systemic infection
33 occurs. In the USA the annual mortality rate due to dog and cat bites is 6.7 per 10⁸ persons, albeit that
34 not all these fatalities are caused by infections (Griego et al., 1995).

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44 for the 16S rRNA gene of *C. canimorsus* was positive for 41% of the dogs (de Poel et al., unpublished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

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

61

62 **The Infectious Agent**

63 **Historical perspective**

64 In 1976 a patient with meningitis and sepsis, caused by an unidentified Gram-negative
65 bacillus, after a recent dog bite was first described (Bobo and Newton, 1976). At that time, the
66 phenotypic as well as the biochemical characteristics of the agent also became known. We now know
67 that this Gram-negative bacillus probably was a member of the *Capnocytophaga* family, very likely *C.*
68 *canimorsus*-(CDC group DF-2 or dysgonic fermentor 2, dysgonic = slow and relatively poor growth of
69 a bacterial culture). One year later, 17 cases of infection after recent dog bites , the majority caused by
70 an unidentified Gram-negative rod were described (Butler et al., 1977). The nature of the infection
71 varied from cellulitis to meningitis , endocarditis to organ failure and fatal sepsis. The organism was
72 given its current name in 1989, based on its CO₂ requirement and usual mode of transmission (Brenner
73 et al., 1989). Since then, *C. canimorsus* infections were found to occur worldwide and have been
74 reported from the United States, Canada, Europe, Australia and South Africa.

75 **Phenotypic and Genotypic Characteristics**

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

81

82 **Cultural properties**

83 Classically, the organism was regarded difficult to culture because of its specific requirements
84 for nutrients and thus may have easily escaped detection. *C. canimorsus* has been shown to require
85 large amounts of exogenous iron for growth (Brenner et al., 1989). It grows slowly on blood (5%
86 sheep blood in Columbia agar) or chocolate agar in 10% CO₂ (Ciantar et al., 2001). Media had to be
87 incubated at 37°C for at least 5 days. Colonies could be not visible for 2-7 days, on blood agar.
88 Initially they are pin point in size and later become larger, convex and smooth. Colonies are non
89 hemolytic with the characteristic shiny spreading edge and finger-like projections of bacteria with
90 gliding motility (Andersen and Pedersen, 1992, Desmukh et al., 2004). Although the color of colonies
91 may vary from pink to yellow, the colonial mass of all isolates is yellow when scraped from the agar
92 plate (Forlenza, 1991). Horse blood agar plates were found to be superior to sheep blood but do not
93 seem to be used often (Westwell et al., 1989; Pers et al., 1996). The organism does not grow on
94 MacConkey agar. Recently, the growth medium was optimized (Heart Infusion agar Difco with 5%
95 sheep blood) and the bacteria were shown to grow in 2 days at 37°C in 5 % CO₂ (Shin et al., 2007,
96 Mally et al., 2008). To our knowledge, these growth conditions have only been used under
97 experimental conditions and not yet in a clinical setting. It is to be expected that faster growth of *C.*
98 *canimorsus* will be reflected in the speed with which diagnostics can be performed and therefore lead
99 to less fatalities due to this organism.

100

101 **Biochemical Characteristics**

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

111

112 **Pathogenicity and Virulence Factors**

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

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

133

134 **Infection in Animals**

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

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

155

156 **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, osteomyelitis, 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 (Sumaraju 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).

212 Asplenic individuals suffer deficient IgM and IgG production and delayed macrophage mobilization.
213 They also produce less tuftsin, a protein derived from IgG that stimulates phagocytosis (August,
214 1988). Liver disease caused by alcohol abuse (24% of cases) and the use of cortisone (3% of cases) are
215 other predisposing factors for the infection (Lion et al., 1996). Hematologic malignancy, neutropenia
216 and chronic lung disease were also considered as predisposing conditions (Dire et al., 1994). Up to
217 40% of cases however occur in previously healthy adults (LeMoal,et al., 2003). Alcohol abuse,
218 asplenia, hemochromatosis, β -thalassemia major and tobacco smoking lead to absorption of twice the
219 amount of alimentary iron as in normal persons. In two cases of immune-competent persons with *C.*
220 *canimorsus* infection, both women, heavy smoking was explicitly mentioned (Finn et al., 1996;
221 Aslam, 1999). An alternative explanation for why these conditions form a risk for *C. canimorsus*
222 infection might be that this two-fold increase in serum iron values much better supports the growth of
223 the poor iron scavenger *C. canimorsus* (Weinberg, 2000). It was suggested that the presence of
224 detectable amounts of *C. canimorsus* in only one quarter of dogs and cats might be due to the fact that
225 positive animals have insufficient amounts of lactoferrin and other iron binding factors in their oral
226 cavity (Weinberg, 2000). Since the 25% is likely to be an underestimation based on data with
227 improved selective cultivation conditions (see above) and PCR (see above), the suggested lack of
228 lactoferrin in *C. canimorsus* positive animals is unlikely. However, iron overload was suggested as a
229 risk factor in a case of *C. canimorsus* infection in a patient receiving numerous blood transfusions over
230 a two year period (Pletschette et al., 1992).

231

232 **Diagnostics**

233 The diagnosis *C. canimorsus* infection is usually made based on the bacterial culture of blood
234 (88% of cases), other body fluids (cerebrospinal fluid, 7% of cases) or less frequently from the bite
235 wound or tissue from the bitten individual (Janda et al., 2006). Polyanethole-sulphonate, an
236 anticoagulant frequently present in automatic blood culture systems, inhibits the growth of *C.*
237 *canimorsus* (Sowden et al., 1995). Swabs of the mouth of the dog that bit the patients have been taken
238 in a number of cases, but growth of *C. canimorsus* was only obtained in half of them (Martone et al.,
239 1980; Howell and Woodward, 1990; Hantson et al., 1991; Valtonen et al., 1995; Finn et al., 1996;

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

252 The diagnosis of *C. canimorsus* infection was evaluated by Janda et al., (2006) with isolates
253 collected over a 30 year period. It was concluded that many laboratories are unable to identify *C.*
254 *canimorsus* isolates and report them as (fastidious) Gram-negative rods. In their identification
255 procedure the authors use a combination of biochemical tests, fatty acid methyl ester analysis and 16S
256 rDNA sequencing (Janda et al., 2006). The number of cases in which broad range PCR followed by
257 DNA sequencing is used for diagnostic purposes is increasing (Ciantar et al., 2005; Gotwein et al.,
258 2006; Janda et al., 2006; Meybeck et al., 2006; Wareham et al., 2007; Le Meur et al., 2008; Kleijnen-
259 Grebien et al., 2008; Papadaki et al., 2008). It should be noted that in one case, amplification of *C.*
260 *canimorsus* DNA from an infected valve was obtained while attempts to amplify the DNA from the
261 positive blood culture of the same patient was unsuccessful, probably due to the presence of
262 polyanethylsulphonate which inhibits the PCR reaction (Wareham et al., 2007).

263

264 **Therapy and Prevention**

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

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

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

297

298 **Prevalence**

299 Worldwide millions of people are bitten by animals each year (one out of every two persons
300 will be bitten by an animal at some point in his lifetime (Greene and Goldstein, 2006). Ninety percent
301 of the bites are by dogs and cats (Griego et al., 1995, Matter and Sentinella, 1998). Less than half of
302 the bites are reported and 18% of these persons seek medical attention (Overall and Love, 2001). Most
303 bites are minor and occur (in descending order of incidence) on the extremities (hands and feet), head
304 and neck and the fuselage. Although 80% of dog bite wounds inflicted on people culture positive for
305 bacteria, the chance that a dog bite gets infected is between 3 and 20 % (Underman, 1987, Goldstein,
306 1992). For cat bites, this is between 20 and 50% (Talan et al., 1999). Usually the infection is caused by
307 a combination of aerobic and anaerobic bacteria. In the Netherlands yearly between 50.000 and
308 100.000 people get bitten by a pet animal. The number of registered bite incidents by dogs or cats in
309 children under the age of ten in The Netherlands is about 4800 per year (Deprés-Brummer et al.,
310 2001). Since 1976, worldwide approximately 200 cases of septicemia, meningitis or gangrene caused
311 by *C. canimorsus* have been reported in humans bitten, scratched or licked by a dog or cat (Brenner et
312 al., 1989, Blanche et al., 1998, Tierney et al., 2006). Even though almost equal percentages of dogs
313 and cats (24% vs. 18%)(Blanche et al., 1998) carry *C. canimorsus* in the oral cavity, the majority of
314 cases is caused by dog bites or dog contact. Cat bites, scratches or contact with cats has been reported
315 in less than 10 % of the cases. The deep, sharp, needle like punctures with relatively little tissue
316 damage through cat bites are probably creating less favorable conditions for the growth of the
317 bacterium than the larger superficial wounds with a lot of tissue damage caused by dog
318 bites.(Carpenter et al., 1987; Scarlett et al., 1991; Mahrer and Raik, 1992; Valtonen et al., 1995;
319 Zimmer-Gallen et al., 1996; McLean et al., 2004; Le Meur, et al., 2008). The risk of infection depends
320 on adequate wound treatment and host factors like age, health status.

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

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

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

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

341

342 **Conclusions**

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

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

351 explain why the bacterium is only detected in cases of septicemia. Penicillin is considered the drug of
352 choice in the case of *C. canimorsus* infection. The length of the treatment varies between reports (14-
353 21 days). (Le Moal et al., 2002).

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

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

368

369 **Future research**

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

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

383

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388

389 **Conflict of interest:**

390 None of the authors (Wim Gaastra, Len J. A. Lipman) has a financial or personal relationship
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393

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606

607 **Figure Legends**

608

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

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

611

Fig.1
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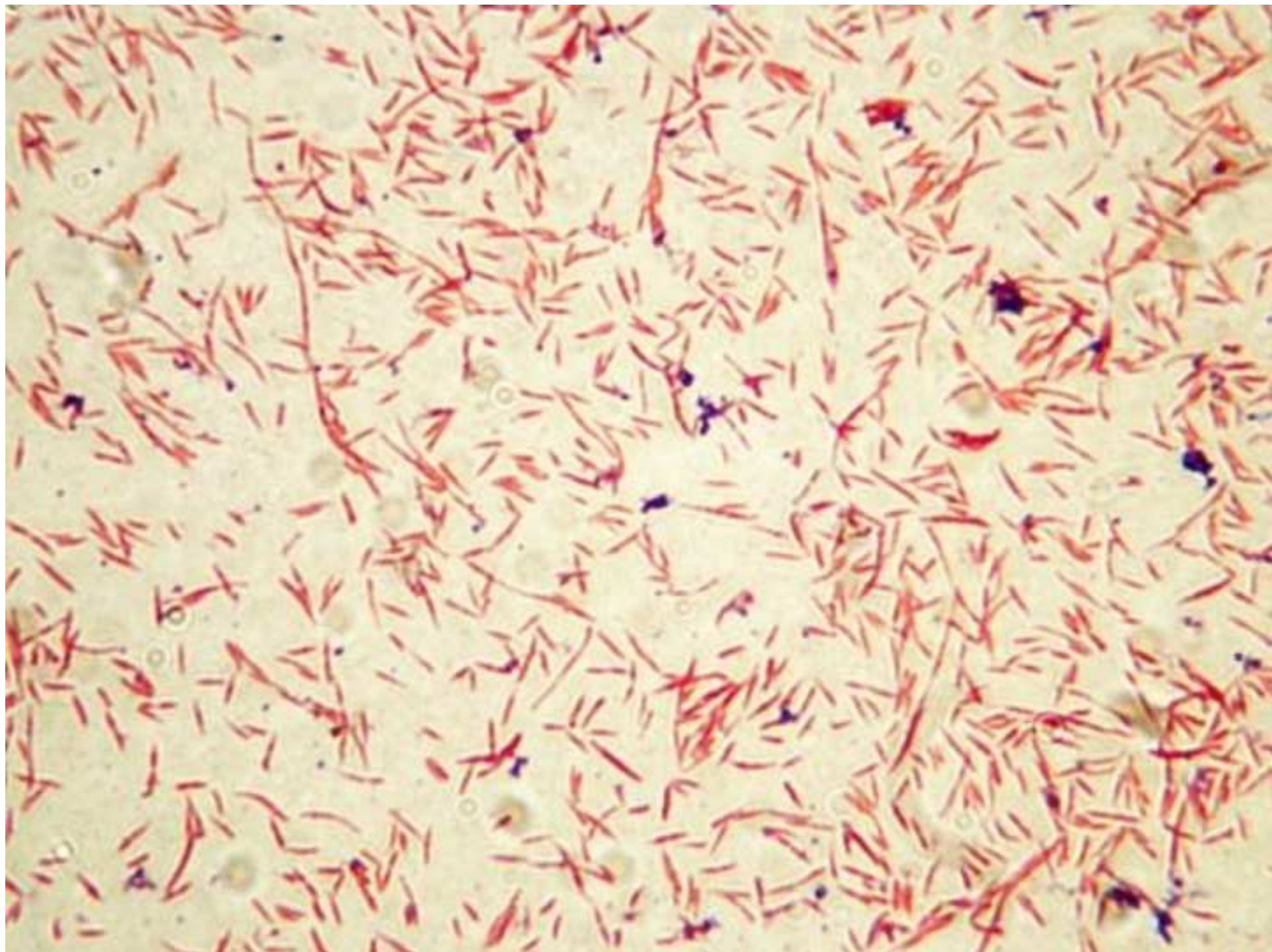


Fig.2

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