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1 **Title**: *Faux paw: Capnocytophaga canimorsus* endocarditis following a dog lick: A case report

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Data summary: No data was generated or reused in the research.

8 **Abstract:**

9 *Capnocytophaga canimorsus* is a fastidious Gram-negative bacterium found in the mouths of
10 dogs and cats. It is a rare cause of infective endocarditis, when it is often associated with dog
11 bites. We present a case of *C. canimorsus* infective endocarditis complicated by aortic
12 regurgitation and root abscess, in a patient with a history of previous infective endocarditis.
13 The patient underwent re-do aortic valve surgery with aortic valve replacement. Blood
14 cultures and 16S ribosomal ribonucleic acid gene amplification and sequencing from the
15 excised valve tissue confirmed *C. canimorsus* as the cause. The patient was treated with
16 beta-lactam antibiotics and discharged home. Rather than secondary to a dog bite, infection
17 most likely occurred due to a dog licking an open wound. It is important to remember that
18 dog contact, often perceived as innocuous, such as being licked, can be a source of serious
19 infection particularly in the context of an open wound. Over a third of households in the
20 United Kingdom own a dog as a pet. With *C. canimorsus* infections thought to be on the rise,
21 in part due to increased pet ownership, there is a need to ensure pet owners, particularly
22 those at risk of infections and chronic skin wounds are educated on such risks, and the
23 appropriate preventative steps.

24

25 **Key words**: *Capnocytophaga canimorsus*, infective endocarditis, dog lick, bacteraemia,

26 **Introduction:**

Capnocytophaga canimorsus is a fastidious Gram negative bacterium[1] which is part of the normal oral flora of dogs and cats. It can sometimes cause human infection, particularly in the immunocompromised,[1-2] and is a rare cause of infective endocarditis (IE), when it is often associated with dog bites[2-3]. We describe the case of a patient with no known immunocompromise presenting with *C. canimorsus* prosthetic aortic valve infective endocarditis complicated by moderate aortic regurgitation and root abscess.

Case Report:

A 55-year-old female attended the emergency department brought in by ambulance with fever, confusion, tachycardia and breathlessness. She had been experiencing night sweats for several weeks, associated with anorexia, chest pain, lethargy and weight loss. She reported feeling "not herself" for months, suffering panic attacks and tremors described as cold, shaking episodes.

She had a significant past medical history of rheumatic fever in childhood and a previous episode of culture-negative native aortic valve infective endocarditis with a suspected aortic root abscess, requiring surgical repair of the aortic root and valve (via patch)39 years prior to presentation. This had been complicated by an embolic stroke, with residual limb weakness, and post-stroke epilepsy. She lived alone with her dog.

Clinical assessment identified an ejection systolic murmur over the aortic area, no early diastolic murmur and new atrial fibrillation. Clinical biochemistry revealed anaemia (Hb 89g/L, reference range: 115 – 160g/L), hypo-albuminaemia (24g/L, reference range: 35 – 50g/L) and raised inflammatory markers: C-reactive protein 126 (reference range: <10mg/L) and white blood cell count 15.15 x 10*9/L (reference range: 4 – 11 x 10*9/L) (Table 1). She was treated as having probable prosthetic aortic valve infective endocarditis and initially received empirical flucloxacillin and gentamicin.

Trans-oesophageal echocardiography (TOE) identified severe aortic regurgitation, a large vegetation on the non-coronary cusp of the aortic valve and a thickened aortic root with an echo-free space, suggestive of an aortic root abscess (Figure 1). This confirmed the diagnosis of prosthetic valve infective endocarditis (PVIE).

Peripheral blood cultures (three sets) taken on the day of admission flagged positive after 3 days with growth in both the aerobic and anaerobic bottles. The morphology on the Gram stain was described as 'possible clusters of fine Gram negative bacilli'. There was persistent fever, accompanied by static C-reactive protein (CRP) and albumin levels (Table 1). The antibiotics were changed to treat for possible HACEK-related PVIE. Flucloxacillin was stopped and switched instead to cefotaxime, and the gentamicin was continued for its synergistic effect. On day 7 of the hospital admission (reflecting its fastidious nature), a matrix assisted laser desorption ionization-time of flight mass spectroscopy (MALDI-TOF-MS) result from growth on the initial blood culture identified *C. canimorsus*. The cefotaxime was changed to benzylpenicillin, and the gentamicin was stopped – an empirical choice based on the identification of the organism, whilst susceptibility results were awaited. Susceptibility

testing identified the *C. canimorsus* as: sensitive to penicillin, sensitive to cefotaxime; and resistant to gentamicin. Repeat blood cultures taken on day 3, flagged positive after 48 hours with growth additionally later identified as *C. canimorsus*. Further repeat blood cultures taken on days 4, 8 and 16 of admission demonstrated no growth at 5 days for the blood culture taken on day 4; and despite prolonged incubation (10 days) for the blood cultures taken on days 8 and 16. Each of the blood cultures were taken following an episode of pyrexia in the patient.

By day 12, there were ongoing symptoms of fever, anorexia, lethargy and breathlessness. The CRP had risen to 141mg/L and the albumin had fallen to 20g/L , suggestive of ongoing uncontrolled infection. The benzylpencillin was changed back to cefotaxime; and a decision was made for source control through surgical intervention.

On re-visiting the history, it transpired that the patient's dog had a habit of licking open wounds. There had been a fall at home in the weeks prior to admission, resulting in a superficial pre-tibial laceration, and the dog had licked it.

The patient underwent re-do cardiac surgery with a tissue aortic valve replacement. Aortotomy identified vegetations on the non- and left coronary cusps (the cusps with previous patch repair), and a normal-looking aortic root with no evidence of abscess. There were no organisms seen on the Gram stain performed on the tissue from the aortic valve, and no growth from its culture. 16S ribosomal ribonucleic acid sequencing (16S PCR) from the excised valve tissue performed locally confirmed *C. canimorsus* with 99.9% similarity. There was a marked clinical improvement post-operatively. The patient's appetite and energy levels returned to baseline. There was no relapse of febrile illness, and the CRP had decreased to 46mg/L. She completed a 28-day total antibiotic course and was discharged home.

Discussion:

C. canimorsus is a rare cause of IE, with the literature comprising largely of case reports[2,4]. Though case numbers are small, *C. canimorsus* infective endocarditis typically presents with fever, and with sepsis in approximately a third of cases[2]. This is consistent with our case; and it is interesting to note that the patient's reported 'panic attacks' and 'tremors' were more than likely rigors. Invasive infection caused by *C. canimorsus* is seen more often in settings of immunosuppression and asplenia (anatomical or functional e.g., in the context of alcohol excess). This was not the case in our patient, which was unusual.

C. canimorsus infective endocarditis appears to affect the aortic valve most commonly[2]; and is typically associated with dog bites[5]. However, as with our case, it is important to remember that dog contact perceived as seemingly innocuous, such as being licked, can be a significant source of infection particularly in the context of an open wound acting as a port of entry. Over a third of households in the United Kingdom own a dog as a pet[6-7]. With *C. canimorsus* infections thought to be on the rise in part due to increased pet ownership[2],

there is a considerable safety benefit to be had in ensuring pet owners are educated on such risks, and the appropriate preventative steps.

The Gram stain appearance of the organism grown from the initial blood culture was notably unusual, in keeping with *C. canimorsus* being an organism uncommonly encountered. Consistent with its recognised fastidious nature[4], it was not an easy organism to grow, posing challenges in its recognition for the laboratory. The appearance on the initial Gram stain was from the aerobic bottle (having flagged positive nearly 12 hours before the anaerobic bottle) and it was difficult to interpret. Multiple agar plates were set up to cater for a broad range of potential organisms. No organisms were seen on the Gram stain from the anaerobic bottle the following day, and there was no growth from the aerobic bottle either. Both bottles and the agar plates were re-incubated, with a plan for terminal subculture at 10 days (it was at day 7 that there was a positive MALDI-TOF-MS result). This highlights just how easily *C. canimorsus* can be potentially missed or misidentified, and the utility and importance of prolonged incubation of cultures for such organisms.

There were several additional peripheral blood cultures taken during the admission that demonstrated no growth even with prolonged culture, despite recurrent pyrexia in the patient. This may have been the result of a combination of antibiotic exposure throughout the admission, and the fastidious nature of *C. canimorsus*[4].

Antimicrobial susceptibility was inferred using reference data including pharmacokinetic and pharmacodynamic cut-off values in guidance provided by the European Committee on Antimicrobial Susceptibility Testing in cases where clinical breakpoints are not available[8]. MALDI-TOF-MS of the bacterial culture, and 16S PCR from the excised valve tissue played a key role in the identification and confirmation of the diagnosis, consistent with that documented in the literature[2]. The ability for the 16S PCR testing to be performed in-house facilitated more timely confirmation of the diagnosis of this uncommon fastidious organism. *C. canimorsus* infective endocarditis is commonly treated with aminoglycoside and beta-lactam antibiotics[2]; and the management of our patient was in alignment with this; although it was interesting and unusual to note the resistance to gentamicin on antimicrobial susceptibility testing.

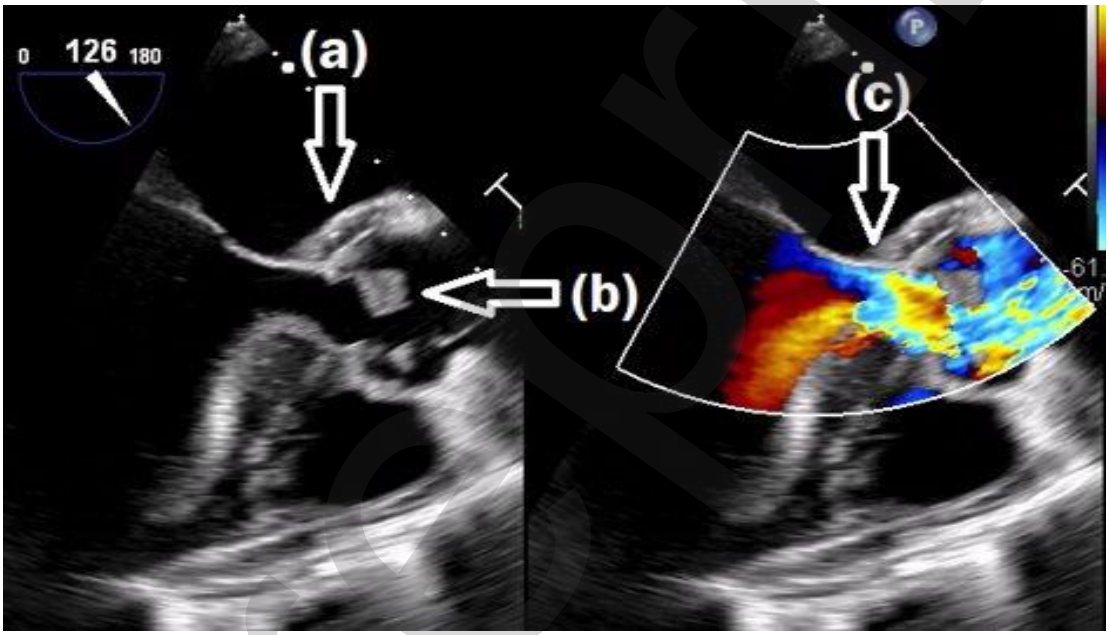
Conclusion:

This case highlights *C. canimorsus* as a rare but important cause of prosthetic valve infective endocarditis[4]. Importantly, it emphasises that *C. canimorsus* infective endocarditis can occur from canine contact other than bites (licking in this case)- contact that may be perceived as harmless by pet owners. It is important as clinicians, that we enquire about this during history-taking in similar such presentations. The case also reinforces the importance of ensuring pet owners are aware of the risks, and the patient safety benefit in doing so.

Table 1: Trend in laboratory blood results over the course of the hospital admission

Day of hospital admission *(Reference range)*	Laboratory blood results			
	Haemoglobin *(115 – 160 g/L)*	White blood cell count *(4 – 11 x 10*9/L)*	C-reactive protein *(<10mg/L)*	Albumin *(35 – 50 g/L)*
0	89	15.15	126	24
4	86	11.26	126	24
7	No result available	No result available	128	20
10	83	7.68	141	No result available
22 (one day post-surgery)	91	6.75	46	26
28 (one-week post-surgery)	109	6.41	No result available	27

Figure 1: Echocardiogram image showing (a): root abscess, (b) vegetation and (c) aortic regurgitation



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Dear Reviewers,

Thank you very much for taking the time to review the case report, *Faux paw: Capnocytophaga canimorsus* endocarditis following a dog lick: A case report. Responses to the comments are enclosed in the table below.

Comment	Response
Line 11: no need to include "C. canimorsus" in parentheses. Call it Capnocytophaga canimorsus once, then C. canimorsus thereafter with no need for parentheses. Line 29: as above	Amended *'Capnocytophaga canimorsus* is a fastidious Gram negative bacterium[1] which is part of the normal oral flora of dogs and cats.'
Line 32: remove parenthetical explanation of IE - no need to describe what it is	Amended '… is a rare cause of infective endocarditis (IE), when it is often associated with dog bites'
Lines 50, 65, 77: please include actual values (and normal ranges) for CRP, WBC, and albumin rather than vague language of 'up' and 'down' - could consider putting these values in a table with time points so that the reader can see the overall trends of the lab parameters	Amended – actual values are now included in the text and in Table 1. 'Clinical biochemistry revealed anaemia (Hb 89g/L, reference range: 115 – 160g/L), hypo-albuminaemia (24g/L, reference range: 35 – 50g/L) and raised inflammatory markers: C-reactive protein 126 (reference range: <10mg/L) and white blood cell count 15.15 x 10*9/L (reference range: 4 – 11 x 10*9/L) (Table 1).'
Line 51 (and throughout): can the authors clarify if this is indeed prosthetic value infective endocarditis (PVIE)? If so, it should be referred to as PVIE since this is a different entity (with different management) than native valve IE (NVIE).	Amended – this was prosthetic valve infective endocarditis, and has now been referred to as such. 'This confirmed the diagnosis of prosthetic valve infective endocarditis (PVIE).'
Line 63: what were the susceptibilities from the laboratory? was it found to be pen-sensitive? was cefinase performed? was the change to penicillin empiric based on the ID of the org or changed based on the antibiogram?	Amended – susceptibilities included. Cefinase was not performed therefore this has not been included. 'The cefotaxime was changed to benzylpenicillin, and the gentamicin was stopped – an empirical choice based on the identification of the organism, whilst susceptibility results were awaited. Susceptibility testing identified the *C. canimorsus* as: sensitive to penicillin, sensitive to cefotaxime; and resistant to gentamicin.'
Line 63, 66 and 78: did the gent continue? for how long? the entire course? was it ongoing during all of the beta-lactam changes?	Amended – as per the above
Line 72: was there a gram stain performed on the tissue? would be interesting to note that here, and provide a photo if possible.	Amended 'There were no organisms seen on the Gram stain performed on the tissue from the aortic valve, and no

	growth from its culture.'
General: were there any follow-up blood cultures done? positive/negative? If so, when were they drawn in relation to the initial cultures and the change in antibiotics?	Amended 'Further repeat blood cultures taken on days 4, 8 and 16 of admission demonstrated no growth at 5 days for the blood culture taken on day 4; and despite prolonged incubation (10 days) for the blood cultures taken on days 8 and 16. Each of the blood cultures were taken following an episode of pyrexia in the patient.'
General: did the patient have a spleen? functional asplenia? this would be worth highlighting given the organism	Amended 'Invasive infection with C. canimorsus is seen more typically in settings of immunosuppression and asplenia (anatomical or functional e.g., in the context of alcohol excess). This was not the case in our patient, which was unusual.'
It could be strengthened slightly by commenting on laboratory recognition challenges, as this fastidious organism can be easily missed or misidentified, and by mentioning whether antimicrobial susceptibility testing was performed or inferred from reference data to contextualise the therapeutic approach. A short note on whether molecular testing was conducted locally or through a reference centre would also add practical value.	Amended 'Consistent with its recognised fastidious nature[4], it was not an easy organism to grow, posing challenges in its recognition for the laboratory. The appearance on the initial Gram stain was from the aerobic bottle (having flagged positive nearly 12 hours before the anaerobic bottle) and it was difficult to interpret. Multiple agar plates were set up to cater for a broad range of potential organisms. No organisms were seen on the Gram stain from the anaerobic bottle the following day, and there was no growth from the aerobic bottle either. Both bottles and the agar plates were re-incubated, with a plan for terminal subculture at 10 days (it was at day 7 that there was a positive MALDI-TOF-MS result). This highlights just how easily *C. canimorsus* can be potentially missed or misidentified, and the utility and importance of prolonged incubation of cultures for such organisms.' 'Antimicrobial susceptibility was inferred using reference data including pharmacokinetic and pharmacodynamic cut-off values in guidance provided by the European Committee on Antimicrobial Susceptibility Testing in cases where clinical breakpoints are not available[8].'
Literature analysis is however weak and should be revised to give a better background to some of the peculiarities of this case report The explanation about the negative peripheral cultures is also shallow and presumptive To what extent are the conclusions supported by the data?	Amended – the discussion has been expanded to explore the peculiarities of the case, including patient factors e.g. the lack of any asplenia, and laboratory recognition challenges (as detailed above).

Reviewer 2: Partially support	
Please upload figures as separate, high resolution, editable files. Acceptable file types are PDF, GIF, TIFF, EPS, JPEG, PNG, and PPT.	Amended – Figure 1 has been removed from the main manuscript document, into a separate file

Thank you for your consideration of this manuscript.

Sincerely,

Dr Jonathan Sandoe and Dr Winifred Garr