## Title
Capnocytophaga canimorsus Sepsis With Associated Thrombotic Thrombocytopenic Purpura



## Journal
The American Journal of the Medical Sciences, 345(1)

## ISSN
0002-9629

## Authors
Ma, Andrew
Goetz, Matthew Bidwell

## Publication Date
2013

## DOI
10.1097/maj.0b013e318262db1a

Peer reviewed

# *Capnocytophaga canimorsus* Sepsis with Associated Thrombotic Thrombocytopenic Purpura

Andrew Ma, MD[1,2] and Matthew Bidwell Goetz, M.D[2,3]

[1] Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, United States

[2] Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States

[3] Infectious Diseases Section, Department of Medicine, VA Greater Los Angeles Healthcare System, Los Angeles, CA, United States

Keywords: Zoonoses, thrombotic thrombocytopenic purpura, *Capnocytophaga*, sepsis,

Running title: *C. canimorsus* Sepsis Associated with TTP

Communicating author

Andrew Ma, MD
8700 Beverly Boulevard, Room 5512
Los Angeles, CA 90048
Email: Andrew.Ma@cshs.org
Telephone: 551-404-2986
Fax: 310-423-2574

Alternate author

Matthew Bidwell Goetz, M.D.
Chief, Infectious Diseases Section (111-F)
VA Greater Los Angeles Healthcare System
11301 Wilshire Blvd.
Los Angeles, CA 90073
Tel: 310-268-3015
Fax: 310-268-4928
Email: matthew.goetz@va.gov

**Abstract**

Capnocytophaga canimorsus, a bacterium commonly transmitted via dog bites, is known to cause sepsis in immunocompromised patients. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome are rare complications of infection. We present a case of C. canimorsus sepsis and thrombotic thrombocytopenic purpura in an asplenic patient and review the relevant literature.

## Introduction

*Capnocytophaga canimorsus*, a pathogen commonly associated with dog bites, is a well-known cause of severe sepsis in asplenic patients. Infections with *C. canimorsus* have also rarely been associated with thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). Cases of *C. canimorsus* infection are increasing while the organism may still be difficult to identify and may be under identified [1]. At the same time, the diagnostic criteria for TTP are not precise and untreated TTP carries high mortality. Therefore a high level of awareness must be maintained to diagnose and treat both *C. canimorsus* and TTP. Herein, we present a case of *C. canimorsus* infection associated with TTP and review the relevant literature.

## Case Report

A 56 year old male presented with progressive fatigue, gait instability, intractable nausea and vomiting five days after sustaining a superficial facial laceration by his dog's teeth. He denied any fevers, chills, headache, diarrhea, abdominal pain, bleeding, or bruising. Past medical history was notable for a motor vehicle accident 22 years ago resulting in a ruptured spleen requiring splenectomy. He denied any active or past alcohol use. Vital signs demonstrated blood pressure of 80/55 and heart rate of 104 beats per minute. The physical exam was significant for 2 small, superficial lacerations on the patient's nose without surrounding signs of infection, a well healed midline abdominal scar, and dry mucous membranes. There were no abnormal pulmonary, cardiovascular, dermatological, or neurological findings. On presentation, platelets were 8 K/μL and the serum creatinine was 5.45mg/dL; six months prior, the platelets and creatinine had been 292 K/μL and 0.82 mg/dL, respectively. Coagulation parameters were within normal limits,

fibrinogen was elevated, and there was no leukocytosis or anemia on admitting laboratory data (Table 1). Recent HIV testing was negative.

After initial fluid resuscitation, the patient developed fever to 102F, altered mental status and hypoxic respiratory failure requiring intubation. Chest radiograph showed pulmonary vascular congestion. Head CT was normal. The patient was empirically treated with vancomycin and piperacillin-tazobactam. Within 48 hours, two sets of blood cultures grew filamentous gram-negative rods. Capnocytophaga canimorsus was suspected and antibiotics were changed to ampicillin-sulbactam. A transthoracic echocardiogram showed no evidence of endocarditis. Further labs showed progressive anemia (hemoglobin 10.4 g/dL), slight hyperbilirubinemia (total bilirubin 1.5 mg/dL), and few schistocytes on peripheral blood smear. A presumptive diagnosis of TTP was made and he was treated with prednisone 1 mg/kg per day plus 3 days of plasma exchange. With these measures, the patient defervesced, blood pressure normalized, renal function improved, and platelet count recovered. Unfortunately the patient's hospital course was complicated by ventilator associated pneumonia, for which he was treated with piperacillin-tazobactam. In total, the patient received 16 days of antibiotics and was discharged in good condition.

**Discussion**

*Capnocytophaga canimorsus* are fastidious, capnophilic, facultative anaerobic, gram-negative fusiform bacteria closely related to *Fusobacterium* and *Bacteroides* species. *C. canimorsus* is found as part of the oral flora of dogs and, less commonly, cats. The bacterium is of low virulence. Risk factors for infection are classically asplenia, alcoholism, and

immunosuppression. Infection commonly takes the form of sepsis, although localized infections such as meningitis and endocarditis also occur. Onset of symptoms can range from 1-8 days and include fever, chills, myalgia, malaise, vomiting, diarrhea, abdominal pain, and headache [1, 2, 3]. Overall mortality is about 30%.

There are numerous antibiotic options for treatment. While other Capnocytophaga species have been reported to produce beta-lactamase, this has not been found in *C. canimorsus* [4]. Active antibiotics for *C. canimorsus* include penicillin, ampicillin, beta-lactam/beta-lactamase combinations, third-generation cephalosporins, imipenem, clindamycin, linezolid, tetracyclines, chloramphenicol, and fluoroquinolones [5].

Our patient was asplenic and exhibited features of TTP without the dysregulation of coagulation characteristic of disseminated intravascular coagulation (DIC). This is unusual since *C. canimorsus* infections are more commonly associated with DIC, with TTP being rarely seen. In three reviews of *C. canimorsus* infections, no instances of TTP were reported [1, 2, 3]. In total, we found 4 cases of TTP and 2 cases of HUS associated with *C. canimorsus* infection in the English language literature (Table 2) [6, 7, 8, 9, 10].

HUS and TTP are overlapping syndromes that can be difficult to distinguish because they share the same diagnostic criteria of microangiopathic hemolytic anemia and thrombocytopenia. Though renal failure, fever, and neurological abnormalities may or may not be seen with either syndrome, the presence of these features is traditionally characteristic of TTP [11]. The pathophysiology of TTP is not completely understood, but studies highlight a deficiency in the

von Willebrand Factor (VWF) cleaving protease, ADAMTS13. A deficiency of ADAMTS13 activity leads to the accumulation of large VWF multimers that activate platelet aggregation causing microvascular thrombi [11, 12]. Treatment with plasma exchange has decreased the mortality due to TTP from 90% to 22% [13].

It is unclear if TTP in C. canimorus infections is attributable to a characteristic of the organism or more generally to the resulting sepsis. It has been shown that sepsis itself can cause a decrease in ADAMTS13 activity and an increased release of large VWF multimers [12, 14]. Sepsis caused by various organisms can also be associated with a clinical diagnosis of HUS/TTP [13, 15].

Regardless of the underlying cause, it is apparent that TTP is associated with *C. canimorsus* infections. When the diagnosis of one is present, it is important to consider a diagnosis of the other in the proper clinical setting. *C. canimorsus* and TTP are each associated with significant mortality; therefore timely recognition and treatment can be critical to successful outcomes.

**Conflict of Interest**

None

**Acknowledgments**

We thank Oliver Caniga, MD for his assistance in gathering the data for this report

**References**

1. Janda JM, Graves MH, Lindquist D, Probert WS. Diagnosing Capnocytophaga canimorsus infections. Emerg Infect Dis. **2006**; 12:340-2.

2. Pers C, Gahrn-Hansen B, Frederiksen W. Capnocytophaga canimorsus septicemia in Denmark, 1982-1995: Review of 39 Cases. Clin Infect Dis. **1996**; 23:71-5.

3. Lion C, Escande F, Burdin JC. Capnocytophaga canimorsus infections in human: review of the literature and cases report. Eur J Epidemiol. **1996**; 12:521-33.

4. Gaastra W, Lipman LJ. Capnocytophaga canimorsus. Vet Microbiol. **2010**; 140:339-46.

5. Jolivet-Gougeon A, Sixou J, Tamanai-Shacoori Z, Bonnaure-Mallet M. Antimicrobial treatment of Capnocytophaga infections. Int J Antimicrob Agents. **2007**; 29:367-73.

6. Finn M, Dale B, Isles C. Beware of the dog! A syndrome resembling thrombotic thrombocytopenic purpura associated with Capnocytophaga canimorsus septicaemia. Nephrol Dial Transplant **1996**; 11:1839-40.

7. Scarlett JD, Williamson HG, Dadson PJ, Fasset R, Peel MM. A syndrome resembling thrombotic thrombocytopenic purpura associated with Capnocytophaga canimorsus septicemia. Am J Med. **1991**; 90:127-8.

8. Kok RH, Wolfhagen MJ, Mooi BM, Offerman JJ. A patient with thrombotic thrombocytopenic purpura caused by Capnocytophaga canimorsus septicemia. Clin Microbiol Infect. **1999**; 5:297-8.

9. Mulder AH, Gerlag PG, Verhoef LH, van den Wall Bake AW. Hemolytic uremic syndrome after capnocytophaga canimorsus (DF-2) septicemia. Clin Nephrol. **2001**; 55:167-70.

10. Tobe TJ, Franssen CF, Zijlstra JG, de Jong PE, Stegeman CA. Hemolytic uremic syndrome due to Capnocytophaga canimorsus bacteremia after a dog bite. Am J Kidney Dis. **1999**; 33:E5.

11. George JN. Thrombotic thrombocytopenic purpura. N Engl J Med. **2006**; 354:1927-35.

12. Claus RA, Bockmeyer CL, Sossdorf M, Losche W. The balance between von-Willebrand factor and its cleaving protease ADAMTS13: biomarker in systemic inflammation and development of organ failure? Curr Mol Med. **2010**; 10:236-48.

13. George JN, Vesely SK, Terrell DR. The Oklahoma thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) registry: a community perspective of patients with clinically diagnosed TTP-HUS. Semin Hematol. **2004**; 41:60-7.

14. Kremer Hovinga JA, Zeerleder S, Kessler P, et al. ADAMTS-13, von Willebrand factor and related parameters in severe sepsis and septic shock. J Thromb Haemost. **2007**; 5:2284-90.

15. Wang Z, Yu Z, Su J, Cao L, Zhao X, Ruan C. Sepsis-induced disseminated intravascular coagulation with features of thrombotic thrombocytopenic purpura: a fatal fulminant syndrome. Clin Appl Thromb Hemost. **2011**; 17:251-53.

**Table 1: Admission Laboratory Data**

| Laboratory Data | Reference Ranges |
|---|---|
| Hgb 15.1 g/dL | 13.3-17.7 g/dL |
| Wbc 8.9 K/µL | 4.5-11 K/µL |
| Plt 8 K/µL | 150-440 K/µL |
| Bun 82 mg/dL | 5-25 mg/dL |
| Cr 5.78 mg/dL | 0.66-1.28 mg/dL |
| PT 12.5 sec | 9.2-12.4 sec |
| PTT 22.2 sec | 24.8-38.8 sec |
| INR 1.2 | |
| Fibrinogen 651 mg/dL | 185-458 mg/dL |
| LDH 203 U/L | 87-165 U/L |

**Table 2: Review of case reports of *Capnocytophaga canimorsus* associated with thombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS)**

| | | Finn et al | Scarlett et al | Scarlett et al | Kok et al | Tobe et al | Mulder et al |
|---|---|---|---|---|---|---|---|
| Age/Sex | | 53 year old female | 72 year old male | 49 year old male | 47 year old male | 50 year old male | 66 year old male |
| Exposure | | Owned dog | Owned cat<br>Received cat scratches | None | Owned dog | Bitten by dog 1 day prior to admission | Bitten by dog a few days prior to admission |
| Risk factors/ Comorbidities | | Tobacco use | None reported | Splenectomy 15 years ago | Alcoholism | None reported | Diabetes mellitus<br>Hypertension<br>Hypercholesterolemia<br>Transient ischemic attack |
| Symptoms/Signs | | Fever<br>Headache<br>Neck stiffness<br>Arthralgia<br>Purpura<br>Confusion<br>Hypotension<br>Oliguria | Fever<br>Malaise<br>Rigors<br>Dyspnea<br>Tachycardia<br>Retinal artery occlusion<br>Splinter hemorrhage<br>Petechiae<br>Purpura<br>Melena<br>Hematuria | Fever<br>Vomiting<br>Diarrhea<br>Sweating<br>Rigors<br>Arthralgia<br>Productive cough<br>Tachycardia<br>Petechiae<br>Vasculitic lesions | Fever<br>Icterus<br>Abdominal pain<br>Dyspnea<br>Melena<br>Hematemesis<br>Confusion<br>Petechiae<br>Tachycardia<br>Tachypnea<br>Anuria | Fever<br>Arthralgia<br>Oliguria | Fever<br>Malaise<br>Chills<br>Vomiting<br>Diarrhea<br>Hematemesis<br>Melena<br>Purpura<br>Hematomas<br>Anuria |
| Diagnostic Data | *Hemoglobin (g/dL)* | 14.5 | 10.4 | 14.5 | 6.6 | Hematocrit 30% | 10.1 |
| | *WBC (K/µL)* | 11.3 | 2.8 | 10.7 | 17.5 | 15.9 | 12.5 |
| | *Platelets ( K/µL )* | 27 | 8 | 26 | <10 | 9 | 2 |
| | *BUN (mg/dL)* | 32 | 106 | 37 | 248 | 143 | 128 |
| | *Creatinine (mg/dL)* | 0.86 | 0.27 | 1.16 | 1.27 | 10.9 | 8.57 |
| | *Coagulation parameters* | INR 1.9 | PT & PTT normal | PT & PTT normal | PT & PTT normal | PT 12.4 sec<br>PTT 19.3 sec | No information |
| | *Fibrinogen (mg/dL)* | 470 | 600 | >500 | Normal | 468 | 730 |
| | *Total Bilirubin (mg/dL)* | 1.4 | No information | No information | 27 | 3.2 | 1.6 |
| | *Lactate Dehydrogenase (U/L)* | No information | 960 | No information | 2800 | 3102 | 3596 |
| Anatomic Pathology | | + schistocytes | + schistocytes | TTP diagnosed with skin biopsy | + schistocytes | + schistocytes | + schistocytes |
| Diagnosis | | TTP | TTP | TTP | TTP | HUS | HUS |
| Treatment | | Benzylpenicillin<br>Netilmicin<br>High dose steroids<br>Plasma exchange<br>Hemofiltration | Gentamicin<br>Flucloxacillin<br>Penicillin<br>Prednisolone<br>Plasma exchange | Imipenem | Amoxicillin/clavulanate<br>Ofloxacin<br>Plasma exchange<br>Hemodiafiltration | Amoxicillin/clavulanate<br>Plasma exchange | Cefuroxime<br>Metronidazole<br>Amoxicillin/clavulanate<br>Plasmapheresis<br>Hemodialysis |
| Outcome | | Survived to discharge | Improved | Improved | Survived to discharge | Survived to discharge | Improved |