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Case Report

Septic shock due to *Capnocytophaga canimorsus* treated with IgM-enriched immunoglobulin as adjuvant therapy in an immunocompetent woman

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Background

Capnocytophaga canimorsus (*C. canimorsus*) belongs to the family Flavobacteriaceae. It is a facultative anaerobic Gram-negative bacillus and belongs to the normal oral microbiota of some mammals, such as cats and dogs. Transmission to humans can occur through the skin after skin abrasion caused by a scratch or a bite.[1] Based on polymerase chain reaction (PCR) analysis, *C. canimorsus* is present in saliva in 70%-74% of dogs and 55%-57% of cats.[2] The estimated incidence of *C. canimorsus* infections is low at 0.5-0.6 per million population,[3] however, another retrospective study showed a prevalence of 4.1 cases per million.[4] This discrepancy might be due to the choice of diagnostic criteria. The initial clinical manifestation of *C. canimorsus* infections is not specific, and their onset can be from 1 to 8 days after contact with an animal. Infections vary in their clinical manifestation from harmless localized skin infections to severe invasive infections resulting in septic shock. Invasive infections are rare and occur primarily in immunocompromised patients (e.g., splenectomy, alcoholism, smoking, corticosteroid therapy, and hemato-oncological diseases). Some case reports describe invasive infections in immunocompetent patients that led to poor outcomes with mortality rates above 30%.[5]

The interaction between the immune system and *C. canimorsus* is not fully elucidated. *C. canimorsus* is enveloped by capsular polysaccharides, which affect the host-pathogen interaction, leading to resistance to the innate immune-system.[6]

IgM-enriched immunoglobulins represent a potentially promising therapy in patients with sepsis and septic shock. They have many relevant mechanisms of action, including opsonization and enhancement of causal pathogens, neutralization of virulence factors, including bacterial endotoxins and exotoxins, and immunomodulation via interaction with complement factors, as well as prevention of hyper-inflammatory responses.[7]

Here, we describe the case of an immunocompetent woman with septic shock caused by an invasive infection with *C. canimorsus* who was treated with immunoglobulin-M-enriched immunoglobulin as adjuvant therapy.

Case Presentation

A previously healthy 51-year-old female employee of an animal shelter was admitted to a community care hospital with clinical signs of septic shock. From the external medical history, it was noted that 2 days prior, the patient had worked a shift in an isolation ward for viral rhinotracheitis in cats and dogs. Despite wearing protective clothing, the patient suffered superficial scratches on the entire right arm. On the day of admission, she had complained of coughing, shivering, and skin mottling and was later found unconscious by her husband. On physical examination, the patient presented with septic encephalopathy and profound centralization. Mechanical ventilation, intravenous antibiotics, volume resuscitation, and vasopressor therapy were started and she was transferred to the intensive care unit (ICU). The initial laboratory values showed a C-reactive protein (CRP) of 129 mg/L, and leukopenia (2.7×10^9/L). The partial thromboplastin time was >160 s, and the international normalized ratio was 2.07. The patient suffered an acute kidney injury (creatinine 2.06 mg/dL, blood urea nitrogen [BUN] 57 mg/dL) and signs of acute liver injury (aspartate aminotransferase [AST] 783 U/L; alanine aminotransferase [ALT] 390 U/L). Aerobic and anaerobic blood cultures were drawn. The brain and chest were inconspicuous. A combination of hydrocortisone (200 mg/day), high-dose meropenem (2g, 4 times a day) and linezolid (300 mg, 2 times a day) was initiated. During the following hours, the patient's clinical condition deteriorated and renal replacement therapy (RRT) was started. Two sets of blood cultures were positive for *C. canimorsus* 48 h after

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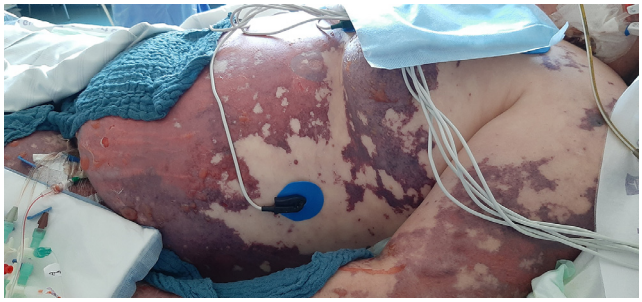


Figure 1. Lateral view of the patient's skin lesions upon admission to our intensive care unit.

admission. The antibiotic regimen was adjusted to meropenem and clindamycin (600 mg/day). The following day, the patient was transferred to our Department of Intensive Care Medicine at the University Hospital Hamburg Eppendorf. Here, the initial blood gas analysis showed a lactatemia of 17 mmol/L. Furthermore, the laboratory work showed increased inflammatory markers with leukocytosis of 16.2×10^6/L, procalcitonin (PCT) of 49.62 µg/L, CRP of 247 mg/L and interleukin (IL) - 6 of 3321 ng/L which peaked at 35,641 ng/L 2 days later. Due to massive disseminated intravascular coagulation (DIC), the patient had developed distal ischemic necrosis of the extremities. Additionally, petechiae and ecchymoses had progressed into purpura fulminans with secondary epidermolysis (Figure 1). The additional laboratory work showed a decrease of IgM (0.31 g/L), and we started the patient on Pentaglobin® with an initial dose of 28 g in the first 24 h followed by 7.5 g/day for the next 6 days until an IgM serum concentration above 0.8 g/L was reached. Figure 2 provides an overview of the time course of septic shock and the impairment of the different organ systems in association with the administration of Pentaglobin®. The further clinical course was complicated by secondary acute respiratory distress syndrome, secondary cholangitis, and regional infarction of the spleen, right kidney, and adrenal gland as well as multiple septic episodes with Stenotrophomonas maltophilia and vancomycin-resistant enterococci. On day 78, serum IgM had again decreased (0.32 g/L), and pentaglobin® administration was repeated for 2 days with an initial dose of 7.5 g and a second dose the following day with 15.0 g (Figure 2). After prolonged intensive care therapy (87 days), the patient's condition had markedly improved, and she could be transferred to an orthopedic rehabilitation center for reconstructive and plastic surgery.

Discussion

In this case of progressive septic shock due to invasive infection with *C. canimorsus*, we saw some peculiarities that may be important for clinical practice. Following the administration of immunoglobulins, we observed sustained clinical improvement. Patients with both a high inflammatory load and IgM deficiency might benefit from early therapeutic IgM-administration. To our knowledge, this is the first case report of severe septic shock due to *C. canimorsus* treated with adjunctive immunoglobulins enriched with IgM.

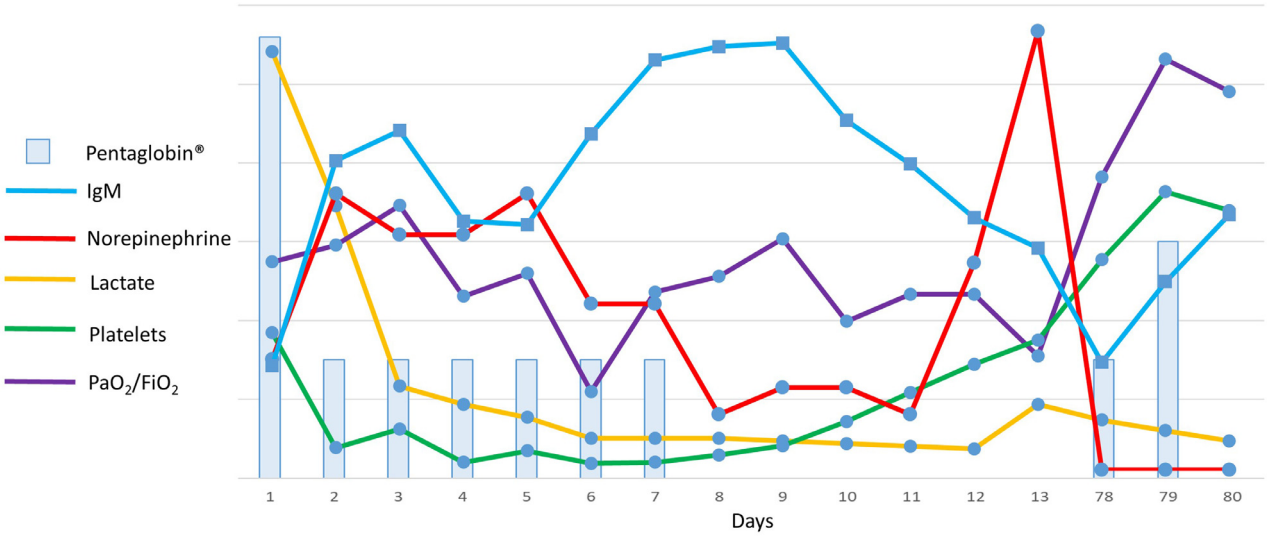
The interaction between the immune system and *C. canimorsus* is not fully understood. Several recent observations may help to understand the high pathogenicity of *C. canimorsus* infections in humans. In 2007, Shin et al.[8] characterized the inflammatory response of human and mouse macrophages to *C. canimorsus* infection. They found that *C. canimorsus* only modestly activates the signaling pathways that lead to the release of pro-inflammatory cytokines, chemokines, and nitric oxide (NO). Specifically, infected mouse macrophages did not release tumor necrosis factor (TNF)-α and IL-1. Furthermore, macrophages infected with live and heat-killed *C. canimorsus* 5 (Cc5), a strain isolated from a patient with fatal septicemia, did not release IL-6, IL-8, interferon-γ, macrophage inflammatory protein-1β, and NO. They suggest a deactivation of the toll-like receptor 4 (TLR4)-dependent nuclear factor kappa B (NF-kB) pathway.[8] This is consistent with Frieling et al.,[9] who described that whole blood produces lower levels of IL-1 and IL-6 in response to *C. canimorsus* compared to other Gram-negative bacteria. Furthermore, Gram-negative bacteria have a complex set of surface polysaccharides that include both lipopolysaccharides (LPS) and capsular polysaccharides (CPS) or exopolysaccharides (EPS). These polysaccharides contribute to pathogenicity of several bacteria as well as commensalism. The capsule has been shown to confer resistance to complement-mediated killing and phagocytosis. Furthermore, it was also reported that *C. canimorsus* has a deglycosylation system for mammalian proteins, including IgG, IgM, and surface glycoproteins from phagocytes.[10] These mechanisms may help the bacterium escape the local inflammatory response to contain the infection. As a result, the systemic inflammatory response to bacteremia causes vasodilatation and septic shock, while concurrent endothelial injury leads to disseminated intravascular coagulation.[11]

IgM and IgA-enriched immunoglobulins have many relevant mechanisms of action, including opsonization and enhancement of pathogen phagocytosis, neutralization of virulence factors, including bacterial endo and exotoxins, and immunomodulation through interaction with complement factors, as well as prevention of hyper-inflammatory responses.[7] There is not much evidence for the use of intravenous immunoglobulins (IVIGs) in patients with sepsis and septic shock. The Surviving Sepsis Campaign Panel has rated the therapeutic use as a "weak recommendation, low-quality evidence".[12] Most of the results are primarily based on the use of Pentaglobin® in clinical trials.[13] In a meta-analysis, Parks et al.[14] evaluated the effect of IVIG on mortality in streptococcal toxic shock syndrome treated with clindamycin. The mortality rate decreased from 33.7% to 15.7% in the IVIG group.

Furthermore, early administration of IgM-enriched immunoglobulins in addition to antimicrobial treatment was associated with a decreased risk of mortality from the ICU in patients with septic shock caused by any pathogen. These findings suggest that the timing of IgM-enriched immunoglobulin treatment may play a critical role in treatment efficacy in the efficacy of patients with hyperinflammation due to septic shock.[15]

Many studies have suggested the presence of clinical phenotypes in patients with sepsis and secondary analysis shows that patients could benefit from specific interventions.[13,16] Along this line, two distinct phenotypes may benefit most from treatment with immunoglobulins enriched with IgM and IgA. These groups can be divided into patients in a hyperinflammatory stage and patients in an immunosuppressed stage.[7,13]

Furthermore, several studies have described low concentrations of IgM, -G, and -A in patients with sepsis and septic shock.



Pentaglobin® dosage(g)	28.0	7.5	7.5	7.5	7.5	7.5	7.5	0	0	0	0	0	0	7.5	15.0	0
IgM (g/L)	0.31	0.92	1.01	0.74	0.73	1.00	1.22	1.26	1.27	1.04	0.91	0.75	0.66	0.32	0.56	0.76
Norepinephrine(μg/kg/min)	0.09	0.24	0.20	0.20	0.24	0.14	0.14	0.05	0.07	0.07	0.05	0.18	0.37	0	0	0
Lactate (mmol/mL)	16.0	10.1	3.2	2.5	2.0	1.2	1.2	1.2	1.1	1.0	0.9	0.8	2.5	1.9	1.5	1.1
Platelets (10^9/L)	131.0	21.0	39.0	7.0	18.0	6.0	7.0	14.0	23.0	46.0	74.0	101.0	124.0	201.0	266.0	248.0
PaO_2/FiO_2(mmHg)	199.0	215.0	253.0	166.0	188.0	74.7	170.0	185.0	221.0	142.0	168.0	168.0	109.0	280.0	393.0	362.0

Figure 2. Laboratory and clinical parameters (norepinephrine, IgM, lactate, platelets, Horowitz index) over time and during IgGAM (Pentaglobin®) administration over 80 days. The red dotted line represents the reference lower value of IgM in blood.
IgGAM: Immunoglobulins G, A, and M; PaO_2/FiO_2: Partial pressure of oxygen/fraction of inspired oxygen ratio.

The mechanism of low concentration has not yet been elucidated. However, it has been suggested that it may be due to their reduced production or secretion due to immunosuppression, vascular leakage secondary to endothelial dysfunction, redistribution into inflamed tissues, over-utilization by the complement system, and excessive catabolism are among the suggestions.[7]

Lastly, regarding mortality, in the CIGMA study, a phase II randomized, placebo-controlled, double-blind trial of patients with severe community-acquired pneumonia, the efficacy and safety of an IgM-enriched immunoglobulin preparation (trimodulin) was assessed. Although the primary endpoint was not met, a *post hoc* analysis of a patient subset with high CRP/low IgM showed a relative mortality reduction of 68% after the administration of trimodulin.[17] Furthermore, different systematic reviews have concluded that the utility of IgM-enriched immunoglobulins in patients with sepsis or septic shock could be associated with a reduction in mortality. A recent meta-analysis by Cui et al.[18] that included 19 studies with a total of 1530 patients, showed that there was a significant reduction in mortality in the IgM- and IgA-enriched immunoglobulin group compared to the control group.

The Surviving Sepsis Campaign (SSC) recommends that appropriate routine microbiologic cultures should be obtained before starting antimicrobial therapy in patients with suspected sepsis or septic shock.[12] Management of a septic patient depends on the rapid identification of the pathogen. This is especially crucial when considering some very aggressive bacteria, such as *C. canimorsus*, and its high mortality from invasive infection resulting in sepsis and septic shock. Diagnosis and cultivation of *C. canimorsus* can be difficult due to the fact that it belongs to slow-growing bacteria. Unfortunately, isolation of the organism is only correctly performed in less than one-third of cases. performed 16S rRNA gene PCR and sequencing directly on blood samples have emerged as reliable diagnostic tools and have reduced the time to definitive diagnoses, which is especially important in patients with septic shock with negative blood cultures.[19]

Conclusions

C. canimorsus infection is an uncommon cause of severe infection that results in septic shock in immunocompetent patients. However, rapid diagnosis and therapy are crucial to increase the chance of survival and reduce the odds of a disastrous outcome. In our case, fast administration of targeted antimicrobial therapy next to adjuvant treatment with IgM-enriched IVIGs and corticosteroids improved the clinical condition of our septic patients.

Author Contributions

Josephine Braunsteiner prepared the data and drafted the manuscript. **Stephanie Siedler** led the clinical team. **Axel Nierhau, Dominik Jarczak** and **Stefan Kluge** supervised and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Ethics Statement

Ethical approval was not required for this study according to local/national guidelines. Written informed consent was obtained from the patient prior to publication.

Conflict of Interest

Axel Nierhaus and Stefan Kluge have received lecture honoraria and travel reimbursement from Biotest AG, Germany, during the last 5 years. All other authors report that they have no conflict of interest.

Data availability

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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