**ABSTRACT**

*Capnocytophaga* is a group of facultative anaerobic gram-negative bacteria present in the oral cavity of humans, dogs and cats, as part of their normal oral flora. Here, we described two cases of bloodstream infections (BSI) caused by *Capnocytophaga* in neutropenic autologous hematopoietic stem cell transplantation (auto-HSCT) patients with mucositis (Grade I and Grade III) identified by Maldi-Tof. They were successfully treated with β-lactam (meropenem and piperacillin-tazobactam). The species *C. sputigena* was confirmed by 16S rRNA gene sequencing in one patient. The review of literature showed that *C. ochracea* was the most frequent species causing BSI in auto-HSCT patients and that the patients usually presented mucositis and were neutropenic at the onset of the infection.

**KEYWORDS:** *Capnocytophaga*. Bloodstream infection. Hematopoietic stem cell transplantation.

**INTRODUCTION**

*Capnocytophaga* is a group of facultative anaerobic gram-negative bacteria, belonging to the *Flavobacteriaceae* family. These organisms are present in the oral cavity of humans, dogs and cats, as part of their normal oral flora. Up to now, there are nine *Capnocytophaga* species reported in human oral microbiota: *C. gingivalis*, *C. granulosa*, *C. haemolytica*, *C. leadbetteri*, *C. ochracea*, *C. sputigena*, *C. genospecies AHN8471*; while *C. canimorsus* and *C. cynodegmi* are described in the oral microbiota of dogs and cats. All the species have been reported as pathogens in humans.

*Capnocytophaga* spp. has been described as cause of bloodstream infections (BSI), both in immunocompetent and immunocompromised hosts. Although mucositis is very frequent during chemotherapy, up to now, few cases of BSI caused by *Capnocytophaga* have been reported in hematopoietic stem cell transplantation (HSCT) patients.

We described here two cases of *Capnocytophaga* BSI in autologous HSCT (auto-HSCT) patients at the Bone Marrow Transplantation Unit of Hospital das Clínicas of University of Sao Paulo observed in 2018, and we also reviewed the main aspects concerning this infection in the literature.
CASE REPORT

**Case 1**

A 23-year-old man who had been diagnosed with Hodgkin’s Lymphoma in 2015 with an IIA initial stage and refractoriness to multiple chemotherapy regimens was admitted to the bone marrow transplantation ward. The patient was submitted to an autologous stem cell transplantation (auto-HSCT) after a conditioning with CBV (cyclophosphamide-carmustine-etoposide).

The patient had a history of obesity grade III, with a body mass index (the weight in kilograms divided by the square of the height in meters) of 53.76 on the admission’s day, systemic arterial hypertension and onychomycosis in both feet. He lived with his parents and two younger brothers and had two dogs that were kept outdoors.

The patient was colonized by *K. pneumoniae* carbapenem-resistant and VRE, he had mobilized peripheral blood progenitor cells (PBPCs) during the chemotherapy with gemcitabine plus vinorelbine in March 2018 with 1,800 mcg of GCSF and collected 5.8 x 10^6 CD34+ cell per kg/body weight by a long-term hemodialysis catheter (permcath) that was preserved for the PBPCs infusion. During this hospitalization, he used prophylaxis against infections with a single dose of ivermectin, cotrimoxazole until D-1, fluconazole in the neutropenic period and acyclovir. On day +1 the patient complained of mouth pain due to grade II oral mucositis, even if he had been on laser prophylaxis daily. On day +2 he presented with low-grade axillary fever (37.8 ºC) and chills, so that blood and urine cultures resulted negative and the catheter was removed.

On day +7, the laboratory identified *Capnocytophaga* spp. from the peripheral veins using Maldi-Tof (BioMérieux, France, Crapone, France). The blood cultures from the peripheral veins yielded a gram-negative rod and on D+14 the species *Capnocytophaga* was removed in both patients and the species was confirmed by sequencing in one patient.

The most important clinical and microbiological characteristics of our case report and the review of cases in the literature are shown in Table 1.

**DISCUSSION**

We described two cases of BSI caused by *Capnocytophaga* in neutropenic auto-HSCT patients with mucositis, that were successfully treated with β-lactam (meropenem and piperacillin-tazobactam). The CVC was removed in both patients and the species *C. sputigena* was confirmed by sequencing in one patient.

Although *C. sputigena* is part of the human oropharyngeal microbiota, it has been reporting causing infections in neutropenic patients with mucositis. *Capnocytophaga sputigena* BSI has been described as well in non-neutropenic patients. A recent report described a patient with diabetes mellitus and gastric cancer that...
This report

Bonatti et al.6 C. sputigena bloodstream infection in hematopoietic stem cell transplantations

García-Cía et al.6 C. sputigena plus Escherichia coli

Table 1 - Clinical and microbiological characteristics of BSI by Capnocytophaga spp in HSCT patients described in the literature and in these two cases report.

| Articles | Isolated species | Site of infection | Underlying disease | Type of HSCT | Mucositis | Day of sepsis onset after HSCT | Risk factor for BSI | Treatment | Identification of bacteria | Outcome |
|----------|------------------|------------------|-------------------|--------------|-----------|-------------------------------|-------------------|-----------|-----------------------------|---------|
| Bilgrami et al.4 | Capnocytophaga sp | Blood stream infection | Hodgkin’s disease | Autologous HSCT | Yes | D+3 | Neutropenia | Gentamicin and clindamycin followed by ampicillin | API AN-Ident System (Analytic Products, Plainview, NY) | Discharged |
| Baquero et al.7 | C. ochraceae | Blood stream infection | acute myeloid leukemia | Autologous HSCT | Yes | D+2 | Neutropenia | Cefazidime, clindamycin followed by piperacillin and subsequently clindamycin | Morphology and the following biochemical reactions | Discharged |
| This report | Capnocytophaga sp | Blood stream infection | Hodgkin’s lymphoma | Autologous HSCT | Yes | D+5 | Neutropenia | Meropenem | MALDI-TOF | Discharged |
| This report | Capnocytophaga sp | Blood stream infection | Peripheral T-cells NOS | Lymphoma | Autologous HSCT | Yes | D+10 | Neutropenia | Piperacillin–tazobactam | MALDI-TOF 16sRNA sequencing | Discharged |

developed an infection by *C. sputigena*. It is a rare opportunistic pathogen that causes infection in HSCT patients. Here we described the first case of BSI caused by *C. sputigena* in an auto-HSCT patient. So far, *C. ochraceae* has been reported as the most frequent species causing BSI in this population of patients, mainly during neutropenia and in patients with mucositis. The two *Capnocytophaga*’s infections reported in this article illustrated the hazardous potential of this bacteria to cause BSI coinciding with the onset of mucositis, which represents the main portal of entry for this organism, particularly the *C. sputigena*, during the conditioning regimen for auto-HSCT. Moreover, our report highlights the importance of a good oral hygiene and the multidisciplinary team care procedures such as the laser prophylaxis in the peri-transplantation period. Interestingly, both patients had previous contact with dogs and presented mucositis as well. Thus, the species identification is essential to establish that the source of infection and in our patients it was probably the mucositis. Regrettably, we could identify the species by...
16S RNA sequencing as *C. sputigena* in only one patient. This is a limitation of our report as the species identification is key to implement infection control measures and patients care as the species can hypothesize the source of infection such as the animal contact.

Since there is no Clinical & Laboratory Standards Institute (CLSI) nor European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendation for susceptibility break points for this genus; the spectrum of antibiotics and the duration of treatment is based on clinical reports. Antimicrobial susceptibility of *Capnocytophaga* spp. using different methods have shown that clindamycin, linezolid, tetracycline, chloramphenicol, imipenem and β-lactamase inhibitor combinations displayed *in vitro* activities against this bacterium. In contrast, most strains are reported as resistant to polymyxin, fusidic acid, fosfomycin and trimethoprim. A recent study, however, demonstrated that a high proportion of *Capnocytophaga sputigena* isolates were β-lactamase-positive and that β-lactam-resistant isolates, resistant to amoxicillin, amoxicillin plus clavulanic acid and third generation cephalosporins, bore the β-lactamase genes bla*<sub>CfxA</sub>* or bla*<sub>CSP-1</sub>*. CSP-1 is a novel extended-spectrum β-lactamase produced by a clinical isolate of *C. sputigena*. Thus, it is important to highlight that *C. sputigena* carrying β-lactamase genes can be resistant to amoxicillin, amoxicillin plus clavulanic acid and third generation cephalosporins.

**CONCLUSION**

*Capnocytophaga sputigena* BSI can occur in auto-HSCT neutropenic patients with mucositis mainly during neutropenia and can be successfully treated with meropenem or piperacillin tazobactam. This report highlights the importance of *Capnocytophaga* species identification to guide the HSCT patients’ care as well as preventive measures during the peri-transplantation period.

**CONFLICT OF INTERESTS**

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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