**Case Report**

*Clostridium perfringens* bacteremia in an 89-year-old man with COVID-19 infection: Case report and brief literature review

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**Abstract**

We present the rare case of bacteremia caused by *Clostridium perfringens* in an 89-year-old rehabilitation center resident with COVID-19 infection and we review the literature regarding *C. perfringens* bacteremia, as well as the association between SARS-CoV-2 and *C. perfringens*.

**Keywords:** *Clostridium perfringens*; Bacteremia; SARS-CoV-2; COVID-19 infection.

**Introduction**

*Clostridium* species are spore-forming anaerobic gram-positive rod bacteria, that are considered important constituents of the human microbiome, but also important agents in invasive infections, including bacteremia. Clostridial bacteremia is the second most frequent anaerobic bacteremia, ranging from 0.12-2% of all blood culture isolates [1-5]. Among clostridium species, *Clostridium perfringens* is the most common species isolated from blood cultures [1-4]. *Clostridium perfringens* is normally part of the human gastrointestinal, genitourinary, and skin microbiota [6] but also a causative agent of skin and soft tissue infections, gas gangrene, myonecrosis, and liver abscess [7,8]. *C. perfringens* bacteremia is a rare clinical syndrome, accounting for less than 1% of all bloodstream isolates [1,9]. Although rare, *C. perfringens* bacteremia may be accompanied with high mortality rate, making it one of the most severe types of bacteremia [10].

**Case Presentation**

A 89-year-old male with a past medical history of atrial fibrillation and benign prostatic hypertrophy transferred to our hospital from a rehabilitation center, with an episode of atrial fibrillation with rapid ventricular response and COVID-19 infection. A day after the admission he presented with acute nausea and diarrhea, up to 3 green watery stools daily.
On admission, physical examination revealed him looking sick, emaciated and sometimes drowsy. He was oriented to place and to person but not to time. Vital signs demonstrated a blood pressure of 120/95 mm Hg, heart rate of 170 beats/minute, temperature of 37.4°C and oxygen saturation of 97% on room air. The cardiac examination revealed tachycardia, with normal heart sounds and no murmurs. His abdomen was soft and nondistended. The remainder of physical examination findings were normal. The performed ECG revealed an atrial fibrillation with rapid ventricular response, thus placing the patient under continuous electrocardiographic monitoring and later a decrease in heart rate was achieved pharmacologically with Digoxin and Lopressor in the emergency department. Because of the patient’s impaired level of consciousness, a brain CT scan was performed without pathological findings.

Complete blood count, comprehensive metabolic panel, urine, and blood cultures were done on admission. White blood cell was 9.64x10^3/mm^3 (NR: normal range 4-11x10^3/mm^3) with a left shift, while procalcitonin was slightly increased at 0.10 ng/ml (NR<0.08 ng/ml). Lactate dehydrogenase was 331 U/L (NR 125-220 U/L), troponin was 46.2 pg/ml (NR<34.2 pg/ml) and C-reactive protein was 9.5 mg/dl (NR <0.5 mg/dl). Total and direct bilirubin were also elevated at 2.21 and 1.04 mg/dl respectively (NR 0.2-1.2 mg/dl and 0.0-0.5 mg/dl respectively), indicating mild jaundice. D-dimer was elevated at 6.92 μg/mL (NR 0-0.5 μg/mL) and given the increased risk for thromboembolism a CT of the chest was obtained, which was negative for pulmonary embolism. The rest of his laboratory test results were within normal limits.

Empirical antibiotic treatment was initiated with intravenous piperacillin/tazobactam and remdesivir while the patient admitted to the infectious diseases clinic for further monitoring and treatment. The following days, a gradual and significant improvement of the patient’s clinical picture was observed.

Stool and blood cultures were requested. Stool specimen was tested for both glutamate dehydrogenase and toxins A/B of C. difficile by an enzyme immunoassay (EIA; C. DIFF QUICK CHECK COMPLETE, Alere/TechLab, Blacksburg, USA), which was negative.

Both sets of aerobic and anaerobic blood cultures (BACTEC Plus Aerobic, BACTEC Lytic Anaerobic, BD BACTEC™ FX40) yielded positive in 24 hours, and the initial Gram stain directly from the bottle revealed Gram-variable rods. The blood culture broth was sub-cultured onto the surface of Columbia (Columbia agar + 5% sheep blood; bioMerieux), chocolate agar (Chocolate agar + PolyViteX™, bioMerieux), and MacConkey agar, which incubated under aerobic and anaerobic conditions. The occurrence of anaerobic growth of Gram-positive boxcar-shaped rods on Gram stain (Figure 1), with negative catalase reaction and the phenotypic characteristic of the presence of double-zone hemolysis indicated the presence of Clostridia species. The microorganism was identified by mass spectroscopy as Clostridium perfringens with a 99.0% confidence value using the Vitek® MS system (bioMerieux) and also by MALDI TOF (Brucker, MS system) with a score value of 2.31.
Figure 1: The colonies of Clostridium perfringens in Blood agar plate are surrounded by a double-zone haemolysis, which consists of an inner clear zone and an outer hazy zone (yellow arrows). Gram stain of Clostridium perfringens.

Literature Review

A PubMed and Google Scholar search of the English-language literature was performed using the keywords “Clostridium perfringens”, “bacteremia”, “SARS-CoV-2” and “COVID-19”. The systematic review of the literature revealed 19 studies that have been published since 1969, describing cases of C. perfringens bacteremia (Table 1). The literature shows that C. perfringens is the most common species identified in the blood cultures of patients with clostridial bacteremia, representing between 21.7-71% of Clostridium species bacteremia [1-5,12,15,18-20]. According to the medical literature, the main risk factor for acquiring Clostridial bacteremia is malignancy [1-6,8,10,12-20] and male gender (summarized in Table 1). The percentage of males with clostridial bacteremia ranges from 27.3-88.2% [3-6,8,10-20]. Other risk factors for acquiring clostridial bacteremia include diabetes mellitus, older age, immunosuppression, haemodialysis, renal insufficiency, digestive surgery, chemotherapy, liver disease and Crohn’s disease [1-4,6,8,10,12,14,16,18-19]. Yang et al. reviewed 93 cases of Clostridium bacteremia and found that 25.8% of patients had hypertension [10], while Benjamin et al. reviewed 80 cases and found that 12% of patients with clostridial bacteremia had alcohol use disorder [19]. The mean age of patients with clostridial bacteremia ranges from 46-76 years, with leukemia patients being younger [3-6,8,10-21].

Regarding the association between C. perfringens bacteremia and SARS-CoV-2, the literature revealed one case of COVID-19 infection associated with quadruple bacterial infection including C. perfringens bacteremia [22]. The present case is the second in the medical literature linking those two pathogens and emphasizes the fact that SARS-CoV-2 impacts the human immunity and promotes co-infections with unusual pathogens like C. perfringens.
Table 1: Review of Clostridial bacteremia.

<table>
<thead>
<tr>
<th>Author</th>
<th>No cases of clostridium spp. bacteraemia/Study period</th>
<th>Clostridium perfringens (%)</th>
<th>Most common comorbidities (%)</th>
<th>Mortality (%)</th>
<th>Males (%)</th>
<th>Mean age</th>
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</table>
| Sarasoa et al. 2022 [12]    | 386/2014-2019                                         | 40.4                       | Malignancy (47%)
Recent digestive surgery (24.7%)
Immunosuppression (25%)                        | 26                      |                                             | 56                      | 76        |
| Yamamoto et al. 2020 [5]    | 40/2004-2018                                          | 60                         | Malignancy                                                                                   | 42.5          | 50.2      | 67.5     |
| Stabler et al. 2020 [4]     | 81/2010-2018                                          | 64.3                       | Cancer (45.7%)
Recent digestive surgery (24.7%)
Chemotherapy (23.5%)
Diabetes mellitus (22.2%)
Renal insufficiency (22.2%)                       | 31.4                      |                                             | 54.3                      | 61.4        |
Diabetes mellitus (25%)
Immunosuppressants (21.4%)
Recent surgery (17.8%)
Liver disease (14.2%)
Cholecystitis/cholelithiasis (14.2%)                       | 32.1                      |                                             | 67.8                      | 71.4        |
| Mållard et al. 2016 [8]     | 11                                                     | 100                        | Older age ≥65 (64%)
Diabetes mellitus (45%)
Malignancy (18%)                                       | 27                        |                                             | 27.3                      | 65.8        |
| Kim et al. 2015 [3]         | 114/2002-2012                                         | 35.6                       | Neoplasm (76.3%)
Gastrointestinal symptoms (73.7%)
Diabetes mellitus (14.9%)
Haemodialysis (5.3%)                                      | 26.3                      |                                             | 68.4                      | 58          |
| Shindo et al. 2015 [16]     | 33/2001-2013                                          | 100                        | Cancer                                                                                       | 15.2          | 57.6      | 75.6     |
| Yang et al. 2013 [10]       | 93/2002-2011                                          | 100                        | Renal insufficiency (49.5%)
Malignancy (41.9%)
Hypertension (25.8%)                                      | 26.9                      |                                             | 58.1                      | 70.7        |
| van Bunderen et al. 2010 [6]| 40/1990-2010                                          | 100                        | Haematological disorder (22.5%)
Pancreatic/gastric cancer (12.5%)
Diabetes mellitus (30%)                                      | 80                        |                                             | 55                       | 65          |
| Fujita et al. 2010 [17]     | 18/2001-2009                                          | 100                        | Hepatobiliary tract diseases
(gallbladder stones, hepatic carcinoma)                                         | 27            | 72.2      | 75       |
Diabetes mellitus                                         | 48            | 44        | 64       |
Hemodialysis  
Malignancy  
Crohn’s disease                                             | 30                        |                                             | NR                       | NR          |
Diabetes mellitus (19%)
Alcoholism (12%)                                               | 28                        |                                             | 59                       | 70          |
Diabetes mellitus (28.3%)
Malignancy (47.8%)                                             | 46                       |                                             | NR                       | NR          |

NR: Not reported, MIH: Massive intravascular haemolysis; Recovery rate.
Conclusion

*Clostridium perfringens* bacteremia, although relatively uncommon, is associated with high mortality due to advanced age and multiple comorbidities. The early recognition of this critical infection and early initiation of appropriate treatment are key factors of a positive outcome. **SARS-CoV-2 impacts human immunity and co-infections with unusual bacteria like *C. perfringens* should be considered in patients with COVID-19 infection.**

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**References**


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