Enfermedades Infecciosas y Microbiología Clínica 43 (2025) 58–59

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Letter to the Editor

Accidental intravenous probiotic injection in an immunocompromised patient: Implications and consequences

Administración accidental intravenosa de probióticos en un paciente inmunodeprimido: implicaciones y consecuencias

Dear Editor,

Upon reviewing the study conducted by Monnerat et al.,[1] on accidental intravenous probiotic injection in an otherwise healthy patient, we aim to contribute to the existing body of knowledge by presenting a similar scenario involving an immunocompromised individual. To our knowledge, the other published cases of bacteremia caused by *Bacillus clausii* are related to the oral administration of the probiotic.[2–7] Of these, four are related to the pediatric population[2–5] and two to the adult population.[6,7]

We present a 64-year-old male diagnosed with chemorefractory gastric lymphoma, who presented to our center for CAR-T cell therapy. While preparing the treatment protocol, the patient was urgently admitted on September 14th, 2022, due to gastrointestinal bleeding and a fever of 39 °C. A blood culture conducted during the diagnostic work-up revealed the presence of *B. clausii*. Analysis shows that it was susceptible to levofloxacin (CMI 0.38), vancomycin (CMI 0.75), linezolid and tedizolid (CMI 0.75). However, it was resistant to meropenem and erythromycin. Antimicrobial susceptibility was interpreted following EUCAST 2022 Clinical Breakpoints (V. 12.0).

Notably, the patient disclosed that he had been hospitalized in his home country (Ghana) on August 4th (Day 0), 2022, due to febrile neutropenia, which was treated with antibiotic therapy. Moreover, he started with profuse diarrhea, so that, he inadvertently received parenterally Enterogermina®.

Despite multiple courses of antibiotherapy (Table 1), bacteremia persisted. On September 23rd (Day 50), we conducted an echocardiogram, which did not reveal endocarditis. A whole-body PET-CT scan undergone October 7th (Day 64) demonstrated tumor progression and focal hyperenhancement of an ulcer in the upper limb, which corresponded to the site of the previous intravenous infusion of the probiotic. Subsequently, an ultrasonographic study performed one day later confirmed the presence of thrombophlebitis in the basilic vein. Given its potential as a spore production reservoir, surgical excision was promptly performed. The removed material revealed necrotic tissue in the hystological examination without any isolations in the microbiological cultures of the tissue. Moreover, the isolation of *B. clausii* in blood persisted after the material removal.

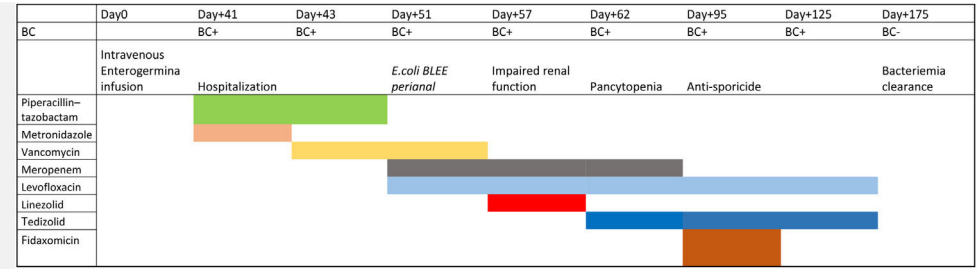
Since bacteriemia was still present, and according to Khatri AM et al.,[2] we decided to start with Fidaxomicin as an anti-sporicide, as previously reported.[2] However, our attempts to utilize this approach were unsuccessful due to the inability to detect *B. clausii* in feces. Stool cultures consistently yielded negative results, and it should be noted that antibiotics of this nature primarily exert a local action.

A subsequent whole-body PET-CT scan conducted on October 31st (Day 88) revealed tumor progression, with no evidence of any infectious involvement. The presence of persistent bacteremia ruled out the possibility of CART-cell therapy. Consequently, it was decided to administer conventional chemotherapy for the patient's underlying condition during their hospitalization period. This approach resulted in an improvement in the patient's clinical status.

The patient was discharged on December 7th (Day 125), with regular outpatient monitoring of his clinical condition and ongoing treatment with Levofloxacin and Tedizolid. In subsequent follow-up visits, although bacteremia persisted, the patient remained asymptomatic, and antibiotic therapy was continued without modifications.

On January 26th (Day 175), the patient was admitted with febrile neutropenia. During the entire follow-up period, the patient underwent periodic blood cultures, with a total of 27 blood cultures, all of which were positive. Interestingly, after the 27 positive blood cultures, no bacterial isolates were detected in the subsequent blood cultures. For each blood culture, 4 flasks (2 aerobic and 2 anaerobic)

Table 1
Clinical findings, blood culture (BC) and antibiotic therapy chronology.



https://doi.org/10.1016/j.eimce.2024.08.004

were submitted. The 2 aerobic flasks were positive with a positivity time of approximately 26 h. The identification method was by mass spectroscopy (Vitek-MS; bioMérieux).

The bacteremia was ultimately resolved after a prolonged duration of antibiotic therapy, lasting 175 days. During this period, the patient received CART-cell therapy for his underlying disease. Unfortunately, two months later, the patient died due to the progression of his oncologic condition.

Enterogermina® is an oral probiotic formulation containing 2 billion spores of *B. clausii. B. clausii* is an aerobic gram-positive spore-forming bacillus[8,9] known for its survival in the acidic environment of the stomach and colonize the intestine even in the presence of antibiotics. Previously, accidental intravenous injection of Enterogermina® has been reported once[1] in an otherwise healthy outpatient, resulting in bacteremia that resolved after 5 months. To gather additional information and potential unpublished cases, similar to Monnerat et al.[1] we reached out to Sanofi-Aventis, the company manufacturing the probiotic. However, the company could not provide specific treatment protocols beyond referring to the published case. Furthermore, they reported that no deaths have been associated with this administration error. In order to prevent future mistakes related to Enterogermina® administration, the company made modifications to the product labeling.

The accidental intravenous administration of Enterogermina® in an immunocompromised patient raises significant clinical considerations. This case highlights the potential risks associated with medication errors and emphasizes the importance of strict adherence to treatment protocols. Persistent and refractory bacteremia associated with intravenous administration of Enterogermina®, although rare, is a serious complication that could be mitigated by modifying its labeling or even its commercial presentation. In both the present case and the previously reported one, blood cultures remained positive for 5 months, necessitating the implementation of alternative therapeutic strategies.

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