Letter to the editor

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Use of fidaxomicin through a nasogastric tube for the treatment of septic shock caused by *Clostridium difficile* infection in a patient with oral cancer admitted to the Surgical Critical Care Unit

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Sir,

Clostridium difficile-associated disease is a clear example of the impact that modern medicine has on a bacterial species with pathogenic potential to develop it[1]. *C. difficile* infection (CDI) is mainly nosocomial, with 80% of cases being hospital-acquired in Europe[2]. Predisposing factors are related with alterations of intestinal microbiota (antibiotic treatments, proton pump inhibitors, chemotherapy and radiotherapy and intestinal stasis due to medication), environmental contamination (prolonged hospital stay and ICU stay), and host-related factors (age and presence of multiple comorbidities).

A 70-year female patient surgically intervened in November 2012 and further treated with chemotherapy and radiotherapy due to an epidermoid carcinoma of the mandible, was admitted to hospital on June 25th, 2013 for surgical resection of carcinoma recurrence. The patient presented several comorbidities (hypothyroidism, recurrent bronchitis episodes, hypertension, seizures…) and was taking proton pump inhibitors as part of her usual treatment. Tracheostomy, left segmental mandibulectomy, mandibular reconstruction using peroneal osteocutaneous flap, osteosynthesis with a reconstruction plate (KLS Martin) and arterial (left facial)-venous (left jugular) anastomosis was performed. Four days of intravenous amoxicillin/clavulanic acid (1000/125 mg/8h) was administered as surgical prophylaxis. The biopsy showed a 7 mm poor differentiated epidermoid carcinoma (pT4a stage, p16 overexpression) without vascular or perineural invasion.

On July 6th, the patient was surgically intervened to remove the peroneal osteocutaneous flap due to necrosis, performing an intraoral soft tissue reconstruction with a left pectoralis major myocutaneous flap and a mandibular reconstruction with a reconstruction plate. The patient was admitted in our Surgical Critical Care Unit due to acute respiratory insufficiency and sepsis, with leukocytosis (15.9 x 10^3/µL, 87.6% neutrophils), C reactive protein (CRP) of 156 mg/L and procalcitonin (PCT) of 2.17 ng/mL. Mechanical ventilation and intravenous treatment with meropenem (2g/8h) and daptomycin (10 mg/kg/day once daily) were initiated. Two days after, daptomycin was withdrawn, and linezolid (600 mg/12h) and amikacin (1g/24h) were administered for 3 days. The antibiotic regimen was maintained for a total of 6 days. On July 9th, the patient presented severe diarrhea, with leukocytosis (31.9 x 10^3/µL, 93.8% neutrophils), CRP of 77.9 mg/L and PCT of 29.8 ng/mL. Fecal samples were collected and sent to the laboratory for *C. difficile* specific testing. The patient required vasoactive support with noradrenalin at doses of 0.5 µg/kg/min. Two days after the onset of diarrhea, the microbiological laboratory reported positive *C. difficile* glutamate dehydrogenase antigen detection (C. diff quik chek complete, Alere Healthcare S.A., Barcelona, Spain), negative detection of toxin A & B (C. diff quik chek complete, Alere Healthcare S.A.) and PCR detection of the toxin B gene (GeneXpert, Izasa S.A., Barcelona, Spain). Intravenous antibiotics were then withdrawn and treatment with fidaxomicin was initiated. Due to the characteristics of the patient, drug administration through the nasogastric tube for enteral feeding was chosen. Twice daily, at the patient's bedside a tablet of fidaxomicin (200 mg) was crushed, mixed with water (20 mL) and administered with syringe through the nasogastric tube, reinitiating enteral nutrition (IMPACT, Nestlé Health Science, Spain) after drug administration. Diarrhea improved within 48h, and five days after initiating fidaxomicin treatment, vasoactive support was not needed. At the end of the 10-days fidaxomicin treatment analytical values were: leukocytes (5.4 x 10^3/mL), CRP (45.7 mg/L) and PCT (0.27 ng/mL). The patient was discharged from the Surgical Critical Care Unit 18 days after admission and remained asymptomatic with negative *C. difficile* antigen tests, 4, 6 and 8 weeks after the onset of *C. difficile* diarrhea.

Nosocomial diarrhea is an important problem in ICU patients, present in 40-90% patients after admission[3], and associated with hypoalbuminemia, enteral nutrition, intestinal ischemia, medications or infection. Among the later, the main cause is CDI[4], which in the ICU setting is one of the main causes of nosocomial infection[5] and considered a frequent adverse event in critical care patients[6].

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We describe a case of nosocomial CDI in a patient presenting multiple risk factors as age (70% patients with CDI are older than 60 years, and 52% >70 years[7]), a localized tumor previously treated with chemotherapy and radiotherapy, prolonged hospital stay, admission in the ICU, intake of proton pump inhibitors and multiple antibiotic exposure. Hospitalization (particularly in the ICU) is important because it brings together several risk factors, including exposure to antibiotics and *C. difficile* spores. Exposure to antibiotics is the most important modifiable risk factor, with prolonged or multiple drug administration presenting an increased risk[8,9]. Our patient had received broad-spectrum antibiotics (amoxicillin/clavulanic acid, meropenem, amikacin), linezolid and daptomycin for treatment of acute respiratory insufficiency and sepsis prior to the onset of diarrhea. Therefore, since the risk of CDI increases as the number of antibiotic compounds increases[9], the patient could be considered a highly risk patient for CDI, more even in the presence of other multiple risk factors.

Although vancomycin and fidaxomicin are the unique compounds approved by the Food and Drug Administration for the treatment of CDI, the guidelines of the Society for Healthcare Epidemiology of America/Infectious Diseases Society of America recommend metronidazole for mild to moderate initial episodes and vancomycin for severe or complicated initial episodes[10]. The recent update of guidelines for CDI treatment by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommend, when oral treatment is not possible, intravenous metronidazol 500 mg/8h plus enteral vancomycin 500 mg/6h for 14 days for the treatment of severe CDI[11]. However, a recent study comparing fidaxomicin and vancomycin in the treatment of CDI in patients with cancer has shown a significantly higher efficacy for fidaxomicin (with a five-fold higher odds ratio for clinical efficacy) with a significantly lower recurrence rate (2.6-fold lower recurrence rate) than vancomycin[12]. In addition, other studies showed significant superiority of fidaxomicin in reduction of recurrences in elderly patients (>75 years) regardless renal impairment[13,14]. Appropriateness of initial treatment is important in the ICU where CDI increases the length of stay[15] and mortality[16], mainly due to the subgroup of elderly patients[17] where prevalence of CDI is highly increasing[18,19] with a higher incidence of severe infection[20,21].

Since the patient had been maxillofacially intervened and she was on mechanical ventilation and enteral nutrition, treatment with fidaxomicin through a nasogastric tube was chosen based on a previously published clinical case with gastric administration in a child[22] and data supporting stability of crushed fidaxomicin tablets in water with high rates of recovery when passed through a nasogastric tube[23]. The patient was successfully recovered from the CDI episode and continued free of recurrences two months after.

To our knowledge this is the first case of an adult critically ill patient with a CDI episode and septic shock successfully treated with fidaxomicin through a nasogastric tube. The possibility of fidaxomicin administration through this route represents an important advantage in the critical care setting where susceptible elderly population with severe comorbidities is frequent and oral administration is not always feasible.

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