References

1. Chi TH, Hung CC, Chen RF, Yuan CH, Chen JC. Spontaneous retropharyngeal emphysema: a case report. Niger J Clin Pract. 2017;20:1213–5, http://dx.doi.org/10.4103/njcp.njcp_3_16. PMID: 29072250.
2. Haro Diaz AM, Toledo del Castillo B, García Morín M, Vázquez López P. Enfisema retrofaríngeo espontáneo, una entidad rara a considerar [Spontaneous retropharyngeal emphysema: a rare clinical entity]. An Pediatr (Barc). 2014;81:e66–77, http://dx.doi.org/10.1016/j.anpedi.2014.04.021. PMID: 25034192.
3. Cho DY, Aaron GP, Shepard KG. Spontaneous Retropharyngeal and Mediastinal Emphysema. Clin Exp Otorhinolaryngol. 2016;9:178–81, http://dx.doi.org/10.21053/ceo.2014.01543. PMID: 27090269; PMCID: PMC4881326.
4. Marín Garrido C, Garzón Calles JA, Naya Gálvez MJ, Esteban Revenga JM, López García C. Neumomediastino y enfisema cervical espontáneos con alteración en la voz [Spontaneous cervical emphysema and pneumomediastinum with voice disorders]. Acta Otorrinolaringol Esp. 2003;54:151–6, http://dx.doi.org/10.1016/s0001-6519(03)78398-8. PMID: 12802992.
5. Lee CC, Chen TJ, Wu YH, Tsai KC, Yuan A. Spontaneous retropharyngeal emphysema and pneumomediastinum presented with signs of acute upper airway obstruction. Am J Emerg Med. 2005;23:402–4, http://dx.doi.org/10.1016/j.ajem.2005.02.011. PMID: 15915427.
6. Macklin MT, Macklin CC. Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: an interpretation of the clinical literature in the light of laboratory experiment. Medicine. 1944;23:281–358.

Javier Arredondo Montero[a,*], Yurema González Ruiz[b], Mónica Bronte Anaut[c]

[a] *Servicio De Cirugía Pediátrica, Hospital Universitario De Navarra, Pamplona, Navarra, Spain*
[b] *Servicio De Cirugía Pediátrica, Hospital Universitario Miguel Servet, Zaragoza, Spain*
[c] *Servicio De Patología, Hospital Universitario De Araba, Vitoria, Spain*

* Corresponding author.
E-mail addresses: Javier.montero.arredondo@gmail.com, jarredondom@alumni.unav.es (J. Arredondo Montero).

https://doi.org/10.1016/j.anpede.2023.01.002

Recurrent *Clostridium difficile* infection treated with bezlotoxumab*

Infección recurrente por *Clostridium difficile* tratada con bezlotoxumab

Dear Editor:

Infection by *Clostridioides* (formerly *Clostridium*) *difficile* is a disease mediated by toxins. This pathogen is a strictly anaerobic gram-positive rod. Its main virulence factors are toxins A and B, encoded by the *tcdA* and *tcdB* gene, respectively.[1] Infection by *C. difficile* is the leading cause of nosocomial diarrhoea associated to the use of antibiotics and its incidence is increasing in the community, which constitutes a significant public health problem due to the associated morbidity and costs.[2]

The European Society of Clinical Microbiology and Infectious Diseases defines infection by *C. difficile* as a compatible clinical picture such as diarrhoea, ileus and toxic megacolon in combination with either microbiologic evidence of free toxins in stool or the presence of toxigenic *C. difficile* in stool without reasonable evidence for an alternative aetiology. Recurrent *C. difficile* infection is defined as recurrence of symptoms within 8 weeks after the onset of a previous episode, and severe infection as an episode resulting in need for intensive care unit admission, colectomy or death.[3]

The usual treatment of *C. difficile* is metronidazole or oral vancomycin, for both mild and severe cases, and rifaximin is a widely accepted alternative, in addition to faecal microbiota transplantation in recurrent cases.[3] Strategies have been developed to reduce the likelihood of recurrence, including bezlotoxumab, an antitoxin B human monoclonal antibody.[4]

Bezlotoxumab was approved for use in humans based on the outcomes of the MODIFY I and II international multicentric, double-blind randomised placebo-controlled trials.[5] These studies demonstrated that the use of bezlotoxumab (10 mg/kg as a single dose) was associated with a greater reduction in the recurrence of *C. difficile* infection and a similar safety profile in adults compared to placebo.

The MODIFY trials were conducted in the adult population (>18 years) treated with standard antibiotherapy (metronidazole, oral vancomycin or fidaxomicin) and showed that its effect was greater in individuals with at least 1 risk factor.[6] The risk factors for recurrence were: age 65 years or greater, history of infection by *C. difficile* in the past 6 months, compromised immunity, severe *C. difficile* infection or isolation of a strain associated with poor outcomes.[6] In addition, it showed that bezlotoxumab reduced the recurrence of infection by *C. difficile* for a period of 12 weeks.[4] Bezlotoxumab has yet to be approved for use in the paediatric population.

We present the case of a female adolescent aged 12 years with non-Hodgkin lymphoma at the prepyloric level causing pyloric stenosis that precluded enteral nutrition (complete liquid diet). The patient had 3 episodes of *C. difficile* infection over a 3-month period. Both the initial infection and the

* Previous presentation: case presented at the XIV National Congress of Paediatric Haematology and Oncology.

2 recurrences followed administration of broad-spectrum antibiotics for management of febrile neutropenia, and the first 2 episodes manifested with diarrhoea. The first episode was treated with metronidazole and the first recurrence with oral vancomycin. In the third episode, diarrhoea was associated with substantial dilation of the colon, ileus, systemic inflammatory response syndrome, disseminated intravascular coagulation and pulmonary embolism, with significant clinical worsening requiring transfer to the paediatric intensive care unit for treatment despite early initiation of antibiotherapy.

On account of the detection of infection by *C. difficile* and the episode being the second recurrence, the decision was made to add bezlotoxumab to the treatment regimen on a compassionate basis, with administration of a single dose of 10 mg/kg intravenously. The patient exhibited progressive improvement, with full resolution of symptoms and negative stool toxin test results and no adverse events associated with the administration of bezlotoxumab. As of this writing, 7 months after the episode, the patient has required an additional course of broad-spectrum antibiotherapy due to febrile neutropenia, but has not had additional infections by *C. difficile*.

In conclusion, infection by *C. difficile* is a public health problem that also affects the paediatric population. Many paediatric patients share the risk factors of adults, and therefore may experience the benefits of bezlotoxumab observed in the adult population. This case report concerns an immunocompromised patient with recurrent severe infection by *C. difficile* who benefitted from its use. Thus, we think it is necessary to study the efficacy and safety of this drug in the paediatric population.

References

1. Rogado-Vegas B, Sánchez-Gundín J, Gómez-Gómez D, Valero-Domínguez M. Bezlotoxumab en prevención de recurrencias de infección por *Clostridium difficile*. Ofil-Ilaphar. 2021;31:112–3, http://dx.doi.org/10.4321/S1699-714X20210001000020.
2. Asensio A, Bouza E, Grau S, Rubio-Rodriguez D, Rubio-Terrés C. Cost of *Clostridium difficile* associated diarrhea in Spain. Rev Esp Salud Publica. 2013;87(1):25–33, http://dx.doi.org/10.4321/S1135-57272013000100004.
3. Ooijevaar RE, van Burden YH, Tercer EM, Goorhuis A, Bauer MP, Keller JJ, et al. Update of treatment algorithms for *Clostridium difficile* infection. Clin Microbiol Infect. 2018;24:452–62, http://dx.doi.org/10.1016/j.cmi.2017.12.022.
4. Johnson S, Gerding DN. Bezlotoxumab. Clin Infect Dis. 2019;68(4):699–704, http://dx.doi.org/10.1093/cid/ciy577.
5. Gerding DN, Johnson S, Rupnik M, Aktories K. *Clostridium difficile* binary toxin CDT: mechanism, epidemiology, and potential clinical importance. Gut Microbes. 2014;5(1):15–27, http://dx.doi.org/10.4161/gmic.26854.
6. Bouza E, Cornely OA, Ramos-Martínez A, Plesniak R, Ellison MC, Hanson ME, et al. Analysis of *C. difficile* infection-related outcomes in European participants in the bezlotuxumab MODIFY I and II trials. Eur J Clin Microbiol Infect Dis. 2020;39:1933–9, http://dx.doi.org/10.1007/s10096-020-03935.

Beatriz Palenzuela Afonso*, Ana B. Caparrós Nieto, Macarena González Cruz, Cristina Martínez Faci

Oncohematología Pediátrica, Servicio de Pediatría, Hospital Universitario de Canarias, San Cristóbal de La Laguna, Santa Cruz de Tenerife, Spain

*Corresponding author.
E-mail address: bpalafo@gobiernodecanarias.org (B. Palenzuela Afonso).

https://doi.org/10.1016/j.anpede.2022.09.010

Is zoledronate a safe and effective treatment option in chronic nonbacterial osteomyelitis?☆

Zoledronato en osteítis crónica no bacteriana, ¿constituye una alternativa segura y efectiva?

To the editor:

Nonbacterial osteomyelitis (NBO) is an autoinflammatory disease that manifests with pain, swelling and/or functional limitation due to inflammation at one or more bone sites, although it is sometimes asymptomatic, and may be acute (<2 weeks) or chronic (>2 weeks). Chronic recurrent multifocal osteomyelitis, the most severe form, manifests with chronic inflammation lasting more than 6 months. The laboratory findings are nonspecific, with mild or no elevation of acute phase reactants. Although a bone scan may be useful to localise active asymptomatic sites, whole body magnetic resonance imaging (MRI) is the test of choice, as it can evince the presence of bone swelling, osteolysis, hyperostosis or sclerosis, which are characteristic features. It is a diagnosis of exclusion based on a combination of clinical, radiological and anatomical/histological findings, based on the Jansson[1] or Bristol[2] diagnostic criteria. Performance of a bone biopsy is particularly indicated in cases with unifocal involvement, of short duration and presenting with osteolysis, as it allows ruling out malignant and infectious disease.

The first-line treatment consists of nonsteroidal anti-inflammatory drugs (NSAIDs), alone or combined with steroid therapy, and there is no consensus regarding the second-line treatment. Different synthetic disease-modifying antirheumatic drugs, biologics such as tumour necrosis factor alpha (TNFα) inhibitors or bisphosphonates (especially in the case of spinal involvement) are used, with significant variability in clinical practice. Of

☆ Previous presentation: this study was presented at the XIV Congress of the Sociedad Española de Reumatología Pediátrica (SERPE), held online on November 25 and 26, 2021, an the 68th Congress of the Asociación Española de Pediatría (AEP), held on June 2–4, 2022 in Palma de Mallorca, Spain.