

He exhibited bradypsychia, inextensible horizontal and rotary nystagmus in dextroversion and levoversion with a vertical component in supraversion, left homonymous hemianopia on confrontation and a slightly unstable gait.

A computed tomography (CT) scan of the head (Fig. 1A) revealed multiple space-occupying lesions with contrast uptake in both cerebral hemispheres, with associated perilesional oedema and midline displacement.

A chest X-ray confirmed left perihilar opacity with probable associated lymphadenopathy (Fig. 1B), consistent with a primary tumour lesion and secondary brain metastases. The patient was started on intravenous dexamethasone.

A chest CT scan was performed, which revealed a paramedastinal cavitary lesion in the apical segment of the left upper lobe (LUL) measuring 7 cm × 4 cm × 5 cm, with nodular lesions in the LUL and ingula, raising suspicion of tuberculosis. A fibrobronchoscopy was performed in which no macroscopic findings were visualised, and samples were sent for cytology and microbiology.

A brain MRI scan (Fig. 1C) showed intraparenchymal lesions in both cerebral hemispheres, arranged juxtacortically and in the basal ganglia. The lesions had a ring shape, featuring a peripheral ring with FLAIR hypointense and surrounding oedema, in addition to lesions in the cerebral peduncle and left cerebellar hemisphere.

Microbiological studies for atypical micro-organisms and human immunodeficiency virus (HIV) as well as the QuantiferON TB® interferon- $\gamma$  release assay (IGRA) were negative, and the patient was confirmed to have good blood sugar control with a glycosylated haemoglobin level of 5.2%. Basic immunological studies and measurement of immunoglobulin and complement levels were normal.

*Nocardia farcinica* sensitive to imipenem, amikacin, levofloxacin, trimethoprim/sulfamethoxazole and linezolid was isolated in a bronchoalveolar lavage culture. As a result, treatment was started with imipenem and trimethoprim/sulfamethoxazole, and the patient's steroid treatment was suspended. In the following 24 h, the patient showed clinical worsening, with a low level of consciousness, lack of response to verbal stimuli and hypotonia and hypoparesis of his left leg. Given the possibility of increased cerebral oedema, as well as the likelihood of a Jarisch–Herxheimer reaction, the patient was put back on the steroid regimen and subsequently followed a favourable clinical course.

The patient completed the cycle of imipenem and trimethoprim/sulfamethoxazole for 3 weeks and his corticosteroids could gradually be reduced. He was then kept on treatment with trimethoprim/sulfamethoxazole for 2 years, with full neurological recovery and pulmonary radiological resolution on a CT scan with minimal residual lesions on a brain MRI scan.

Central nervous system infection with *Nocardia* is rare, occurring primarily in immunosuppressed patients, though it has been reported in immunocompetent patients. In our case, no apparent risk factor for developing this infection was detected.

## ***Clostridioides difficile* associated disease risk and proton pump inhibitors in critically ill children**



### ***Asociación del tratamiento con inhibidores de bombas de protones con la enfermedad por Clostridioides difficile en niños en estado crítico***

Proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA) are frequently used in critically ill patients for prevention gastrointestinal hemorrhage.<sup>1</sup> However, they can lead

*Nocardiosis* is an infection caused by an aerobic Gram-positive bacterium belonging to the genus *Actinomyces*.<sup>1,2</sup> In most cases, it is contracted by inhalation through the respiratory tract.<sup>2</sup> Involvement of the central nervous system is rare. The most common presentation is a single lesion, with a higher rate of mortality compared to other aetiologies of brain abscess (30%).

Most cases reported in the literature correspond to immunosuppressed patients,<sup>2</sup> but it has also been reported in immunocompetent patients<sup>1,3</sup> and patients with chronic obstructive pulmonary disease.<sup>4</sup>

Treatment of forms of cerebral involvement should be maintained over a prolonged period of time. *N. farcinica* usually shows resistance to trimethoprim/sulfamethoxazole, so the antibiogram is essential when adjusting the antibiotic therapy. It is advisable to start treatment with two drugs, subsequently reducing to one of them, and maintain this regimen for a minimum of 6–12 months (at least 12 months in immunosuppressed patients). In serious cases, the addition of a third drug, normally linezolid, can be contemplated.<sup>5</sup>

It is important to consider nocardiosis, specifically *N. farcinica*, in patients with pneumonia who follow an unfavourable course with conventional antibiotic treatment,<sup>6</sup> especially in pseudotumour and cavitary forms, as well as in differential diagnosis of single or multiple focal cerebral lesions, regardless of whether patients are immunocompetent.

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Lucía Ordieres-Ortega \*, María Dolores Pulfer,  
Juan Carlos Cano-Ballesteros

*Servicio de Medicina Interna, Hospital General Universitario Gregorio Marañón, Madrid, Spain*

\* Corresponding author.

*E-mail address:* [lucia.oomere@gmail.com](mailto:lucia.oomere@gmail.com) (L. Ordieres-Ortega).

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to bacterial overgrowth with an increased risk of *Clostridioides difficile* associated disease (CDAD). Association between PPI and the risk of *C. difficile*-associated diarrhea has been supported by several studies.<sup>2,3</sup> There are few data about the incidence of CDAD in critically ill children<sup>4</sup> and the relationship with gastric acid suppression.

We conducted a retrospective, observational, study including critically ill child with CDAD or *C. difficile* carriage (CDC) during 6 years. CDAD was defined as the presence of abdominal distension, abdominal pain and/or liquid stools associated with signs of systemic inflammatory response syndrome and/or a rise in the acute phase reactants. CDC was defined as the isolation of the bacillus

**Table 1**  
Comparison between patients treated with Ranitidine and Omeprazole.

	Ranitidine	Omeprazole	p
Number of children	1655	356	
Positive culture	0.4%	4.5%	<0.001.
<i>Clostridioides difficile</i> associated disease	0.2%	2.8%	<0.001
Asymptomatic colonization	0.4%	1.7%	<0.001.
Mortality	0%	0.5%	1.000

in the absence of signs of infection. Toxigenic *C. difficile* was isolated by stool culture. Cytotoxicity assay was performed in human fibroblast (MRC-5) cell culture and the isolated strains of *C. difficile* (CD) were then retested for toxin production. The strains were typed by ribotyping assay.

2526 patients were admitted to the Pediatric Intensive Care Unit (70% of them were cardiac patients). 1655 took ranitidine, 356 PPI, 178 both drugs and 337 did not receive any treatment.

Twenty-two patients (1.1%) had a positive culture for CD. The mean age was  $1.5 \pm 1.9$  years and 54.5% were males. 13 children were diagnosed as CDAD (incidence of infection of 0.6%) and 9 as asymptomatic carriage. All of them were cardiac patients and received broad-spectrum antibiotic therapy. The incidence of a positive culture was 4.5% with PPI group and 0.4% with ranitidine ( $p < 0.001$ ). The incidence of both CDAD and asymptomatic colonization was significantly higher in patients taking PPI (2.8% and 1.7% respectively) than with H2RAs (0.2% and 0.4% respectively),  $p < 0.001$ . (Table 1). Only one child had recurrent CD and was on PPI therapy for a long time. Two patients died, both of which were in the PPI group.

Colonization of the feces occurs in 16–35% of hospitalized patients, increasing proportionally in relation to the length of hospital stay and, in particular, after antibiotic therapy. Patients can be asymptomatic or present with fulminant colitis. The most common presentation is diarrhea, fever, colicky abdominal pain, and leukocytosis in a patient treated with broad-spectrum antibiotics.

Although CDAD is relatively rare in children, mainly before 12–24 months of age, its incidence among hospitalized children is increasing,<sup>5,6</sup> especially in those with oncological, postsurgical or critical illness.<sup>4</sup>

Some studies show an association between CD and PPI,<sup>7</sup> but few have analyzed the association between CD and acid suppressant drugs in children<sup>8,9</sup> and in critically ill adult patients.<sup>10</sup> Our study is the first that analyzed the association between these two factors in critically ill children concluding that PPI may increase the incidence of CD more than H2RAs. It is important, to distinguish between true disease and asymptomatic carriage due to the high prevalence of fecal colonization in children.

Several factors may be involved in this association. PPI induce a more potent gastric acid suppression that may alter the intestinal microbiota and stimulate the growth of CD. It also induces a delay in gastric emptying which can predispose to bacterial overgrowth. Moreover, the presence of bile salts in gastric contents may contribute to spore germination in the stomach. Second, in PPI inhibit neutrophil bactericidal activity, chemotaxis and phagocytosis and may favor CD infection.

Our study is a retrospective study and there are other factors that can predispose to CD infection which have not been analyzed, such as immunological status or the concomitant use of other drugs that are associated with this infection.

In conclusion, the use of PPI in critically ill children may increase not only the asymptomatic carriage but also the risk of CDAD which can worsen the prognosis of these patients. For this reason, the use of gastric acid suppressant therapy, especially PPI, should be bounded to patients with a high risk of gastrointestinal

bleeding. On the other hand, although CD carriage rates are high in the pediatric population, critically ill children are exposed to several factors that make it necessary to provide an adequate epidemiological surveillance.

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María José Solana<sup>a,b,c</sup>, Amaya Bustanza<sup>a</sup>, Jorge López<sup>a,b,c</sup>, Jesús López-Herce<sup>a,b,c,d,\*</sup>

<sup>a</sup> Pediatric Intensive Care Department, University General Hospital Gregorio Marañón, Madrid, Spain

<sup>b</sup> Gregorio Marañón Health Research Institute, Madrid, Spain

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<sup>d</sup> Public Health, Pediatric and Maternal Department, Medicine School, Complutense University of Madrid, Spain

\* Corresponding author.

E-mail address: [pielvi@hotmail.com](mailto:pielvi@hotmail.com) (J. López-Herce).

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