



Letters to the Editor

Streptococcus pneumoniae*: An Unusual Pathogen in Neonatal Sepsis of Vertical Transmission[☆]**Streptococcus pneumoniae*: un patógeno poco habitual en la sepsis neonatal de transmisión vertical**

Dear Editor,

Streptococcus pneumoniae (pneumococcus) is a microorganism with high morbidity in children, especially when related with the respiratory tract (in the form of pneumonia) and as a focus of infection in the otorhinolaryngological region (otitis). The most severe complication of pneumococcal infection is invasive pneumococcal disease, be it either as sepsis or meningitis. In the neonatal period, these forms of presentation of pneumococcal infection (pneumonia, sepsis or meningitis) are relatively infrequent but they are related with high morbidity and mortality.

In the neonatal period, pneumococcal sepsis may have an early or late onset. The transmission of the germ in these cases is not clear, and 2 possible forms are described: vertical by vaginal colonization of pneumococcus, and horizontal due to local infections or infections by non-vaccine serogroups.

We present a case of early neonatal infection due to vertical transmission of *S. pneumoniae*.

The patient is a 2-day-old newborn who had been born at full term and with proper birth weight. There was no obstetrical history of interest (water had broken spontaneously and less than 8 h before the birth, vaginal–rectal exudate culture for *Streptococcus agalactiae* [SGB] was negative, previous infection by toxoplasmosis, negative HBV, past rubella infection) who was brought to our neonatal unit due to continuous loud crying, irritability, and whining.

On physical examination, we observed: poor general state, apparent illness, continuous crying. Lung auscultation revealed: overall hypoventilation with disperse rhonchus. Constant wheezing that was audible without a stethoscope. Cardiac auscultation was normal. The examination of other organs showed no significant findings.

During the first few hours after admittance, the patient presented a declining general condition, with tachypnea, increased whine, and fever of 38.6 °C.

Hemogram showed 6800 leukocytes per microliter with left shift (1% metamyelocytes and 6% rod neutrophils) and an infection rate of 0.2. The white, red, and platelet series were normal. Coagulation was normal. Blood biochemistry was normal: sodium 129 meq/L, C-reactive protein 384 mg/L, and procalcitonin

0.22 ng/ml. Cerebrospinal fluid (CSF) showed normal cytochemistry. Urine testing was negative. In addition, blood, CSF, and urine sample were taken for culture.

Chest radiography showed: bilateral interstitial infiltrate with less aeration of the right lung and an image of right retrocardiac alveolar infiltrates.

Empirical intravenous antibiotic treatment was initiated with ampicillin and gentamycin, antipyretics, and plasma therapy.

On the third day, the culture results came back negative both in the urine and CSF, while the blood culture was positive for *S. pneumoniae*. The antibiotic treatment was changed to cefotaxime, according to the antibiogram.

After the blood culture results and as the setting was not epidemiologically compatible, the vaginal culture of the mother was repeated, which came back positive for *S. pneumoniae* 5 days later.

The baby was discharged from the hospital 15 days later after completing antibiotic treatment, with a normal physical examination and diagnosis of early-onset neonatal sepsis due to *S. pneumoniae*.

Currently, according to the study by the Grupo de Hospitales Castrillo, SGB is the etiological agent that most frequently causes sepsis by vertical transmission (33.3%), followed by *Escherichia coli* (32.3%) and *Listeria monocytogenes* (7.1%), but the incidence of *S. pneumoniae* is not registered because it is low.¹ Studies in the United States estimate an incidence of 1%–10% of all neonatal sepsis.²

S. pneumoniae is not part of the usual vaginal flora, and the incidence of its colonization in pregnant women is exceptional (0.03%–0.75% of cases).³ Strategies for the prevention and treatment of SGB are also effective for infections caused by *S. pneumoniae*.

In Spain, there are 16 published cases of neonatal pneumococcal disease^{4–6}: 14 with early-onset^{4–6} and 2 with late-onset.⁶ Our case was of the early disease type.

The administration of heptavalent pneumococcal vaccines over recent years, and most recently the 10- and 13-valent types (including the 7F, 3, and 6A serotypes, which are an important cause of invasive pneumococcal disease worldwide), has reduced the transmission of diseases due to pneumococcus in the general population (from 50–100 to 9 cases for every 100 000 people) and, consequently, the incidence of neonatal invasive pneumococcal disease has decreased.

Vaccination during the third trimester of gestation could be a measure to follow in the future, although there are no conclusive studies that currently confirm this.¹

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Carlos Hermoso Torregrosa,* Manuel Carrasco Zalvide, and María Teresa Ferrer Castillo

Servicio de Pediatría, Hospital Juan Ramón Jiménez, Huelva, Spain

* Corresponding author.

E-mail address: carloshermoso2@hotmail.com

(C. Hermoso Torregrosa).

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The Potential Role of Racecadotril in the Treatment of Diarrhea Associated With Roflumilast^{*}

Potencial papel de racecadotril en el tratamiento de la diarrea asociada a roflumilast

Dear Editor,

Roflumilast is a new inhibitor of phosphodiesterase-4 (PDE4) that is marketed for the treatment of chronic obstructive pulmonary disease (COPD). The PDE4 enzyme hydrolyzes and selectively inactivates cyclic adenosine monophosphate (cAMP). This inhibition increases cell levels of cAMP, reducing most pro-inflammatory processes, and remodeling that are dependent on these cells.¹

A recent group analysis has demonstrated that roflumilast can be used to reduce exacerbations and improve dyspnea and lung function in patients with COPD who receive concomitant treatment with long-acting β_2 agonists (LABA), without increasing adverse effects.² In this study, the distribution of the adverse effects was similar in patients with or without concomitant treatment with LABA. Nevertheless, the study shows an association between roflumilast and the appearance of diarrhea with an incidence between 7.7% and 19.1%. Although the average duration of this adverse period is 11–12 days,³ the intensity of the diarrhea should be evaluated in each case in order to decide if the treatment should be maintained or not. Due to the temporary nature of this adverse effect and the benefits of the use of roflumilast, it is possible that some cases may benefit from receiving treatment for diarrhea. The mechanism of action of this diarrhea has been associated with higher levels of cAMP in intestinal epithelial cells, and this increase causes an imbalance between the concentrations of Na⁺ and K⁺, which in turn promotes intestinal hypersecretion.

Racecadotril is a powerful selective inhibitor of enkephalinase, which is active orally. Enkephalinase is an enzyme that is responsible for the degradation of the enkephalin that is abundant in the intestinal villi, where the electrolyte exchange takes place. Curiously, enkephalins have antisecretory effects in the intestine by inhibiting the production of cAMP. Thus, racecadotril quickly resolves the acute diarrhea and has an incidence of adverse effects that is similar to placebo,⁴ without inducing the proliferation of bacteria.⁵ Unlike opioids, this drug does not have central or peripheral side effects, such as respiratory depression or the inhibition of the intestinal transit.

The anti-diarrheal effects of racecadotril have been studied in several assays, both in acute as well as chronic diarrhea, in adults, and in children, and a good effectiveness/safety profile has been found with a quick start time within the first 24 h. The dosage in adults is an initial 100-mg capsule followed by 1 capsule 3 times a day, preferably before meals. The treatment should not last more than 7 days.

Due to the mechanism of action, it is plausible to hypothesize that racecadotril can have an effect on diarrhea induced by roflumilast by counteracting its effects on the cell levels of cAMP. Unfortunately, to date there have been no clinical assays dealing with the efficacy and safety of this medicine for treating this potential new clinical indication, and, as far as we know, there are none presently underway (clinicaltrials.gov). With this letter, we would like to raise interest in this potential effect and promote the creation of clinical assays studying the use of racecadotril in the treatment of diarrhea associated with roflumilast.

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Jose Luis López-Campos,* César Gutiérrez, Carmen Calero

Unidad Médico-Quirúrgica de Enfermedades Respiratorias, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío, Seville, Spain

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* Corresponding author.

E-mail address: lcampos@separ.es (J.L. López-Campos).

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