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EDITORIAL

Azithromycin in acute bronchiolitis

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Acute bronchiolitis is a leading cause of hospitalization due to respiratory problems in infants and young children. Among the possible etiologic agents, viruses predominate, the most common being respiratory syncytial virus (RSV) and rhinovirus.[1]

In humans and in animal models, RSV infection is followed by the production of interleukins, such as IL-12 and IL-18, and chemokines, such as IL-8, IL-10, CCL5, macrophage inflammatory protein-1α, CCL2, and eotaxin,[2] all of which are potent inflammatory mediators. Host factors, as well as genetic factors (polymorphisms) and environmental factors, can be critical in determining the severity of RSV-induced disease, even when they are related to age, recent infection, pollution, and exposure to allergens. In addition, studies indicate that individuals who had acute RSV- or rhinovirus-related bronchiolitis in the first years of life are at an increased risk of developing asthma later in childhood.[3]

Although viral etiology is responsible for the majority of cases of acute bronchiolitis, treatment with antimicrobials might be indicated, either because of a suspected bacterial coinfection or simply because of their anti-inflammatory effects. The use of antimicrobials has been widespread, especially in hospitalized patients. However, the use of antibiotics in early life has been associated with the development of recurrent wheezing or asthma later in life.[4] A study using the Taiwanese National Health Insurance Research Database 2010 (from 2005 to 2010) documented the relationship between the risk of new-onset asthma and the use of antibiotics in hospitalized patients with bronchiolitis, specifically azithromycin (adjusted OR = 2.87; 95% CI: 1.99-4.16).[5]

Macrolides, especially azithromycin, have been used as adjuvant therapy in the treatment of some lung diseases and viral bronchiolitis; in addition to their bactericidal effect, their use is justified because of their anti-inflammatory, antineutrophil, and antiviral effects.[6]

Studies evaluating the effect of treatment with azithromycin in hospitalized patients with acute viral bronchiolitis have produced different results.[7-9] That might be explained, in part, by the different variables considered in those studies (e.g., age, dose, duration of treatment, etiologic agent, presence of atopy, and clinical outcomes).

A systematic review and meta-analysis[7] evaluated the clinical effects of the treatment with azithromycin in hospitalized patients with bronchiolitis. That study included 14 double-blind, placebo-controlled studies, collectively involving 667 children receiving active treatment and 661 controls. The global analysis of the data revealed no significant differences between the groups in terms of the length of hospital stay or use of supplemental oxygen; however, there was a significant reduction in the time to relief of wheezing and cough in the treatment group, as well as in the nasopharyngeal colonization by *Streptococcus pneumoniae*, *Haemophilus* sp., and *Moraxella catarrhalis*.[7]

The importance and participation of the airway microbiome in the integrity and health of the airways is increasingly evident. The development of this microbiome starts in the first moments of life and is influenced by the type of delivery (vaginal or not), breastfeeding, environmental exposures, and the environment in which the child lives during the first days of life.

At birth, most children are colonized by *Staphylococcus* sp. or *Corynebacterium* sp. prior to a more stable colonization with *Alloiococcus* sp. or *Moraxella* sp. An imbalance in this microbiome is probably closely related to the development of respiratory diseases, such as wheezing in infancy and asthma. Lower abundances of bacteria of the phyla Bacteroidetes and Firmicutes, as well as a predominance of bacteria of the phylum Proteobacteria, have been documented in patients with asthma.[8]

Another systematic review and meta-analysis[9] evaluated the effects of macrolides on the airway microbiome and the production of cytokines in children with bronchiolitis. After treatment with macrolides, there was a significant reduction in the isolation of *S. pneumoniae*, *Haemophilus influenza*, and *M. catarrhalis* in the nasopharyngeal samples, although there was no reduction in that of *Staphylococcus aureus*. There was also a significant decrease in serum levels of IL-8, IL-4, and eotaxin three weeks after the treatment with clarithromycin.[9] Macrolides can reduce the levels of IL-8 in plasma and in the airways but have failed to demonstrate an antiviral effect in children with bronchiolitis.[9]

In this issue of the *Jornal Brasileiro de Pneumologia*, Luisi et al.[10] analyzed secondary data of a randomized, double-blind, placebo-controlled study involving infants (< 12 months of age) hospitalized for acute viral bronchiolitis (clinical diagnosis) and treated with oral azithromycin (10 mg/kg per day) or placebo for seven days. During the first phase of the study, 184 patients admitted to university hospitals were randomized to treatment with azithromycin or placebo. All treatment protocols for acute viral bronchiolitis were followed at those hospitals. The variables studied at the end of hospitalization were length of hospital stay and the need for supplemental oxygen.[11] The two groups were similar regarding clinical parameters

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at admission, and approximately 15% of the children had a family history of asthma. A virus was isolated in 63% of the sample, RSV being isolated in 94% of those cases. There were no differences between the groups regarding the two variables under study.[11]

In a secondary analysis, Luisi et al.[10] contacted the parents or guardians of those children via telephone three and six months after hospital discharge in order to complete a standardized questionnaire to identify the presence of recurrent wheezing and hospital readmissions.[10] Of the initial sample of patients, 67% of the parents/guardians participated. Among those patients, 54.3% had had RSV-related bronchiolitis. The rate of recurrent wheezing was significantly lower (approximately 50%) among those treated with azithromycin three months after discharge, which was not true at six months after discharge. There were no differences regarding the rate of readmissions.[10]

The possibility of reducing recurrent wheezing with the use of azithromycin is encouraging, although various aspects still need to be better clarified before it can be recommended for the treatment of bronchiolitis. As pointed out by Luisi et al.,[10] the number of children followed was relatively small and further studies are needed in order to confirm these findings. The identification of clinical markers that provide better preventive responses after the use of azithromycin is desirable, aiming to reduce possible adverse events and antimicrobial resistance associated with the indiscriminate use of the medication.

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