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EDITORIAL

Defining the burden of respiratory syncytial virus infection☆,☆☆

Definindo o fardo da infecção pelo vírus sincicial respiratório

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Respiratory syncytial virus (RSV) remains one of the great threats to child health associated with considerable acute and long-term morbidity.[1] RSV is the main cause of viral lower respiratory tract infection (LRTI) in young children in both developed and developing countries, and worldwide almost 34 million new cases occur every year. In the United States, RSV is the most common cause of hospitalization in infants.[2,3] In the developing world RSV accounts for 3.4 million hospitalizations for LRTI in children < 5 years of age.[4] Nevertheless, the global burden of RSV extends well beyond hospitalization and into the outpatient setting.[5,6]

There are well-characterized risk factors for severe RSV disease including prematurity, chronic lung disease (CLD), congenital heart disease (CHD), trisomy 21, neuromuscular disorders or an immunocompromised state. In addition, recent studies have identified other conditions to be associated with an increased risk for severe RSV disease, such as chromosomal abnormalities or malformations of the upper airway. In reality, pediatricians are well aware that any ''non-previously healthy infant'' is actually at higher risk for hospitalization and developing severe RSV disease.[7–9] To complicate matters further, the majority of children that are hospitalized for RSV LRTI do not have any identifiable risk factors for severe disease. Two recent large studies, one retrospective and hospital-based, and the other one prospective and population-based, showed that 73% to 79% of children < 2 years of age requiring hospitalization for RSV LRTI were previously healthy and had no risk factors for severe disease.[9,10]

In temperate climates, RSV infections predictably occur in outbreaks each year and last 4 to 6 months, starting from late fall through early spring, but they can vary considerably between regions within a country or state. These differences on RSV endemic activity have been attributed in part to the effect of latitude, UV-B radiation, relative humidity or temperature, and need to be further characterized.[11]

Despite the disease burden, an effective vaccine or specific therapy are lacking largely due to our limited understanding of the immune response to RSV and how it relates to disease severity. The only effective pharmacologic means of preventing RSV infection involves the administration of passive prophylaxis with palivizumab during the RSV season. Countries have used different approaches to define the onset and offset of the RSV season. In the United States the Center for Disease Control and Prevention (CDC) uses laboratory isolate data to define the seasonality of RSV, while in Canada the active RSV season is based on epidemiologic data (number of admissions for RSV within a week).[12] Palivizumab is a neutralizing humanized monoclonal antibody (IgG_1) that targets the RSV F (fusion) protein. It has a half-life of

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28 days, requiring monthly administration during the RSV season, which emphasizes the importance of defining the local epidemiologic activity of RSV within a country, which will enable the implementation of an anti-RSV prophylaxis program in a cost-effective manner and curtailed to each RSV season.

Palivizumab was approved by the FDA in 1998 for prevention of severe RSV disease in preterm infants and children with chronic lung disease (CLD), and subsequently in 2003, for prevention of severe RSV disease in children with congenital heart diseases (CHD). Since then it has been implemented in more than 60 other countries.[13,14] Both placebo-controlled and comparative studies have demonstrated the efficacy of palivizumab for the prevention of RSV-associated hospitalizations in high-risk children.[13,15] More recently, a randomized prospective controlled study has also shown the long-term benefits of RSV prevention. In otherwise healthy preterm infants (33-35 weeks of gestational age) anti-RSV prophylaxis resulted in a significant reduction of wheezing episodes during the first year of life.[16] To date, this monoclonal antibody remains the only available agent for prevention of severe RSV infection in high-risk children.

The incidence of RSV-associated acute LRTI is highly variable within countries and regions and has been partially characterized in Latin America.[17] In reality, unless the burden of a disease is demonstrated locally, the real problem tends to be minimized; therefore it is essential to define the local epidemiology of RSV within each region and the site-specific rates of RSV-associated hospitalizations. The work published by Piñeros et al.[18] in this issue of *Jornal de Pediatria* represents a first step to address these questions in Colombia. In this prospective observational study authors characterized the frequency, seasonality, presence of prematurity and CLD, and mortality in infants with RSV and non-RSV LRTI requiring hospitalization over one calendar year at 6 Colombian cities. A total of 717 infants hospitalized with LRTI both previously healthy and children with risk factors for severe disease were enrolled. Authors used rapid RSV antigen testing for identification and confirmation of cases. During RSV epidemics, RSV antigen tests have a sensitivity of $\sim$ 80-90%, but contrary to molecular testing, which has superior sensitivity and specificity, the positive predictive value of rapid antigen tests can change based on the prevalence of the circulating disease, and thus rates of false positive results can significantly increase during the ''non-viral season''. Nevertheless, they documented endemic RSV activity throughout the year, with a peak during the April-June trimester and a slight decline during the October-December trimester. These peaks did not necessarily coincide between cities, possibly reflecting the differences in climatologic conditions. Median age of infants with RSV LRTI (216 [30%]) and non-RSV LRTI (501 [70%]) was 3 months, and gender, duration of hospital stay and presence of prematurity or CLD was similar between groups.

A large hospital-based cohort study conducted in Texas over 6 calendar years (2002 to 2007) compared outcomes of care between children < 2 years of age hospitalized with RSV and non-RSV bronchiolitis. Because 95% of the study subjects had a viral diagnostic test performed, the authors were able to compare the differences in demographic, clinical, microbiological, radiologic characteristics, and the presence of risk factors predictive of severe disease. Children hospitalized with RSV LRTI had a more severe disease in all outcomes measured, specifically RSV + children had longer duration of hospital stay, need for supplemental oxygen requirement, need and duration of ICU stay and need and duration of invasive and non-invasive ventilatory support, which has also been shown in other studies.[9] In addition, they found that the proportion of children with underlying medical conditions was significantly higher for those with non-RSV bronchiolitis, which may possibly reflect the impact of targeted anti-RSV prophylaxis. In their study, Piñero et al.[18] did not find differences in duration of hospitalization between infants with RSV and non-RSV LRTI or in the prevalence of underlying medical conditions. These discrepancies could be attributed in part to selection bias or to the different anti-RSV prophylaxis programs implemented within each specific country or region, which will need further confirmatory studies. On the other hand, Piñero et al.[18] found that the overall mortality was low in infants hospitalized with RSV LRTI (0.8%) and absent in the non-RSV group, but it significantly increased in high-risk patients (5.8%).

As the application of molecular diagnostic assays for respiratory viruses becomes readily available, physicians raise questions concerning the value of such tests in clinical practice. Different arguments favor the use of viral diagnostic tests and the importance of viral testing. On the one hand, it is key to define the activity of RSV for the implementation of a cost-effective anti-RSV prophylaxis program, and, on the other hand, from the infection control perspective, it is critical to isolate patients according to etiology to prevent hospital-associated infections, which carry considerable morbidity and mortality. In addition, defining the etiologic agent for bronchiolitis may have therapeutic implications. Lehtinen et al. found that a 3-day treatment with oral prednisolone in children with acute bronchiolitis caused by human rhinovirus (HRV) was associated with a significant reduction in wheezing episodes in the subsequent 12 months. In contrast, there was no benefit in children with bronchiolitis caused by RSV.[19] Lastly, different groups of investigators found decreased concentrations of inflammatory cytokines in the respiratory tract in the more severe forms of RSV disease[20–23] and suggest that weak rather than exaggerated innate immune responses are associated with enhanced disease severity. Certain therapies, such as corticosteroids, are still misused in an effort to blunt the pro-inflammatory response to RSV. The addition steroids in this clinical scenario raise the possibility of worsening this impairment of the host immune response.

In summary, the study by Piñero et al.[18] emphasizes the importance of carefully characterizing the activity of RSV in each country and the different regions within each country, which will lead to an accurate assessment of the burden of RSV. The information gathered from this study, in addition to help implementing general infection control practices, such as hand washing or limiting the number of visits from sick contacts especially during the peak months of RSV circulation, will help with the implementation of a cost-effective anti-RSV prophylaxis program and to determine the priorities for the use of the existing prophylaxis.

Conflicts of interest

Octavio Ramilo has had financial relations with companies that are involved with respiratory viruses research or product as follows: Advisory boards: Gilead, Abbvie, Alios, Quidel. Honoraria for Lectures and Co-Chair Medical Conferences: Abbvie. Cover part of travel expenses to present clinical study at a scientific conference: MedImmune. Research Grant: Abbott Molecular.

Asuncion Mejias has relations with companies that are involved with respiratory viruses research or product as follows: Advisory Boards: Alios, Janssen Infectious Diseases BVBA, honoraria for lectures at CME conferences: Abbvie; research grant: Gilead.

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