



EDITORIAL

The importance of viral testing in infants and young children with bronchiolitis*



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As a major pathogen affecting the lower respiratory tract, respiratory syncytial virus (RSV) represents the leading cause of hospitalization in infants and young children worldwide, and is the second leading cause of infant mortality beyond the neonatal period.¹ Infections due to rhinovirus, on the other hand, have been considered to be restricted to the upper respiratory tract, where the temperature of mucosal surfaces are relatively cold (33–35°C) and optimal for viral replication. Nevertheless, recent studies have increasingly recognized the important role that rhinovirus (RV) plays in severe lower respiratory tract illnesses in children, including bronchiolitis, pneumonia, recurrent wheezing, and asthma.²

In the study published in this issue of the journal, Bastos and colleagues provided data regarding the causative agents of severe bronchiolitis in hospitalized children < 2 years of age.³ They found that of the 173 nasopharyngeal (NP) aspirates analyzed using a 15-plex PCR assay, a respiratory virus was identified in 87% of children and viral coinfections in 23% of them. Overall, RSV alone or in combination with another respiratory virus, was the most common pathogen identified in 78% of children, followed by rhinoviruses in 20%. Within

the positive viral cohort, 34% of infants required use of the intensive care unit (ICU), 21% mechanical ventilation, and five children died, two with rhinovirus infection, two with RSV lower respiratory tract infections (LRTI) and one child with meningitis.

Unfortunately, analyses of disease severity according to the infecting respiratory virus, and whether certain rhinovirus genotypes were more prevalent in the most severe cases or whether higher viral loads or viral coinfections played a role on clinical outcomes were not performed. Nevertheless, the study by Bastos and colleagues, underscores the morbidity and the mortality, that is not negligible, in young children with RSV or RV LRTI. Another important take-home message from the study is that rhinoviruses can also cause severe bronchiolitis in infants, highlighting the importance of viral testing for patient phenotypic classification.

The diagnosis of bronchiolitis is clinical and several guidelines do not recommend viral diagnostic testing.⁴ The main reasons supporting these recommendations are likely related to the costs associated with the tests, combined with the perception that viral testing does not alter patient management. However, as shown by Bastos et al., bronchiolitis is not a single entity, and it is important to recognize that the clinical phenotype, target age, and the host immune response to different respiratory viruses also differs.⁵

There are several reasons to support respiratory viral testing. First, from the clinical perspective, identification of the

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respiratory virus or viruses facilitates **patient management**. It helps the treating physician with the infant evaluation and assessment of the risk for disease progression or the development of complications. Of all viruses that cause respiratory infections in young children, RSV has been consistently identified as a risk factor for severe disease.⁶ In these infants, disease severity typically peaks on days 4-5 after symptom onset. This is different from other respiratory viruses that tend to be associated with a milder clinical course and faster recovery.⁷ In addition, it is well known that neonates and young infants with RSV infection have an increased risk for apnea, especially if they are born prematurely. Thus, a very young infant with RSV infection or early on the disease course may need to be monitored carefully for the risk of disease progression.

As shown by Bastos and colleagues, it is not uncommon in clinical practice to identify more than one respiratory virus during the acute illness. Although various studies suggest that viral coinfections are associated with enhanced disease severity and a more protracted clinical course,^{7,8} viral coinfections is an area that deserves further prospective studies to understand not just whether the detection of more than one respiratory virus has different clinical implications, but the impact of specific viral coinfections in acute and long-term clinical outcomes.

The specific management of infants with bronchiolitis differs according to the infecting virus and should be individualized. Adenoviruses or human metapneumovirus (hMPV) infections can be associated with high grade fever. On the other hand, a temperature of 39°C and over in an infant with RSV LRTI should prompt a thorough clinical examination to exclude a superimposed bacterial infection such as acute otitis media (AOM), which occurs in > 50% of children during or soon after the acute disease.⁹ Furthermore, emerging evidence indicates that bacterial superinfections involving the lower respiratory tract are not as infrequent as traditionally reported in infants with RSV infection.¹⁰ Another point of controversy is the potential benefit of systemic corticosteroids. While multiple studies have demonstrated the lack of benefit of steroids in infants with RSV LRTI,¹¹ their role in bronchiolitis caused by other respiratory viruses is being recognized. The peak age for severe RSV infection is in infants <6 months, independent of the atopic background, while infants with rhinovirus bronchiolitis tend to be older, and commonly have eczema or a previous episode of wheezing. Two randomized clinical trials using oral prednisolone in infants with a first episode of rhinovirus bronchiolitis showed a significant reduction in the development of recurrent wheezing and asthma.¹² Thus, it is critical to distinguish between children with RSV versus RV infections as they are likely to respond to different treatment modalities.

Second, viral diagnosis informs the **infection prevention** policies that should be implemented. As illustrated by Bastos and colleagues, viral coinfections were identified in 23% of children, which is in agreement with previous studies that have reported rates of viral coinfections of 20%-30% in children hospitalized with bronchiolitis.¹³ Of all viral coinfections, RSV-RV represents the most common association, as was reported in the aforementioned study.³ Relying exclusively on national or local trends of viral circulation, or rapid RSV antigen testing for patient placement and cohorting is likely not sufficient. The isolation of children with RSV

infection requires contact precautions, while for rhinovirus infections both contact and droplet precautions are indicated. Implementation of targeted infection control procedures informs the rational use of personal protective equipment, and importantly minimizes the risk of transmission to other patients and healthcare workers. The prevention of healthcare-associated respiratory viral infections to other hospitalized patients is especially relevant, as these infections have been associated with poor clinical outcomes, the need for mechanical ventilation, prolonged hospitalizations, and mortality.¹⁴

Third, viral diagnosis also informs **antimicrobial stewardship** efforts. On the one hand, viral identification has been shown in different studies to reduce the unnecessary use of antibiotics.¹⁵ On the other hand, viral diagnosis allows for targeted antiviral treatment, that is currently available for influenza and SARS-CoV-2 infections, with several antivirals against RSV looming in the pipeline.¹⁶ During the 2009 H1N1 influenza pandemic, different entities recommended empiric treatment with oseltamivir to patients presenting with influenza-like-illnesses (ILI) without the need for confirmatory influenza testing. However, as illustrated in a study conducted in children during that influenza pandemic, comprehensive viral PCR testing helped with patient management and targeted use of antivirals.¹⁷ In that study, of 1,120 children evaluated with ILI, < 10% had confirmed influenza infection. In fact, rhinovirus followed by parainfluenza and hMPV were the respiratory viruses more frequently identified, and thus those children were not treated with oseltamivir.

Fourth, defining and tracking **epidemiologic trends**, including the onset and offset of the RSV season, is of critical importance for planning the administration of prophylaxis with palivizumab to high-risk children. The circulation of RSV should be monitored at the local level, as the onset of RSV activity can vary among regions and communities. This has been recently illustrated with the unprecedented off-season surge of RSV in the summer of 2021 in many countries including the United States, after RSV skipped a respiratory season in the first year of the COVID-19 pandemic.¹⁸ From the global point of view, viral monitoring helps to identify emerging pathogens that can cause severe respiratory illnesses (i.e. bronchiolitis or pneumonia), or other unusual or severe presentations such as acute flaccid myelitis (AFM). The recent enterovirus (EV)-D68 outbreaks or the SARS-CoV-2 pandemic underscore the relevance of understanding the epidemiology of emerging viruses to help inform clinical practice.¹⁹

Fifth, **counseling families** about the disease course and possible long-term sequelae associated with certain respiratory viruses should not be dismissed. Of all the pathogens that cause bronchiolitis in infants, both RSV and rhinovirus through different mechanisms, are associated with the development of wheezing and/or asthma, and families should be counseled about this possibility.²⁰

Altogether, the study by Bastos et al. illustrates the burden and complexity of bronchiolitis in infants, the varied clinical course, and the importance of viral diagnosis. Partially driven by the COVID-19 pandemic, we are now in an ideal situation to take advantage of the breadth of molecular tools available for viral diagnosis. Instead of

dedifferentiating bronchiolitis and grouping all children with this disease in the same category, we should place our efforts to define the different viral-driven clinical phenotypes. In the era of precision medicine, this will assist with clinical decision-making processes and the implementation of targeted interventions tailored to each patient, with the ultimate goal of reducing both the acute and long-term pulmonary morbidity associated with each specific virus.

Conflicts of interest

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