



## EDITORIAL

### Testing for respiratory viruses in the neonatal intensive care unit (NICU): Ready for prime time?☆



### Pruebas de virus respiratorios en la unidad de cuidados intensivos neonatales: ¿listos para el prime time?

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Emerging studies such as the one by Gonzalez-Carrasco et al.<sup>1</sup> in this issue of *Anales Españoles de Pediatría* suggest that respiratory viruses are in our NICUs, even though their occurrence remains an under-recognized phenomenon outside of outbreak situations. Premature infants may not present with the classic respiratory or "cold" symptoms that are observed commonly in older infants and children, and therefore, the possibility that a viral respiratory pathogen is responsible for episodes of clinical deterioration is often not considered.

The development of greatly improved molecular diagnostic methods such as the polymerase chain reaction (PCR) for the detection of respiratory viruses in nasopharyngeal (NP) specimens has allowed their precise identification in conditions such as bronchiolitis and pneumonia. Despite the potential benefits, premature infants who are in fact at a higher risk for severe disease and outcomes, do not routinely undergo testing for respiratory viruses in the NICU. As shown by Gonzalez-Carrasco et al., PCR technology will aid not only in the recognition of respiratory viruses in premature infants in the NICU, but also in understanding the impact that these viruses have on their clinical care and disease processes. The awareness about the probable harmful role of respiratory viruses in premature infants is especially relevant in this era of family-centered care in NICUs, which by maximizing visitation by parents and families also carries the risk for the neonate's acquisition of traditional community pathogens resulting in hospital-associated infections.

☆ Please cite this article as: Mejias A, Ramilo O, Sánchez PJ. Pruebas de virus respiratorios en la unidad de cuidados intensivos neonatales: ¿listos para el prime time?. *An Pediatr (Barc)*. 2015;82:378–380.

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The prevalence of respiratory viral infections in the NICU was first documented in 2012 using PCR assays in a prospective surveillance study performed in 2 NICUs in the United States over a 1-year period.<sup>2</sup> Preterm infants <33 weeks of gestation who were in the NICU since birth underwent sequential NP testing for respiratory viruses up to the time of discharge. Fifty two percent of infants tested positive for a respiratory virus at least once during the study. Compared with infants that tested negative, virus-positive infants had significantly worse outcomes assessed by: longer length of stay, need and duration for intubation, more episodes of desaturation and duration of oxygen requirement, incidence of bronchopulmonary dysplasia (BPD) and more clinical deterioration episodes. The current study by Gonzalez-Carrasco et al. confirms these results in a different part of the world and using different PCR platforms, further emphasizing the need for respiratory viral testing in the NICU.<sup>1</sup> Over 18 months (9/2011–5/2013), the authors performed a prospective surveillance study for 16 respiratory viruses in the NICU mostly in preterm infants of <32 weeks' gestation but also in older gestational age infants who had underlying comorbidities and an anticipated length of stay in the NICU of >2 weeks. Testing for respiratory viruses in NP aspirates was performed the first day of age, then weekly until discharge, as well as whenever there were any respiratory symptoms defined as cough, respiratory distress, rhinorrhea, or apnea, regardless of the presence of fever. A respiratory virus was identified at least once during the NICU stay in 22% (13/60) of infants. The most frequently identified virus was rhinovirus (RV), followed by adenovirus, coronavirus and human metapneumovirus (hMPV). Infants born at <32 weeks' gestation and with birth weight <1500 g tested positive for a respiratory virus more frequently than greater gestational age infants, possibly reflecting their more prolonged hospitalization, however transmission was not documented. Although duration of hospital stay was not significantly different between infants who tested positive and negative, BPD was more common in the viral positive group. The contribution that these respiratory viruses may have on development or worsening of BPD remains unknown. Unfortunately, other outcomes such as need and duration of oxygen therapy or invasive mechanical ventilation were not compared between the two groups.

Diagnosis of a respiratory viral infection also can inform antimicrobial stewardship efforts in the NICU. Premature infants in the NICU are frequently evaluated for possible bacterial sepsis, yet their cultures can be negative for bacterial pathogens. These infants are often treated with prolonged antibiotic therapy due to the possibility of falsely negative culture results. In a single-center prospective study conducted in a German NICU over 18 months, Kidszun et al.<sup>3</sup> performed respiratory viral multiplex PCR testing on 60 infants (median gestational age, 26 weeks, and birth weight, 720 g) who had intravenous (IV) antibiotic therapy initiated for possible late-onset sepsis. Six (10%) infants had a respiratory virus (1, RSV; 5, picornavirus) detected, which was more than the number of bacterial blood stream infections (3 or 5% of infants). There were no cases of bacterial–viral co-infection. Importantly, there were no clinical signs or laboratory findings that helped differentiate viral versus bacterial infection, and specifically no “cold” symptoms in any of the infants in whom a respiratory virus was identified.

Similarly, the VIRIoN-I study that was performed in two NICUs in the United States over a 13 month period found that 8% (8/100) of inborn infants who were evaluated for possible late-onset sepsis and treated with IV antibiotic therapy had a respiratory virus (4, enterovirus/rhinovirus; 2, coronaviruses; and 2, parainfluenza-3 virus) detected by PCR testing of NP samples.<sup>4</sup> Importantly, there were no viral–bacterial co-infections. Timely results obtained from respiratory viral PCR testing ultimately may help curtail unnecessary antibiotic therapy in NICUs.

Undoubtedly, the introduction of respiratory viral PCR testing into the clinical arena has revolutionized the diagnosis of these infections. However, such a testing can also be a double-edged sword, as the identification of viral nucleic acid in respiratory secretions may not be sufficient to establish causality. This is especially relevant for respiratory viruses such as RV, coronaviruses and bocavirus that have been detected at high rates in healthy asymptomatic children and adults. In the study by Gonzalez-Carrasco and colleagues, 4 infants had a respiratory virus identified yet had no clinical signs of infection (3, RV; 1, coronavirus). The meaning of viral detection in these situations is still unclear: it could represent false-positive results, prolonged shedding from a preceding infection, or a “true” asymptomatic infection. The tools to discriminate between pathogen detection and true infection are lacking. White blood cell counts and C-reactive protein are of little value and the role of viral loads as a surrogate of disease severity is still inconclusive. Studies using whole blood RNA expression profiles have shown a significantly superior capacity than WBC and procalcitonin for discriminating bacterial from viral infections<sup>5</sup> and even whether viral identification actually represents a real and ongoing infection or just colonization.

The study by Gonzalez-Carrasco et al. clearly argues for performing more respiratory viral testing in the NICU using optimal molecular assays. In addition to performing these tests in the presence of respiratory symptoms or apnea, such testing should be considered strongly in the setting of “culture-negative sepsis” – that is, an unexplained clinical deterioration associated with sterile cultures – in which prolonged antibiotic therapy is contemplated. The field is ready for the implementation of more routine viral testing, but ultimately, simultaneous analyses of host responses will be needed to establish causality. Prospective studies that incorporate these tools and determine the acute and long term morbidity of these infections in preterm infants are warranted.

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