Viral co-detection in infants hospitalized with respiratory disease: is it important to detect?

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Until relatively recently, our view of acute viral respiratory illnesses in early childhood was somewhat limited. We "understood" the following: children were exposed to respiratory viruses by exposure to other children; all children would be exposed to common respiratory viruses during the first year or two of life, with many infections remaining subclinical and the minority becoming severe enough to warrant medical attention or hospitalization; human rhinovirus (HRV) did not cause lower airway infections in children; and normal children did not "carry" viruses in their upper airway. We also "knew" that lungs were normally sterile and, unlike the upper airway, the gastrointestinal tract, and the skin, did not have a resident microbiome. With data collected from community-based birth cohort studies and advances in diagnostic techniques, we now understand that many of our earlier concepts were flawed.

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Systematic studies of respiratory infections in community-based birth cohort studies, the Childhood Asthma Study from Perth, Australia[1] and the Childhood Origins of Asthma study from Wisconsin, USA[2] have changed a number of these previously held beliefs. Both studies collected nasal samples from children at times of acute respiratory infections as well as control samples collected when the children were well. These studies firmly established that HRV was responsible for a considerable number of acute lower respiratory illnesses in early life, including those associated with wheeze, and that HRV could be identified in nasal samples collected from approximately 20% of children when they were completely well.[1] In addition, definitive proof has been provided that HRV does infect the bronchial epithelium[3] and can persist in the airways of children after resolution of acute clinical symptoms.[4] There is also definitive proof that the lower airways of healthy individuals are not sterile and have resident bacterial and viral populations,[5,6] and that this resident microbiome may be disordered in disease.[5,6]

Another commonly held concept was that individuals were rarely infected with more than one virus simultaneously. In the current issue of this journal, De Paulis et al.[7] report on viral coinfections in infants hospitalized with acute lower respiratory infections. They conducted a retrospective analysis of 395 hospitalized infants from whom nasopharyngeal aspirates had been collected. Children were excluded if they had been previously hospitalized (n = 44), had a comorbid condition (n = 15), or if medical or virology information was missing (n = 32). Viral infections were identified in 72% of the remaining children, and 80% of these (176/219) were infected with respiratory syncytial virus (RSV). Almost 1/3 of those infected with RSV (31.3%) were coinfected with another virus; 24 with adenovirus, 16 with human metapneumovirus, and 15 with less common respiratory viruses. Six additional children were infected with two viruses without RSV infection. Unfortunately, the authors did not have the ability to look for infection with HRV in their study; so, the coinfection rate may have been underestimated. These authors[7] did not find an increase in clinical severity in infants infected with RSV who were coinfected with another respiratory virus.

There is no consensus in the literature regarding whether viral co-detection in children hospitalized with lower

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respiratory illnesses is associated with an increased severity of disease (Table 1). The term co-detection is more accurate than coinfections, especially when using molecular diagnostic techniques, because the detection of a viral presence does not necessarily mean that this organism is pathogenic in that individual child. Rates of reported viral co-detection in young children range from 14 to 44%, although not all studies included HRV in their viral panel (Table 1). In the majority of studies that have tested for HRV, this is the second or third most common virus detected. Thus, estimates of viral co-detection in studies that have not included HRV are likely to underestimate the true rate. Ten recent studies

Table 1 - Impact of viral coinfection on clinical disease severity in children hospitalized with respiratory illnesses

Study	Setting	Population	Most common viruses identified	Co-detection	Effect of co-detection
Richard et al.[8] Retrospective 2003/2004	Hospital, France	Infants < 1 y, AVB short-stay unit (n = 92) or PICU (n = 88)	Virus in 96.1% (PCR/IF) RSV (70.6%, 73.6%) HRV (18.5%, 25.3%)	24.4%	Increased risk of PICU (OR = 2.7 [95%CI 1.2-6.2])
Cilla et al.[9] Prospective 2004/2006	Hospital, Spain	Children < 3 y, CAP (n = 315)	Virus in 66.9% (PCR/culture) RSV 19.8% Boca virus 14.2% HRV 13.6%	27%	More frequent in infants Increased hospitalization (67.2% vs. 46.1%, p = 0.005)
Calvo et al.[10] Prospective 2000/2003	Hospital, Spain	Children < 2 y, ARI (n = 749)	Virus in 65.9% (PCR) RSV 35.4% Adenovirus 19.3% HRV 13.5%	17.4%	Higher fever Longer hospitalization
Canducci et al.[11] Prospective 2004/2006	Hospital, Italy	Children < 2 y, ARI (n = 322)	Virus in 46.6% (PCR) RSV 28% hMPV 14.3% [HRV not tested]	14%	RSV mono-infection more severe
Aberle et al.[12] Prospective 2000/2004	Hospital, Austria	Infants < 1 y, LRI (n = 772)	Virus in 77% (PCR) RSV 28% HRV 32%	26%	RSV coinfection with more severe clinical course
Suryadevara et al.[13] Prospective 2007/2010	Hospital, USA	Children < 2 y, ARI (n = 201)	Virus in 93% (PCR) RSV 58% HRV/enterovirus 33%	28%	No impact on severity
Nascimento et al.[14] Prospective 2006/2007	Hospital, Brazil	Children < 2 y, AVB (n = 77)	Virus in 93.5% (PCR) RSV 63.6% HRV 39%	44%	No impact on severity
Stempel et al.[15] Retrospective 2003/2004	Hospital, USA	Children < 2 y, AVB (n = 180)	Virus in 93% (PCR) RSV 71% Adenovirus 15% [HRV not measured]	23%	No comments
Marguet et al.[16] Prospective 2002/2004	Hospital, France	Children < 1 y, AVB (n = 209)	Virus in 94.7% (PCR/IF) RSV 60.3% HRV 21.5%	21.5% (RSV/HRV)	RSV infection more severe than HRV No impact of coinfection
De Paulis et al.[7] Retrospective 2005	Hospital, Brazil	Children < 2 y, LRI (n = 304)	Virus in 72% (PCR) RSV 80.4% Adenovirus 9.1%	25.1%	No impact on severity

95%CI = 95% confidence interval; ARI = acute respiratory illness; AVB = acute viral bronchiolitis; CAP = community-acquired pneumonia; hMPV = human metapneumovirus; HRV = human rhinovirus; IF = immunofluorescence; LRI = lower respiratory illness; OR = odds ratio; PCR = polymerase chain reaction; PICU = pediatric intensive care unit; RSV = respiratory syncytial virus; y = year.

have used molecular techniques, alone or in combination with conventional diagnostics, to determine the viral etiology of acute respiratory illnesses in children less than 3 years of age (Table 1). Of these studies, four[8-10,12] reported an increase in clinical severity in children with more than one virus detected, one[11] reported that infection with RSV alone was more severe than when a second virus was detected, four[7,13,14,16] reported that co-detection was not associated with an increase in clinical severity, and one study[15] did not comment on clinical severity. These studies from Europe, Brazil, and North America do not allow a determination as to why this inconsistency in outcome is seen. Although co-detection is reported more frequently in younger children in some studies,[15] and respiratory illnesses, especially acute bronchiolitis, are frequently more severe in younger children, age alone does not explain the disparate reports in the literature.

Given that the impact of viral co-detection on the clinical severity of acute respiratory illnesses requiring hospitalization is not clear, is it important to detect the presence of more than one virus? Certainly, and the realization that HRV is responsible for a large proportion of wheezing illnesses in young children in the community[1,2,17,18] has changed thinking about the role of respiratory viral infections in the inception of asthma. Those who wheeze with HRV infection in early life appear to be at a greatly increased risk of developing subsequent asthma.[17,18] This knowledge has also highlighted the importance of synergistic interactions between respiratory viral infections and allergic sensitization in early life in raising the risk of asthma.[18] We have no knowledge about the long-term consequences of detecting more than one virus during acute respiratory illnesses, either in the community or requiring hospitalization. Therefore, do these epidemiological observations justify increased efforts to detect multiple viruses in children requiring hospitalization? Probably not.

The major reasons for viral diagnostics in children requiring admission to hospital for acute respiratory illnesses are: to make the correct diagnosis so that the correct treatment can be used, and to limit nosocomial infection by instituting appropriate infection control measures. In many parts of the world, children admitted with the typical picture of acute viral bronchiolitis and who have RSV detected in a nasopharyngeal aspirate will not be treated with antibiotics. The likelihood of an antibiotic being prescribed is increased if no respiratory virus is isolated, especially if the child looks sick. In regions where this practice is common, it is important that the viral diagnostics includes methods to detect HRV. In parts of the world where malnutrition and poverty are common or where the risk of bacterial coinfection is increased, antibiotics are likely to be used more liberally based on clinical severity, regardless of the results of the viral diagnostics. Specific antiviral agents are rarely indicated for treating acute respiratory illnesses, especially acute viral bronchiolitis or community-acquired pneumonia; thus, knowledge of the specific infecting virus is not really important for determining therapy. When immunofluorescence is used for initial detection of RSV, there may be little to gain from molecular techniques to diagnose other viruses when a positive result has already been obtained.

Knowledge of the infecting virus is important for instituting appropriate infection control procedures to limit cross infection. Rooming a child with RSV with one with RSV and HRV, or with RSV and human metapneumovirus, may not be a good idea. In an ideal world, every child hospitalized with an acute respiratory illness would be housed in a single room. However, that is not realistic in many children's hospitals.

In summary, knowledge of viral coinfection in young children requiring hospitalization for acute respiratory illnesses is certainly of academic interest and may aid in the institution of appropriate infection control measures to prevent nosocomial infection. However, there is no clear advantage in detecting viral coinfection to determine the appropriate treatment for the individual child.

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