Journal of Infection (2014) 68, S115—S118

BIAM British Infection Association

www.elsevierhealth.com/journals/jinf

Respiratory syncytial virus: How, why and what to do

Rosa Rodriguez [a], Octavio Ramilo [b,*]

[a] Hospital Materno-Infantil Gregorio Marañón, Madrid, Spain
[b] Nationwide Children's Hospital and Ohio State University, Columbus, OH, USA

Accepted 20 September 2013
Available online 27 October 2013

KEYWORDS
Respiratory Syncytial Virus, RSV;
Viral coinfections;
Bronchiolitis;
Palivizumab;
RNAi

Summary Bronchiolitis is the leading cause of hospitalization of infants and young children worldwide. Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis in infants. Studies conducted using molecular diagnostic assays confirmed that RSV accounts for over 50% of bronchiolitis in young children requiring hospitalization. Those studies demonstrate that it is common to identify RSV in association with a second viral agent but it is yet unclear whether the simultaneous detection of two or even three viruses is associated with increased disease severity. Despite extensive efforts, a vaccine for prevention of RSV infection is not yet available. Palivizumab a humanized monoclonal antibody directed against the F protein of RSV is the only agent licensed to prevent severe RSV disease in high-risk children. Among the new antivirals being developed for treatment of RSV infections, an RNA-interference based agent has demonstrated promising results for treatment of lung transplant recipients with acute RSV infection.

The virus

RSV is a member of the Mononegavirales in the Paramyxoviridae family, and Pneumovirinae subfamily. RSV is an enveloped virus with a negative sense, single-stranded RNA genome. These viruses are 150—200 nm in diameter with a helical nucleocapside. RSV has 10 genes encoding 11 proteins—there are 2 open reading frames of M2. The NS1 and NS2 proteins inhibit type I interferon activity. N protein encodes the nucleocapsid protein that associates with the genomic RNA forming the nucleocapsid, and the M protein encodes the Matrix protein required for viral assembly. The G protein is a surface protein that is heavily glycosylated. It functions as the attachment protein. The F protein is another surface protein that mediates fusion, allowing entry of the virus into the cell cytoplasm and also allowing the formation of syncytia. The F protein is relatively conserved in both subtypes of RSV A and B; antibodies

* Corresponding author. Nationwide Children's Hospital, Section of Infectious Diseases, Room ED161, Columbus, OH 43215, USA. Tel.: +1 614 722 3416.
E-mail address: octavio.ramilo@nationwidechildrens.org (O. Ramilo).

0163-4453/$36 © 2013 Published by Elsevier Ltd on behalf of The British Infection Association.
http://dx.doi.org/10.1016/j.jinf.2013.09.021

directed at the F protein are neutralizing. In contrast, the G protein differs considerably between the two subtypes.[1]

Epidemiology and global burden of RSV

Acute lower respiratory infection (ALRI) is the leading cause of global child mortality. Respiratory syncytial virus (RSV) is the most frequent viral pathogen causing ALRI in young children. The global burden of RSV is significant.[2,3] A recent meta-analysis suggests that RSV causes up to 33.8 million ALRIs among children under age 5 (22% of all Lower Respiratory Tract Infections) each year. At least 3.4 million cases required hospital admission, and an estimated 66,000—199,000 of children died, nearly all in developing countries.[2] In the United States, RSV is the most common cause of hospitalization in infants, with an estimated hospitalization rate of 2350/100,000 (95% CI, 2220—2520) in children less than 1 year of age.[4] However the estimates of RSV-associated ALRI incidence are highly variable within countries or regions and between regions. The RSV-associated ALRI incidence estimates are more likely to underestimate than to overestimate true incidence in developing countries.

Results of a study of a large hospital-based cohort in Texas (Children's Medical Center Dallas) conducted from 2002 to 2007 offer a comprehensive description of the burden of bronchiolitis in the inpatient setting.[5] Because 95% of children hospitalized with bronchiolitis had a viral diagnostic test performed the authors were able to compare the differences in demographic, clinical, microbiological, and radiologic characteristics and the presence of risk factors predictive of severe disease in children younger than 2 years with RSV versus non-RSV bronchiolitis. In agreement with previous studies conducted in the 1990s, the proportion of hospitalizations for bronchiolitis significantly increased during the study period, from 3.3% in 2002 to 5.5% in 2007. Whereas the percentage of hospitalizations attributed to non-RSV bronchiolitis decreased throughout the study, those caused by RSV significantly increased during the same period so that, during the last 4 years of the study, they were double the number of non-RSV bronchiolitis hospitalizations (63%—67% vs 33%—37%, respectively).[5]

Seventy three percent of children hospitalized with RSV infection had no underlying medical conditions. In fact, 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. There were several factors that were independently correlated with the severity of illness regardless of the etiology of the bronchiolitis. Although prematurity, chronic lung disease (CLD), and congenital heart disease (CHD) have been previously associated with severe disease in patients with RSV infection, the authors also found that trisomy 21, respiratory abnormalities and neuromuscular disorders were also associated with increased disease severity. RSV infection, per se, was an independent predictor for severe bronchiolitis. Altogether, these findings underscore the need for an effective RSV vaccine and, in the mean time, the necessity to develop novel strategies that may allow the implementation of anti-RSV prophylaxis in broader patient populations.

Vitamin D and bronchiolitis

Vitamin D status is determined largely from ultraviolet B ray exposure at all ages. Vitamin D also is available from dietary sources, which are more important at higher latitudes at which ultraviolet B ray exposure is inadequate for skin synthesis of vitamin D during winter. The diverse sources of vitamin D, which involve environmental conditions and complex behaviors, complicate vitamin D research. Fortunately, serum 25(OH)D levels provide an excellent measure of overall vitamin D status.

In a recent population-based study of 922 healthy New Zealand children, Camargo et al. found that low cord-blood levels of 25(OH)D were associated with a higher risk of respiratory infection during the first months of life and a higher risk of cumulative wheeze throughout early childhood.[6]

Additional studies conducted in Finland[7] and the Netherlands[8] found a similar association between low cord-blood vitamin D levels and increased risk of respiratory infections and more precisely RSV bronchiolitis. These are intriguing observations, and it is possible that the inverse correlation between cord-blood 25(OH)D levels and respiratory infections may explain the association between low vitamin D levels and wheezing. Although it is unclear how a single cord-blood level could explain wheeze risk over several years, the authors suggest that it is possible that vitamin D levels during pregnancy might affect the subsequent development of the immune system. More recently, a randomized trial conducted during winter in Mongolia showed that vitamin D supplementation was associated with reduced risk of acute respiratory infections.[9] Taken together, these studies indicate a potentially important role for vitamin D in modifying the risk of respiratory infections.

Molecular diagnosis and co-infections

The development of sensitive molecular diagnostic assays has increased the number of viruses detected in respiratory samples compared with conventional methods. A number of studies have used PCR-based assays to study the etiology of bronchiolitis in hospitalized children. Using these methods several investigators have identified viruses in >90% cases of bronchiolitis. In hospitalized infants, RSV was the most frequent agent of bronchiolitis in winter, but other viruses were present in up to 47% of the patients. Those studies confirmed that RSV is the most frequent etiologic agent of bronchiolitis as a single pathogen (40—45%) and second as a copathogen (18—20%) followed by rhinovirus (HRV), human metapneumovirus (hMPV) and adenovirus as single pathogens. Although the clinical characteristics were similar amongst them, the seasonality was different.[10—13]

The use of molecular techniques for viral detection has increased the identification of multiple viruses in a single sample. The prevalence of co-infections in some studies has ranged from 19 to 35% in young children with diverse types of respiratory tract infection admitted to hospital or evaluated in the emergency department. The question as to whether infection by multiple viruses is associated with increased disease severity remains