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New options in the treatment of respiratory syncytial virus disease

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Summary Respiratory syncytial virus (RSV) remains a significant cause of morbidity and mortality in infants, immunocompromised patients and the elderly. Despite the high disease burden, an effective vaccine or specific therapy are lacking which is largely due to our limited understanding of the immune response to RSV and how it relates to clinical disease severity. Current treatment for RSV remains largely supportive and RSV-specific options for prophylaxis and/or treatment are limited to palivizumab and ribavirin. There are a number of promising compounds currently under development, including new monoclonal antibodies and small molecules. These newer antivirals have the potential to impact both the prevention and treatment of RSV disease in the main target populations.

Global burden of RSV disease

Respiratory syncytial virus (RSV) is an enveloped, negative-sense, single-stranded RNA virus that belongs to the family *Paramyxoviridae*. Human RSV exists as two antigenic subgroups, A and B, which can co-circulate during the same season and exhibit genome-wide sequence divergence. Its genome contains 15,222 nucleotides that encode eleven proteins. The two glycosylated surface proteins, the F and G proteins, are crucial for the infectivity and pathogenesis of the virus. The attachment (G) protein targets the ciliated cells of the airways and mediates adherence of the virus to the host cells. The fusion (F) protein initiates viral penetration by fusing viral and cellular membranes. This protein also promotes direct cell-to-cell spread of RSV, thereby inducing the production of the characteristic syncytia. The F and G proteins carry the antigenic determinants that elicit the production of neutralizing antibodies by the host.[1,2] Nevertheless, the F protein represents the major target for antiviral drug development, especially in its prefusion form (PreF), which has shown to be highly superior at inducing neutralizing antibodies compared to its postfusion (postF) form.[3—5]

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Respiratory syncytial virus (RSV) is one of the great threats to child health associated with considerable acute and long-term morbidity.[6–11] This RNA virus represents the leading cause of viral lower respiratory tract infection (LRTI, including bronchiolitis and pneumonia) among infants and young children globally. In addition, RSV is also a major pathogen in the elderly and immunocompromised individuals.[12,13] Just in 2005, 3.4 million children were hospitalized for RSV LRTI worldwide. The burden of RSV disease however, is significantly larger in the outpatient setting where it is associated with considerable acute and long-term morbidity.[7] Moreover, in the developing world is only second to malaria as a cause of death during the first year of life.[11] Essentially all children are infected by this virus within the first two years of life, as RSV invariably causes yearly outbreaks.[14] The reinfection rate in children infected as infants is estimated to be 74–83% in their second year, and 46–65% in their third year,[15] which together with the observation that RSV-immune adult volunteers could be repeatedly reinfected with a single viral strain demonstrates the inadequacy of the immune response to this virus which is neither complete nor sustained.

Pathogenesis of RSV

Epidemiologic studies have identified selected groups of infants (premature infants, children with chronic lung or congenital heart disease, immunodeficiency and more recently children with comorbidities), at high risk for severe disease and mortality. However, the majority of children hospitalized with RSV LRTI are previously healthy with no known risk factors for severe disease.[6,16] Of those hospitalized infants, 10–20% will develop a disease severe enough to require admission to the intensive care unit (PICU). Despite the high disease burden, an effective vaccine or specific therapy is lacking which is largely due to our limited understanding of the immune response to RSV and how it relates to clinical disease severity.

Studies and clinical practice have shown that there is great variability in the severity of the disease among infected children.[7] Indeed, in the clinical setting it is impossible to predict, based on the physical examination and available diagnostic tools, which patients will show progressively worse disease and will require hospitalization and even ICU care, and which patients can be discharged home safely. The difficulties in determining the likelihood of disease progression, have led investigators to search for clinical risk factors and/or biomarkers, such as cytokines, that can help predicting RSV disease severity with no definitive results. It has been proposed that the combination of both, viral factors and the host immune response likely contribute to the severity of RSV disease (Fig. 1).[17–21]

Role of viral loads

Several studies have attempted to correlate RSV loads measured in the respiratory tract by culture or real time (RT)-PCR with disease severity with contradictory results.[18,20,22–24] It should be mentioned that these studies included heterogeneous patient populations and of different ages at different stages of their infection, likely introducing confounders in the analyses. To address these issues a recent multicenter prospective study that included 1764 children <2 years of age hospitalized with RSV LRTI showed that those with higher genomic RSV loads had a higher risk of PICU admission and longer duration of hospitalization adjusted for other variables.[25] The effect of different viral subtypes (RSV A and B) as well as of viral genotypes on the severity of the illness has also been studied.[26] While some studies identified a significant correlation between RSV type A and disease severity others failed to confirm those findings.[27] Nevertheless, during typical RSV outbreaks, which in temperate climates each year predictively last from late fall through early spring, a limited number of RSV strains tend to circulate. Thus, it remains unclear why previously healthy children infected with the same viral strain display such a wide variation of clinical manifestations, and suggests that an abnormal host immune response or host immune "insufficiency" greatly contributes to the different disease phenotypes.

Host immune response

Until recently, it was postulated that severe RSV infection was associated with an exaggerated inflammatory response. Others and we have shown that host innate immune responses are actually inadequately activated or even suppressed in infants with severe RSV disease.[19,21,28,29] These observations represent a paradigm shift and suggest that weak, rather than intact or robust innate immune responses are associated with enhanced acute disease severity and may contribute to the chronic/persistent airway disease observed in a subset of children after RSV LRTI (Fig. 1).

We recently characterized innate immune functional responses in a cohort of previously healthy infants

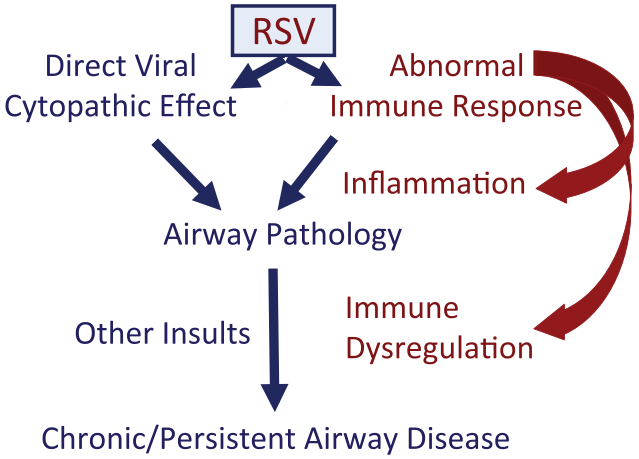

Figure 1 Pathogenesis of RSV bronchiolitis. The combination of both, viral factors and the host immune response contribute to the severity of RSV disease. However, rather than an exaggerated innate immune response, recent studies have shown that impaired responses, coupled with other factors (environmental, size of the airway) are associated with enhanced acute disease severity and may contribute to the chronic/persistent airway disease observed in a subset of children after RSV LRTI.