Paediatric Respiratory Reviews 16 (2015) 232–240

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Mini-symposium: Biomarkers and Phenotype

Biomarkers of respiratory syncytial virus (RSV) infection: specific neutrophil and cytokine levels provide increased accuracy in predicting disease severity

Paul M. Brown, Dana L. Schneeberger, Giovanni Piedimonte *

Center for Pediatric Research, Pediatric Institute and Children's Hospitals, The Cleveland Clinic

EDUCATIONAL AIMS

The reader will come to:

- Understand that RSV infection of the lower airways is the primary cause of acute bronchiolitis in infants and children worldwide.
- Learn the evidence linking early-life RSV lower respiratory tract infections to the development of childhood asthma.
- Recognize the multifaceted role of nerve growth factor (NGF) and other neurotrophins in the pathophysiology of RSV bronchiolitis.
- Know that a limited number of host biomarkers have been identified recently as predictive of RSV bronchiolitis severity outcomes.

ARTICLE INFO

Keywords:
Asthma
Brain-derived growth factor (BDNF)
Bronchiolitis
Lung development
Nerve growth factor (NGF)

SUMMARY

Despite fundamental advances in the research on respiratory syncytial virus (RSV) since its initial identification almost 60 years ago, recurring failures in developing vaccines and pharmacologic strategies effective in controlling the infection have allowed RSV to become a leading cause of global infant morbidity and mortality. Indeed, the burden of this infection on families and health care organizations worldwide continues to escalate and its financial costs are growing. Furthermore, strong epidemiologic evidence indicates that early-life lower respiratory tract infections caused by RSV lead to the development of recurrent wheezing and childhood asthma. While some progress has been made in the identification of reliable biomarkers for RSV bronchiolitis, a "one size fits all" biomarker capable of accurately and consistently predicting disease severity and post-acute outcomes has yet to be discovered. Therefore, it is of great importance on a global scale to identify useful biomarkers for this infection that will allow pediatricians to cost-effectively predict the clinical course of the disease, as well as monitor the efficacy of new therapeutic strategies.

INTRODUCTION

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infections (LRTI) in infants and pre-school children. As virtually all children are infected with this virus at least once by 2 years of age, current estimates suggest RSV infection is responsible for greater than 60% of all acute LRTI in young children and more than 80% of all acute LRTI in infants under one year old worldwide [1,2]. RSV LRTI are typically hallmarked by the development of bronchiolitis, defined as inflammation of the bronchiolar airways leading to obstruction [3]. Accordingly, bronchiolitis is the principal cause of hospitalization in infants under one year of age in the U.S., accounting for 16.4% of total hospitalizations in this age group [1], while more than one third of children will have developed bronchiolitis at some point prior to becoming two years old [4]. The clinical severity of bronchiolitis ranges from mild forms manageable on an outpatient basis to severe cases that require mechanical ventilation or extracorporeal membrane oxygenation (ECMO) in intensive care units (ICU) [2]. Highlighting the potential threat posed by bronchiolitis, a recent retrospective study found the ICU admission rate for all children under age 2 with bronchiolitis to be 22%, with 89% of the ICU admission cases testing positive

* Corresponding author. Cleveland Clinic Pediatric Institute, 9500, Euclid Avenue, A-111; Cleveland, OH 44195, USA. Tel.: +216.444.2344; fax: +216.445.3797.
E-mail address: PIEDIMG@ccf.org (G. Piedimonte).

http://dx.doi.org/10.1016/j.prrv.2015.05.005
1526-0542/

for RSV infection and 47% ultimately requiring mechanical ventilation [5].

Early-life RSV infection has also been shown to lead to chronic airway dysfunction, with an increased risk of subsequent wheezing episodes that lasts for several years after the acute infection [6–9]. This characteristic of the virus has been the basis of a longstanding debate as to whether RSV infection is simply a trigger that uncovers an intrinsic predisposition, or rather a causative agent contributing to the inception of childhood asthma [10,11]. In addition to a plethora of studies focusing on the role of the innate and adaptive immune systems, other studies have looked into the effects of RSV on airway innervation and reactivity both during and after infection and have shown that specific neurotrophic proteins and their cognate receptors are upregulated by this infection leading to persistent airway hyperreactivity [12–14]. In addition, the establishment of a lytic RSV infection cycle has been shown to involve a series of pro-survival mechanisms - including host immune system evasion and prevention of apoptosis by infected host cells – mediated through modulation of nerve growth factor (NGF) activity [12,15–17].

Even with intensive research focused on RSV since its discovery in 1956 [18,19], pediatric clinicians currently lack an effective vaccine capable of preventing the infection and must instead rely on supportive therapies aimed at managing complications of bronchiolitis (e.g., nasal suctioning, hydration, supplemental oxygen) [2,20]. Once the infection is established, clinicians will empirically assess the trajectory of a patient's symptoms in an attempt to predict its evolution, and will tailor their management strategy accordingly [21]. Over time, clinical observation has led to the identification of specific risk factors for severe RSV bronchiolitis: premature birth (<32 weeks gestational age), male sex, lack of breastfeeding, chronic lung disease, hemodynamically-significant congenital heart disease, and severe immunodeficiency amongst others [22–28]. However, numerous studies have also demonstrated that a majority of children hospitalized with RSV bronchiolitis lack these risk factors and were healthy prior to their clinical event [5,29,30]. As a result, efforts aimed at identifying novel biological markers measurable in the host during the course of RSV bronchiolitis have multiplied in hopes of developing a clinically effective method to predict disease severity outcomes. To this end, some advances in the development of biomarkers of RSV bronchiolitis have been made over the last several years and the primary purpose of this review is to state the need and discuss potential solutions for such biomarkers in more detail.

CHARACTHERISTICS OF RSV INFECTION

The highly contagious nature of RSV stems from its ability to survive outside of a host up to 6 hours on hard surfaces and on the skin for 20 minutes [31]. This prolonged viability permits the inoculation of mucous membranes in the eyes or nose and allows the virus to spread quickly from the hands of adult hosts to infants and young children [32,33]. Upon inoculation, RSV first infects the nasopharyngeal epithelium of the upper respiratory tract and subsequently spreads towards its more competent replication site in the bronchiolar epithelium within 1-3 days with peak infectivity achieved around 5-days post-inoculation [15,34]. Host innate and adaptive immune responses are continuously triggered during this spread to the lower airways, but fail to effectively clear RSV in young children and immunocompromised individuals [23,35,36].

The inherent ability of RSV to manipulate host innate, adaptive, and memory immune responses is a contributing factor to an inability to develop a fully effective vaccine against the virus [17]. From initial failings in vaccine development leading to increased mortality in 1966 [37,38] to more recent RSV vaccine approaches that initially showed promise [20], there still remains a void of safe and effective prophylaxis, other than the passive protection provided by the humanized monoclonal antibody palivizumab (Synagis®; marketed by MedImmune, LLC) [39–43]. As the prohibitive costs of this intervention limit its use to a minority of high-risk infants, the need for research aimed at identifying reliable biomarkers of RSV bronchiolitis in parallel with safe and effective therapy remains strong [44].

IMPACT OF RSV INFECTION ON PEDIATRIC HEALTH

In the U.S. population under one year of age, RSV-associated LRTI account for approximately 126,000 hospitalizations (25.2 per 1,000) [45] with estimated direct costs ranging from $394 million to $1.1 billion annually [46,47]. When examining the global burden of RSV infection on developing nations, a systematic review and analysis of available literature estimated that nearly 33.8 million new cases of RSV-associated LRTI occur worldwide in children under 5 years of age leading to approximately 3.4 million hospitalizations annually [48]. These figures also fail to take into account the rates of hospitalization and mortality that RSV infection imparts on the elderly, a population now recognized as extremely susceptible to the virus and for which the associated health care costs are surely tremendous [49–53]. When taken together on a global scale, high RSV-associated LRTI hospitalization rates coupled with the increasing price of healthcare potentially cost the world hundreds of billions of dollars annually and put significant strain on infected individuals, health care providers, and health care systems alike.

In the U.S., mortality associated with RSV infection is uncommon in the 21st century due to effective hygiene and supportive care, with the approximately 40 deaths per year mostly occurring in infants with complex chronic conditions or in those with life-threatening conditions preexisting the infection [54]. In contrast, the global impact of RSV infection on infants and young children is staggering: worldwide, RSV-associated LRTI are the second leading cause of pathogenic mortality in infants less than one year of age [48]. Varied estimates place the global mortality rate somewhere between 200,000 and 1 million deaths annually in children under 5 years of age [2,48]. Therefore, the need for effective strategies aimed at reducing RSV bronchiolitis morbidity and mortality rates has never been greater with the development and implementation of these tactics holding the potential to save hundreds of thousands of lives around the globe each year.

RSV INFECTION AND ASTHMA DEVELOPMENT

In immunocompetent children, RSV is fully cleared from the lower airways within 8 days after initial infection though its ability to cause persistent airway dysfunction is well documented [31,55]. Multiple prospective epidemiological studies have associated these respiratory sequelae, chiefly recurrent episodes of wheezing and asthma development within the first decade of life, with early-life RSV LRTI [9–11,56]. Mechanistic studies have demonstrated the involvement of both neurological networks [14,57–60] and immune cells [61–63] within infected host tissues as being directly involved in post-infection airway obstruction. Numerous studies have also underscored the important effects that NGF and other neurotrophins have on airway tissues such as smooth muscle and fibroblasts during both acute bronchiolitis and chronic asthma [64–66]. The interplay between neural and immune networks has been described in numerous publications [2,55,61] and has led to continued and vigorous debate within the field of pediatric asthma as to which avenue has a greater impact on chronic sequelae development: nerves and nerve-derived