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Respiratory syncytial virus - current treatment options and future possibilities for prophylaxis

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ABSTRACT:

The respiratory syncytial virus (RSV) is responsible for a great deal of lower respiratory tract infections in infants, which result in hospitalizations and death in extreme cases. Almost all children have been infected by the time they turn two years old, but the most vulnerable to developing medical complications are preemies and infants with congenital heart diseases. Understanding the function of RSV F (fusion) protein turned out to be crucial in developing immunoprophylactic drugs, such as Palivizumab and Nirsevimab. Due to limited options of treatment, the search for optimal prophylactic strategy is expanding. This includes monoclonal antibodies and mRNA vaccines. Bringing attention to these methods of treatment will help expand the knowledge of healthcare providers, especially pediatricians and general practitioners.

AIM OF THE STUDY

We would like to present the current knowledge of the virus itself, possible treatment options, which are up to standards with evidence based medicine, as well as prophylactic strategies that are either available or processed in clinical trials at this moment. Bringing attention to these methods of treatment will help expand the knowledge of healthcare providers, especially

pediatricians and general practitioners, who will come into contact with RSV – infected children the most often.

MATERIALS AND METHODS

Literature available in the PubMeb database, ScienceDirect and Cochrane Library was reviewed using the following keywords: “RSV pathogenesis”, “RSV treatment”, “RSV prophylaxis”, “RSV epidemiology”.

CONCLUSIONS

There are multiple risk factors for RSV infections. Being able to identify those traits and possessing up-to-date knowledge about current treatment and prophylactic options will increase the chances of recovery, as well as prevent medical complications in the future.

KEYWORDS: “RSV pathogenesis”; “RSV treatment”; “RSV prophylaxis”; “RSV epidemiology”

INTRODUCTION

RSV is a highly prevalent viral pathogen, being most commonly associated with causing lower respiratory tract infections (LRTIs) in infants. Apart from the need for hospitalization and intensive care, such infections can have a dramatic impact on the patient’s health in the distant future, as some studies report the correlation between an RSV infection during infancy and developing childhood asthma [1]. Despite being discovered in the 1950s, there are still very limited options for preventative care and treatment, which combined with the mortality rate and possible medical complications, serve as a great socioeconomic burden [2]. We would like to present the current knowledge of the virus itself, possible treatment options, which are up to standards with evidence based medicine, as well as prophylactic strategies that are either available or processed in clinical trials at this moment.

EPIDEMIOLOGY

RSV is among the most prevalent viral pathogens with studies claiming up to 70% of children have been infected by the time they turn 1 year old, and almost all of them by 2 years of age

[3]. It's the leading cause for lower respiratory infections not only in children, but also the elderly and those struggling with immunosuppression [4]. In 2015, it was estimated that worldwide, RSV was the cause for about 118,200 deaths in children under 5 years of age [5]. Only humans can be hosts for RSV [6], its transmission routes include direct contact and the airborne route via large saliva or mucus droplets. The increase of viral outbreaks in the northern hemisphere is observed during autumn and winter, which is important to take into account when developing efficient prophylactic programs [7]. What's interesting, the recent COVID 19 pandemic caused a drastic decrease in RSV detections, mainly because of social distancing and increased hygienic practices. However, a subsequent increase of RSV cases and out of season outbreaks have been reported in several countries. This shift in epidemiology should be monitored in order to assess the best preventative care [8].

PATHOGENESIS

RSV is a single-stranded RNA virus, containing 10 genes which encode 11 proteins, including: structural proteins, such as N (nuclear) and M (matrix) proteins; NS-1 and NS-2 (non-structural) proteins; phosphoproteins and L polymerase proteins, which are required for forming functional polymerase complexes; G (glycoproteins), SH (small hydrophobic) and F (fusion) proteins, which are on the external side of the viral lipid envelope and lastly, the regulatory M2 proteins. Upon entering the host's airway, the RSV invasion targets the apical surface of respiratory airway cells using the RSV G protein. One-third of this 298-amino acid glycoprotein contains a membrane anchor at its N-terminus [9], allowing the virus to attach itself to the target membrane. Subsequently, the host cell proteases cleave inactive RSV F protein precursor into two subunits, F1 and F2, which are connected via a disulfide bond. The complex undergoes further conformational changes until the exposure of the fusion peptide, which inserts itself into the host cell membrane, inciting the fusion [10].

Apart from forming an active fusion complex, the RSV G and RSV F proteins serve a crucial role in modifying the immune response to the virus in order to create an environment more suitable for viral replication. As previously stated, the RSV G protein can be found on the viral envelope, bound to its external side (RSV mG). Additionally, it is also possible to synthesize this protein in a soluble form (RSV sG). This is a part of the "antigen decoy" strategy, which is commonly used by various viruses worldwide [11]. The RSV sG mediates the evasion of the host's immune response. Studies show that the possible explanation for this occurrence involves an inference with opsonization, ADCC and complement-mediated

cytotoxicity, all of which being vital to effective viral clearance [12]. Other RSV proteins, namely the NS-1 and NS-2 are associated with INF expression [13]. That information turned out to be useful in estimating the severity of RSV infection, as higher concentrations of mucosal INFs correlated with decreased chances of hospitalization in both younger and older infants [14]. It is speculated that the mechanisms mentioned above are key to understanding the pathogenesis of lower respiratory tract infections caused by RSV. In order to compensate for the insufficient response from cytotoxic lymphocytes, the host's immune system mainly depends on neutrophils, macrophages and apoptosis. Although these mechanisms certainly help to fight off viral infections, they also damage neighboring cells, regardless if they are infected or not, creating an abundance of dead epithelial cells in the airways [15]. As a result, bronchioles can be obstructed by the accumulation of mucus and cell debris, leading to bronchiolitis, which includes symptoms such as: fever, productive cough, increased respiratory effort and chest congestion [16].

TREATMENT

An RSV infection can entail severe complications, including death in extreme cases. One of the most susceptible group of patients are prematurely born infants, but other risk factors worth mentioning are: maternal and passive smoking, low birth weight, family history of asthma or atopy, air pollution and even the presence of siblings or other children in the house [17]. Furthermore, some analyses bring to attention the possibility of an increase in RSV infections and complications in the adult population as a result of the SARS-CoV-2 pandemic [18]. This shows that the current situation calls for an appropriate anti-viral treatment. However, the regimen for an RSV infection mainly consists of symptomatic treatment. Over the course of the years a plethora of different strategies have been implemented, some of which have turned out to be ineffective. In this section we will go through the most prominent of them in detail.

RIBAVIRIN

Ribavirin is a drug with anti-viral properties, which is broadly used in treating infections caused by RNA viruses, such as hepatitis C and Lassa fever. [19] After being discovered in 1972, its exact mechanism would remain unknown for years to come. Nowadays it is believed that ribavirin's effects are connected to mutations of the viral genome. The chemical structure is analogous to adenosine and guanosine, and as a result it can be incorporated into the RNA

during replication, leading to a phenomenon known as ”error catastrophe”, in which the excess of mutations causes the genome to lose its meaning. This prevents the viral population from successfully multiplying [20]. Nearly 40 years ago, aerosolized ribavirin was approved for treating patients with LRTIs caused by RSV, yet it still stands as the only drug licensed by the FDA for this specific use. During randomized trials, which aimed to assess the success rate of ribavirin treatment in RSV infected infants with LTRIs, it was discovered that the mortality rate, along with the days of hospitalization and ventilation, were decreased compared to placebo. However, after taking into consideration the size of the analyzed groups, it is impossible to estimate the exact efficiency of ribavirin. Nonetheless, these findings suggest that ribavirin treatment has a positive effect on this group of patients [21]. On the downside, aerosolized ribavirin, on top of being more expensive than alternatives, possesses a risk of causing teratogenic side effects to healthcare workers and other patients [22]. As of today, there is a huge demand for large scale studies that could compare oral and intravenous forms of ribavirin to currently licensed aerosol, as well as the possibilities of coupling them with other medications, such as corticoids.

BRONCHODILATORS

Bronchodilator therapy is commonly used for treating patients with asthma. It includes drugs such as β2 agonists, anticholinergics and corticosteroids. Although relaxing the bronchial muscles and widening the air passages is an effective way of relieving asthmatic symptoms, the same cannot be stated about bronchiolitis, which is the main medical complication of an RSV infection. Meta-analyses show that bronchodilators are not successful in reducing hospitalization time or improving oxygen saturation [23]. Nowadays, the AAP guideline for bronchiolitis does not recommend their use, opting for supportive care with oxygen supplementation if necessary. Despite that, many infants still receive inadequate care [24], which highlights the importance of practicing evidence-based medicine.

PREVENTION

Due to the lack of options when it comes to treatment, as well as possible connections between recurrent wheeze and asthma in children after an RSV infection during infancy [25]. There is a dire need for prophylactic strategies. As of today, there are a couple of choices, some of which still need to be licensed. They include monoclonal antibodies, nanobodies, vaccines and maternal immunization.

PALIVIZUMAB

Palivizumab is a humanized monoclonal antibody which targets the RSV F protein of both A and B subtypes of the virus. After being approved by the FDA in 1998, studies have reported it to be more effective at neutralizing and reducing viral replication than the options available at the time – RSV-IGIV and felvizumab to name a few. What is more, it is also well tolerated by high-risk infants and has no reactivity towards other prophylactic methods [26]. In order to prevent LRTI, palivizumab is injected intramuscularly every month during RSV season. Patients who benefit the most from this treatment are children under 24 months of age with congenital heart disease, bronchopulmonary dysplasia or prematurity. In a study that aimed to estimate the efficacy of palivizumab in preventing RSV infections and any adverse effects in high-risk children, it was concluded that although there was little to no change in mortality rates in participating groups, the hospitalization time and number of wheezing days were reduced. It is also speculated that it reduced RSV infections at a two years' follow-up, however, more evidence is needed to support that claim [27]. It's worth mentioning that there was an attempt to assess the effectiveness and tolerability of palivizumab prophylaxis for children with cystic fibrosis. Unfortunately, only one randomized trial was identified, so definite conclusions could not be made [28].

NIRSEVIMAB

Nirsevimab is a fairly new medication, as it was approved in November 2022. It's a human IgG1κ monoclonal antibody with prolonged action, that similarly to palivizumab aims to prevent RSV-caused LRTIs in infants. The key difference between these two drugs is that unlike palivizumab, which needs five monthly doses, nirsevimab is only administered once [29]. This serves as a huge advantage, as the need for multiple injections is an obstacle in providing efficient prophylaxis in low resource settings [30]. A recent study that compared nirsevimab with a placebo group showed that this treatment reduced cases of medical attended and hospitalized LRTIs caused by RSV infections in otherwise healthy infants [31].

MOTAVIZUMAB

Motavizumab, previously known as MEDI-524, was developed to be an evolved version of palivizumab, having an additional chain of amino acid residues. Similarly, it targets the RSV F protein to neutralize the virus [32]. Clinical trials showed great efficacy in reducing

hospitalizations and medically attended LRTIs, while maintaining safety. Studies reported that motavizumab was more effective compared to its predecessor – palivizumab [33]. However, despite promising results, it was later concluded that motavizumab treatment had a higher risk of cutaneous events. Therefore, in 2010 the development was discontinued [34], [35].

ALX-0171 (GONTIVIMAB)

ALX-0171 is a nanobody which is currently in trials in order to assess its effectiveness and safety in treating children with an RSV infection. A phase 2b clinical trial published in 2021 compared nebulized AXL-0171 administration in children with RSV – related LRTIs to a placebo group. The findings include reduced median time for the viral load to drop below detectable levels using both plaque assay and RT-qPCR for measurement. However, the clinical outcomes did not differ significantly from the placebo group. While serious adverse effects were more common in AXL-0171 group by 6 percentage points, it was concluded that the majority of them were unrelated to its use [36].

REGN-2222 (SUPTAVUMAB)

Suptavumab is a human monoclonal antibody, that was supposed to serve as a form of prophylaxis against RSV. It targets the F protein of both RSV subtype A and B. Comparing it to palivizumab in vitro and in cotton rat model showed promising results, as it was more potent in neutralization. Unfortunately, that didn't translate well into human clinical trials. After comparing placebo with suptavumab in a double-blind, randomized trial it was concluded that neither RSV hospitalizations nor outpatient treated LRTIs were reduced. The main reason for that is attributed to large scale mutation of the RSV subtype B, which prevented suptavumab from binding to the RSV F protein. Therefore, the development was discontinued [37].

MATERNAL IMMUNIZATION

Another promising strategy of immunoprophylaxis is maternal immunization. It's a method that utilizes the transport of maternal immunoglobulins through the placenta into the fetal blood. It's a naturally occurring phenomenon, which begins to take place during the second trimester of the pregnancy, continuing until the birth. The antibodies are meant to protect the newborn in the first months of its life [38]. Currently, one of the most common examples of

using maternal vaccines are the Influenza and Tdap (Tetanus, Diphtheria, acellular Pertussis) vaccines. They are recommended to be administered during the third trimester of each pregnancy [39]. A similar strategy has been adopted regarding the RSV. A study published in 2019 monitored pregnant women and infants after administering an F – protein RSV vaccine during the third trimester. The vaccine appeared to be safe, as it didn't cause any severe reactogenic reactions, nor did it have any impact on the pregnancy, delivery or the well – being of the mothers and the infants. Furthermore, the percentages of both medically significant and severe LRTIs were reduced in the vaccine group compared to placebo over the course of 6 months of infant's life, though the clinical impact of this treatment was observed beyond that period [40] . In another study, it was also discovered that women who were vaccinated presented higher concentrations of RSV F – protein specific antibodies. This opens the possibility of providing further protection to infants, however, another study needs to be conducted to draw this conclusion [41].

mRNA VACCINES

While the development of the first mRNA vaccine against RSV began over 20 years ago, it was unfortunately halted because of instability in storage. It was resumed recently, as more technologies allowing the self – replication of the RNA were developed in the early 2010s [42], [43] . Considering the success of the mRNA vaccines against COVID-19 after the pandemic, it was to no surprise that the search for an RSV counterpart accelerated. To summarize the current knowledge, there are three candidates developed by Moderna, which are currently in clinical trials. All of them target the RSV F protein and show a promising response of the host's immune system, while remaining safe. However, they are yet to be tested on children and infants. Despite that, such vaccines will be a great and efficient strategy in protecting the elderly and adults who are also at risk of developing RSV – caused LRTIs [44].

CONCLUSIONS

With more treatment and prophylaxis options that ever before, there is a possibility of significantly reducing the load of RSV infections in the future. It is especially important for general practitioners and pediatricians to educate themselves on this matter, in order to provide the best possible healthcare to children, who are at the biggest risk of developing serious medical complications as a result of the RSV infection. It is also crucial to inform

pregnant women and parents about methods of protecting their infants, as preventing RSV is safer than treating it. We believe that this article will be beneficial in said aspects.

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