

Expert Opinion

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A review of palivizumab and emerging therapies for respiratory syncytial virus

Kristin A Shadman[†] & Ellen R Wald

University of Wisconsin School of Medicine and Public Health, Department of Pediatrics, Madison, WI, USA

Introduction: Respiratory syncytial virus (RSV) is an important pathogen in children and adults; however, current treatment options are primarily supportive. Palivizumab, the only approved specific monoclonal antibody for RSV is used prophylactically to reduce morbidity in a select population of high-risk children.

Areas covered: The development and current use of palivizumab; the potential role of palivizumab as preventive therapy in patients with cystic fibrosis, asthma and compromised immune systems; and explores the limited research in which palivizumab has been used for treatment of RSV. The modified recommendations for the use of palivizumab espoused by the American Academy of Pediatrics and research on the cost-effectiveness of this product are presented. In addition, the authors discuss the development of enhanced monoclonal antibodies including motavizumab, which was recently denied FDA approval for preventative therapy. The authors explore the historical and current efforts to develop a vaccine targeting RSV. The current status of antiviral drug development is also reviewed. The literature search included RSV-Ig, palivizumab, and emerging drugs and vaccines for the treatment of RSV as keywords and titles from 1997 to 2011.

Expert opinion: Although there are potential drugs and vaccines in development to prevent or reduce the effects of RSV infection, palivizumab remains the only licensed product to reduce the severity of disease in high-risk pediatric patients.

Keywords: bronchiolitis, monoclonal antibody, motavizumab, palivizumab, respiratory syncytial virus

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1. Introduction

Respiratory syncytial virus (RSV) was initially recognized as a respiratory pathogen in 1956 [1-3]. It is a negative-sense single-stranded RNA virus and a member of the *Paramyxoviridae* family. The virus is made up of a nucleocapsid surrounded by a viral envelope composed of host cell plasma membrane. The RNA genome of RSV encodes 11 proteins, including fusion protein (F) and glycosylated attachment protein (G), which are primary targets for host neutralizing antibodies [4]. RSV strains belong to one of two antigenic subgroups, either A or B, whose overall antigenic relatedness is approximately 25%. G protein is divergent between the two groups with just 1 – 7% antigenic relatedness, whereas approximately 50% of the F protein is conserved and the F proteins of the A and B subtypes are 95% identical [4-6]. Studies have shown very little antigenic drift of F protein over a 30-year period [7].

RSV infects human respiratory epithelial cells in the nasopharynx where it replicates to high titers and spreads to the lower tract through respiratory secretions [8]. RSV infection presents with a spectrum of signs and symptoms as shown in Table 1.

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Article highlights.

- Respiratory syncytial virus (RSV) is an important respiratory pathogen, responsible for significant morbidity and mortality globally.
- Palivizumab is the only approved drug approved that reduces morbidity from RSV in select populations.
- Expansion of palivizumab usage is limited by cost and paucity of evidence for efficacy in expanded populations.
- Development of a vaccine has been elusive, but provides the best option for widespread prevention of disease related to RSV.
- Multiple antiviral drugs targeting RSV are in development.

This box summarizes key points contained in the article.

Upper tract infections include the common cold, sinusitis and otitis media. Lower tract infections include bronchiolitis, pneumonia and laryngotracheobronchitis. RSV can precipitate wheezing in patients with asthma and it is known to worsen symptoms of chronic obstructive pulmonary disease and congestive heart failure [9,10].

RSV infections occur repetitively throughout the lifespan, as initial infection does not confer enduring immunity. Cellular and humoral responses induced by RSV result in clearance of the infection. Although complete immunity does not occur, this adaptive response does play a role in modifying future infections, which become milder with each occurrence [11]. Repeat infections may be partially explained by antigenic diversity within subgroups A and B, however, it is also possible to be re-infected by the same strain [12-15]. Virtually all children have been infected by 2 years of age. Approximately 20 – 40% of children will have lower tract infections; 1 – 2% will have severe disease necessitating hospitalization [16-19].

Recently, a prospective population-based surveillance of acute respiratory infections was conducted among children less than 5 years of age in three counties in the USA. The study reported that RSV was associated with 18% of specimens acquired from children with acute respiratory infections. RSV accounted for 20% of annual hospitalizations, 18% of emergency department visits and 15% of office visits for acute respiratory illnesses. The data extrapolated to the entire population of the USA estimated that 2.1 million children less than 5 years of age had an illness related to RSV that necessitated medical care. Approximately 3% were hospitalized, 25% were seen in emergency departments and 73% were treated in pediatric office settings. Young age and prematurity were the only independent risk factors correlated with severity of disease. Interestingly, children between 2 and 5 years of age with respiratory symptoms comprised 61% of outpatients that tested positive for RSV. Only 3% of all outpatients with confirmed RSV disease had been given the diagnosis of an RSV-related illness highlighting the underestimation of the burden of this disease [20].

Worldwide the incidence of severe lower respiratory tract disease related to RSV has been estimated to be 3.4 million to 4.3 million young children under the age of 5 years. The burden of disease is disproportionately borne by developing nations where approximately 99% of the cases of severe disease occur. Worldwide the estimated mortality in 2005 was 66,000 to 199,000 deaths in children younger than 5 years with 99% of those deaths in developing countries [21].

RSV has long been recognized as a source of significant morbidity and mortality in vulnerable infant populations. In comparison with influenza, RSV is responsible for greater than nine times as many deaths in children less than 12 months of age [22]. Infants with congenital heart disease, neuromuscular disorders, immunodeficiencies (both congenital and acquired), cystic fibrosis, bronchopulmonary dysplasia and prematurity are at considerable risk of severe lower tract disease [11]. Approximately one third of children with congenital heart disease admitted for disease related to RSV required intensive care, and up to 2.5% died of complications of RSV [23]. Although these high risk populations are recognized as important, the majority of cases of severe lower tract disease occur in full term otherwise healthy infants. Other risk factors for severe RSV infection include more than one sibling, maternal smoking, male sex, white race and maternal education less than 12 years [24-26].

In addition to children, the elderly share the burden of disease; RSV is reported to be more common than influenza with similar rates of hospitalization and mortality in this population [27]. Individuals with cystic fibrosis, reactive airway disease or compromised immune systems are also at risk of severe RSV disease [9,28-29].

The cornerstone of management of RSV infections remains supportive care including: maintenance of an airway, providing adequate hydration and preventing hypoxemia or hypercarbia. At this time no vaccine is available to prevent disease. Fortunately, passive immunization has been developed to reduce severity of disease.

2. Development of passive immunity

2.1 Use of IVIG and RSV-Ig

Initial passive prophylaxis was achieved with the use of conventional intravenous immunoglobulin (IVIG), which was successful in reducing severity of disease, as well as length of stay in infants infected with RSV who were hospitalized. Further improvements were made by producing IVIG that was enriched with higher levels of RSV neutralizing antibodies. The pivotal study conducted by the PREVENT study group enrolled: i) infants with bronchopulmonary dysplasia who were less than 24 months old; or ii) infants less than 6 months of age who were born at 35 weeks or less gestation. A reduction was seen in total hospital days for RSV-related disease, incidence of hospitalization, number of days of oxygen supplementation and in scores reflecting moderate or severe lower tract respiratory disease [30]. RSV-Ig (RespiGam) was

Table 1. Signs and symptoms of infection with respiratory syncytial virus.

<i>Symptoms</i>
Nasal congestion
Otalgia
Fever
Cough
Tachypnea
Wheezing
Feeding poorly
Apnea in infants
<i>Signs</i>
Nasal flaring
Retractions
Stridor
Crackles
Tachypnea
Wheezing
Fever
Hypoxemia

approved by the FDA in 1996 for infants with bronchopulmonary dysplasia or a history of premature birth at less than 35 weeks gestation [31].

Although RSV-Ig was an important step in reducing rates of hospitalization and severity of disease, there were many limitations. RSV-Ig was an intravenous infusion, which required starting an IV in small infants with poor venous access and administration of the product over several hours. It was a human blood product and thereby carried a small, but real, risk to the recipient of transmitted infections [32]. The fluid load was substantial for some infants with tenuous pulmonary function and similarly to other polyclonal IVIG infusions it had the potential to interfere with live viral vaccines such as measles, mumps, rubella and varicella [33,34]. Lastly, the infant patient population with cyanotic congenital heart disease showed a trend toward higher rates of fatality. An additional study limited to children with congenital heart disease or cardiomyopathy showed a significant reduction in the rate of hospitalization for lower tract respiratory disease, however the rate of hospitalization for specific RSV-related lower respiratory tract infections was not significantly reduced. A trend was seen toward more frequent deaths in the cardiac patients with cyanotic heart disease who were undergoing corrective surgery, as well as an increase in cyanosis following infusion that necessitated urgent surgery. The combination of increased adverse events and limited efficacy in preventing hospitalizations related to RSV led to a prohibition in the use of RSV-Ig in patients with cyanotic heart disease [34]. RSV-Ig is no longer available since the development of palivizumab.

2.1.1 Development and implementation of palivizumab

The limitations of RSV-Ig led to the development of palivizumab, a humanized, murine, monoclonal antibody

that binds to RSV F protein. *In vitro* studies showed a high affinity of palivizumab for both RSV A and B isolates with 50 – 100 times more potency than RSV-Ig [35]. The recombinant antibody was humanized by adding six of its complementarity determining regions into the framework of a human antibody [7].

The IMPact-RSV study group conducted a Phase III study as a multinational, randomized, double blind, placebo-controlled trial. Eligibility criteria included children either: i) 35 weeks gestation or less and 6 months of age or younger; or ii) 24 months old or younger with a diagnosis of bronchopulmonary dysplasia requiring ongoing medical support. Children with congenital heart disease were excluded except those with patent ductus arteriosus or hemodynamically insignificant septal defects. Children received either 15 mg of study drug/kg or placebo every 30 days. The endpoints of the study were hospitalization for respiratory disease due to RSV or occurrence of lower tract disease associated with RSV while hospitalized for an unrelated illness. The results showed a 55% reduction in hospitalization as a result of RSV disease in children with and without bronchopulmonary dysplasia, as well as in premature infants less than 35 weeks. The rates of adverse reactions were similar between the two groups including mortality rate [36].

The administration of palivizumab was postulated to be safer than RSV-Ig in children with congenital heart disease because it was approximately 100 times less volume and 50-fold smaller protein load. A second multinational, randomized, double-blind placebo-controlled trial was conducted to evaluate the safety and efficacy of palivizumab in infants with hemodynamically significant cardiac disease. Children were eligible if they were less than 24 months of age and had documented hemodynamically significant congenital heart disease that had not been fully corrected surgically. Patients were excluded for unstable cardiac or respiratory status, hospitalization (unless anticipated discharge was in the next 21 days), other end organ damage, anticipated cardiac transplantation, anticipated survival less than 6 months, extracorporeal membrane oxygenation and mechanical ventilation. In addition, patients could not have acute RSV disease, HIV or previous receipt of any monoclonal or polyclonal antibody, that is RSV-IG or IVIG. The primary endpoint was RSV hospitalization or death outside the hospital related to RSV infection. The results showed a 45 % relative reduction in rates of hospitalization for the palivizumab group (5.3% admitted versus 9.7%). The largest trend of decreased hospitalization was observed in patients without cyanotic heart disease, although the study was not powered to perform subgroup analysis. Secondary endpoints were significant for reduced days of hospitalization and days of increased oxygen supplementation in the palivizumab group. Trends toward decreased intensive care, mechanical ventilation and length of stay were seen in the palivizumab group, but these results were not statistically significant. No difference was seen in rates of adverse events between the two groups [37].

Palivizumab (Synagis) was approved by the FDA on 6 June 1998 with an indication for use as prophylaxis against serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease [38]. Recommendations for the use of palivizumab were first published in a policy statement from the American Academy of Pediatrics in 1998. Several iterations of that policy statement have been issued. The most recent recommendations in 2009 reflect an effort to balance benefit and cost in the administration of palivizumab (Table 2) [39]. The target population was children who have consistent and reliable predictors of severe disease. The recommendations for i) children with hemodynamically significant congenital heart disease who are less than 24 months of age, ii) children with chronic lung disease who require medical management and are less than 24 months of age, and iii) infants born before 32 weeks are the same as in 2006 [40]. Those recommendations include five doses of palivizumab on a monthly basis corresponding to the RSV season and usually beginning in November. Some infants with chronic lung disease or heart disease will qualify for two seasons of administration, up to the age of 24 months. Infants with a gestational age of 32 – 34 weeks 6 days born within 3 months of the start of RSV season or during RSV season now qualify for prophylaxis if they either attend daycare or have at least one sibling living in the home who is less than 5 years old. The 32 – 34 weeks 6 days age group should receive prophylaxis until they reach 90 days of age or a maximum of three doses. Additional vulnerable populations include those with significant congenital abnormalities of the airway, cystic fibrosis or neuromuscular disorders that prevent adequate handling of respiratory tract secretions; however, no specific recommendations are made regarding these populations [39].

The most debated changes in the recommendations are those pertaining to the reduction in coverage for the 32 – 34 weeks 6 days group. The strongest association of hospitalization has been linked to decreasing gestational age and the need for respiratory support at 36 weeks of post conceptual age [41]. Evaluations of cost effectiveness have shown divergent results particularly in infants greater than 32 weeks of age without chronic lung disease. Studies funded by the manufacturer have shown prophylaxis to be either cost-effective or associated with cost saving [42]. Other studies, as shown next, have not replicated those results [42-44].

Many considerations come into the analysis of cost effectiveness including estimates of the cost of hospitalization, estimates of infant weight to determine dosing, assumptions of reduced mortality, social effects such as lost work days, and quality of life adjustments for potential asthma sequelae. A decision analysis study which took many of these considerations into account combined published data on the risk of RSV hospitalization by gestational age, the seasonal pattern of RSV hospitalization, national costs of RSV hospitalizations, cost of palivizumab injection visits, cost of

emergency department visits, drug costs with an adjustment for weight according to standard growth curves for 2000 g infants, and cost of work hours missed by parents for visits and hospitalization. The study also attempted to incorporate probability of asthma as well as quality of life data with and without asthma. They did not include any assumptions regarding reduction of mortality, as this was never been shown in the pivotal studies [36,37]. The results showed that, irrespective of gestational age at birth, the added cost of prophylaxis with palivizumab was greater than savings accrued from reduced hospitalization. The expected cost of the prophylaxis group was greatest in infants less than 29 weeks [43]. This result is probably related to the initial IMPact study, which showed an 80% reduction in hospitalization rates for infants with gestational ages of 32 – 35 weeks treated with palivizumab compared with a 47% reduction in the group with gestational ages less than 32 weeks [36]. When the study's cost effectiveness analysis assumed a causal relationship between RSV and asthma, the results showed an incremental cost-effectiveness ratio of greater than \$200,000 per quality-adjusted year of life for all gestational ages [43]. Direct cost analysis of palivizumab prophylaxis in the 32 – 35 week age group of North Carolina's Medicaid program showed a large cost increase for those infants treated with palivizumab compared with no prophylaxis [44]. Other studies have shown similar results, less restricted to this age group of 32 – 35 weeks [43,45].

Prophylaxis of the Canadian Inuit infant population has shown substantial cost savings due to the large burden of severe lower tract disease observed in this community, as well as higher costs associated with medical evacuation required for hospitalization and higher rates of intensive care treatment [46]. Others have pointed out that the rates of hospitalization for RSV in infants born between 32 and 35 weeks gestational age are similar to those for infants with lower gestational age in the IMPact trial. Since there is strong evidence of the efficacy of palivizumab in this age group they argue that those infants who are less than 3 months of chronological age are at risk of severe RSV and should receive the full five doses of palivizumab [47]. One of the authors recently published a budget impact model that calculated per-member-per-month cost for each policy assuming a one million member hypothetical plan. The calculated cost to cover the 32 – 35 week infants, representing 0.08 % of the plan was estimated to result in an increase of payer cost by 9 cents per member per month [48].

2.1.2 Palivizumab and asthma

The role of RSV and the subsequent development of recurrent wheezing in childhood has attracted much attention. Prospective studies of RSV lower tract infections and subsequent rates of wheezing have demonstrated a wide range of 25 – 80% greater occurrence of recurrent wheezing compared with uninfected controls [49,50]. A prospective, matched, double cohort multicenter infant study in Canada and Europe attempted to further clarify RSV's role in subsequent

Table 2. Recommendations for the use of palivizumab from the committee on infectious diseases of the American Academy of Pediatrics: 2006 [40] versus 2009 [39].

Infants with	2006 guidelines	2009 guidelines
Chronic lung disease receiving medical therapy	Consider five doses per season for children less than 24 months old. May consider prophylaxis for a second RSV season	Unchanged
Congenital heart disease (CHD)	Consider up to five doses per season for children less than 24 months old with hemodynamically significant CHD	Unchanged
GA ⁺ less than 28 weeks	Administer all five doses during RSV season in the first 12 months of life	Unchanged
GA ⁺ 29 to 32 weeks	Administer all five doses during RSV season beginning in first 6 months of life	Unchanged
GA ⁺ 32 to 35 weeks	Refers to 32 weeks 1 day through 35 weeks 0 days. Administer all five doses if RSV season beginning in first 6 months of life and patient has two of five risk factors	Refers to 32 weeks 0 days through 34 weeks 6 days. Administer a maximum of three doses of prophylaxis up to 90 days of age, which ever is sooner, if RSV season begins in first three months of life and patient has one of two risk factors
Risk factors	Day care attendance, school age siblings, exposure to environmental air pollutants, congenital abnormalities of the airways or severe neuromuscular disease	Day care attendance or one or more siblings younger than five years living in the household
Congenital abnormalities of the airway or neuromuscular condition that impairs handling of respiratory tract secretions	Included in consideration of risk factors	Specific consideration for up to five doses in the first year of life

GA: Gestational age.

development of wheezing. Simoes *et al.* followed a group of premature infants without chronic lung disease from 19 months of age for an additional 24 months to evaluate subsequent development of wheezing. Premature infants treated with palivizumab and not hospitalized for RSV disease were compared with a cohort of premature infants who had not received palivizumab. Physician-diagnosed recurrent wheezing was seen in 8% of the treated group compared with a rate of 16% in the untreated group. However, this industry-sponsored study was limited by lack of prospective randomization which, as the authors point out, would be unethical given the known benefits of palivizumab in premature infants. Further limitations of the study included: i) an inability to generalize to term infants, ii) an inability to assess long-term difference in rates of wheezing with last follow-up at 24 months from initial enrollment, and iii) a lack of blinding of both parents and physicians to the treatment group assignment which may have influenced the rate of detected wheezing. There were also some statistically significant differences between the two groups: the treated group tended to be more premature and of lower birth weight while the untreated group tended toward having more siblings and having siblings in daycare [51].

Multiple other common childhood viruses, including human metapneumovirus, parainfluenza and human

coronavirus NL63, have been implicated in the development of recurrent wheezing in childhood [52-54]. Several studies have shown that rhinovirus is the most important cause of the development of wheezing at 3 and 6 years of age particularly in atopic children [55,56]. Another study found that both rhinovirus and RSV interact with atopy in infants to promote development of asthma [57]. As a result of these findings, Simoes *et al.* re-examined their initial data to determine if there was a protective effect of the use of palivizumab on subsequent episodes of wheezing in patients with a family history of atopy or asthma compared with those patients without such family history. They found that the subgroup of children without a family history of atopy had a reduction of risk of physician-diagnosed wheezing by 80%. The subgroup of children without a family history of asthma had a 68% reduction of relative risk of physician-diagnosed wheezing. These results were in contrast to the lack of reduction in risk for those patients who had a family history of asthma or atopy. The study suggests that the children who receive the most protective effect of palivizumab are those premature infants without chronic lung disease who do not have a family history of asthma or atopy [58]. These results must be interpreted within the context of the limitations of the initial study, as described earlier in this section.

2.1.3 Palivizumab in other populations

Trials of palivizumab have been undertaken in young children with cystic fibrosis (CF), as well as immunosuppressed children and adults. The current American Academy of Pediatrics (AAP) recommendations for use of palivizumab do not suggest for or against usage in these populations, but instead offer consideration of usage [39]. Although infants with CF have about the same rate of RSV infection as control populations, they experience a higher rate of morbidity with prolonged hospitalization, persistent hypoxemia, and impaired lung function for several months after a lower respiratory tract infection [59]. RSV infection may also lead to airway inflammation that predisposes patients with CF to experience their initial infection with *Pseudomonas aeruginosa* [28,60-61]. Chronic infection with *Pseudomonas* is linked to significant morbidity and decline of quality of life [62]. Currently all 50 states of the USA screen their newborns for CF. Given this link to chronic *Pseudomonas* infection, administration of palivizumab to all infants with CF seems prudent. Unfortunately the Phase IV study of palivizumab in infants with CF failed to demonstrate significant differences in outcomes including hospitalization [63]. A recent survey of 83 CF centers in the USA and Canada reported that 74% of physicians had prescribed palivizumab for infants with CF who were less than 1 year of age, but only 41 % of those physicians felt that it was the standard of care [64]. A retrospective study in one Canadian hospital using historical controls showed a trend toward fewer hospital days and less detection of RSV in acute respiratory illnesses in those patients with CF who had received palivizumab. The results did not achieve statistical significance, partially due to the limited numbers of participants [65]. An additional recent retrospective study using the Palivizumab Outcomes Registry showed that none of the infants with CF who had received palivizumab ($n = 91$) were hospitalized. This data was compared with historical controls from Abman *et al.* and Armstrong *et al.* who reported hospitalization rates related to RSV disease for infants with CF to be 14.6 and 8.75%, respectively [28,61,66].

Another identified at-risk population consists of patients who have either congenital or acquired immunodeficiencies. The AAP does not have specific recommendations for administration of palivizumab in this population, although expert opinion is that they may benefit from prophylaxis. No randomized trials of prophylaxis have been conducted in this population [40]. The two small Phase I trials conducted in adult patients who have undergone hematopoietic stem cell transplants indicate that palivizumab is well-tolerated [67]. Despite the lack of recommendations in immunocompromised patients, a survey of pediatric solid organ transplant centers found that 49% of responding programs used RSV prophylaxis for either candidates or recipients of organ transplants. The majority of these centers extended its use to children 0 – 24 months of age [68].

Other pediatric populations identified as potentially at risk for severe lower respiratory tract infections due to RSV

include those with either Down's syndrome or neuromuscular disorders. These patients have higher rates of intensive care unit (ICU) admissions, mechanical ventilation and mortality [69-72]. There have been no studies specifically addressing the use of palivizumab in these populations. Furthermore, the initial pivotal studies did not show a reduction in ICU admissions, mechanical ventilation or mortality for those treated with palivizumab compared with controls [36]. Further studies, similar to the IMPact studies, will be needed to evaluate if patients affected by these diseases have a reduction in hospitalization rates, days of hospitalization, days of increased oxygen or days with an elevated lower respiratory tract infection. The current AAP recommendations do not specifically address the use of palivizumab in Down's syndrome, however based on expert opinion they do recommend that patients who have compromised ability to handle secretions due to neuromuscular conditions should receive five doses of palivizumab during the first year of life [39].

RSV has been implicated as a causative agent in up to 24 – 28% of patients experiencing acute exacerbations of chronic obstructive lung disease [73,74]. To date there have been no trials of palivizumab in this population. One would assume that the cost per dose would be very high in an adult, as estimates of cost for a 4.5 kg infant are close to \$1000 per dose [43].

2.1.4 Treatment with palivizumab

The data regarding treatment with palivizumab is sparse. There have been two placebo-controlled, randomized trials to date. The first was conducted in 1998 in children less than 24 months of age who required mechanical ventilation for RSV. The patients received 15 mg/kg of palivizumab intravenously but did not receive ribavirin. Of the 35 children in this trial six had chronic medical conditions. The study showed a significant decrease in RSV titers in tracheal aspirates but no reduction in the concentration of RSV in nasal aspirates in those patients treated with palivizumab. Clinically the difference in mortality rate was not statistically significant with 1 death in 18 placebo patients and no mortality in the palivizumab group. In addition, there was no difference in days of hospitalization, need for mechanical ventilation or supplemental oxygen use between the two groups [75]. The second small study was a Phase I/IIa trial of palivizumab dose escalation in previously healthy children less than 24 months of age who were hospitalized for lower respiratory tract disease caused by RSV. The dose escalation from 5 to 15 mg/kg was tolerated without any difference in adverse events. The study was not powered to determine efficacy, however there was no statistical difference in days of hospitalization, need for mechanical ventilation, requirement for intensive care, mortality, days of oxygen supplementation or severity of respiratory score [76].

The majority of case reports and small retrospective studies in immunocompromised patients have been in recipients of solid organ and stem cell transplants. Overall these studies

provide conflicting evidence about the benefit of using intravenous palivizumab in combination with ribavirin to decrease rates of progression to lower respiratory tract disease and reduce mortality in pediatric and adult populations [77-81]. Recipients of hemopoietic stem cell transplants are particularly vulnerable, as they have impaired T-cell immunity, which increases their risk of acquiring RSV as well as reducing their ability to eradicate the virus. Stem cell transplant may lead to increased severity and duration of disease resulting in mortality rates that range from 7 to 83% of patients who have lower respiratory tract disease due to RSV [82]. The true incidence of RSV infection in this population is challenging to estimate, as patients with mild illness may not be tested for RSV. Palivizumab is usually not started until lower tract disease occurs which may impair maximum effectiveness [75]. Currently the clinical guidelines from the American Society of Transplantation recommend using either palivizumab or RSV-Ig in combination with ribavirin if patients have RSV lower tract disease [83].

2.2 Motavizumab

Motavizumab is also a recombinant humanized monoclonal IgG antibody targeting RSV F protein. This investigational monoclonal antibody was developed through affinity maturation of palivizumab to achieve greater binding affinity and virus neutralizing activity. The compound differs from palivizumab by six changes in the complementarity determining region and one framework change on the heavy chain as well as five changes in the complementarity determining regions and one framework change on the light chain. *In vitro* studies reported an approximately 20-fold increase in ability to neutralize RSV compared with palivizumab. Additional results showed substantial reduction of RSV titers in the nose and lung of the cotton rat model [84].

A Phase III, double-blinded, randomized, multinational study was conducted between November 2004 and May 2006 in both the northern and southern hemispheres to compare motavizumab to palivizumab administered at 15 mg/kg at 30 days intervals. Inclusion and exclusion criteria were the same as the original IMPact study. Motavizumab was judged to be non-inferior to palivizumab based on a 26% relative reduction in RSV hospitalizations compared with palivizumab. The overall incidence of hospitalization in both groups was low at 1.4 and 1.9%, respectively, which contributed to the lack of achievement of superiority of motavizumab over palivizumab. Motavizumab was found to be superior to palivizumab in reducing outpatient medically attended lower respiratory illness by 50%. A *post hoc* analysis also showed a reduction of incidence of mechanical ventilation and days of ventilation in patients treated with motavizumab, although the total number of patients in the two groups was small. Adverse reactions were similar in both groups except for increased agitation and insomnia among the palivizumab recipients and increased skin reactions among recipients of motavizumab. Skin reactions related to motavizumab included

urticaria, allergic dermatitis and eyelid edema which were consistent with possible cutaneous hypersensitivity [85].

Currently licensure of motavizumab has not been granted. The FDA expressed concern over the increase in hypersensitivity reactions in recipients of motavizumab and requested additional studies to further define the frequency as well as severity of hypersensitivity reactions [86]. At present MedImmune has discontinued its program of development of motavizumab for prophylaxis against RSV; however, motavizumab remains in development for possible treatment of RSV [87].

3. Emerging drugs and vaccines

3.1 Vaccines

Current treatment of RSV is primarily supportive. Successful development of vaccines against RSV has been elusive. The first vaccine for RSV was a formalin-inactivated version developed in the 1960s. Unfortunately, RSV-related disease in the vaccinated group manifested as a severe illness with high rates of hospitalization and death [88]. Efforts to identify a viable vaccine candidate have continued in recent years (Table 3).

Two vaccine candidates produced by MedImmune are in clinical trials. The first is MEDI-559, which is a live attenuated intranasal vaccine in Phase I/IIa trials. It is given in three doses to healthy 1 to < 24-month-old children [89]. Results of this trial have not been published yet. The second vaccine candidate is MEDI-534, which is a live, attenuated, intranasal vaccine against RSV and parainfluenza virus type 3 (PIV 3). This vaccine has undergone Phase 1 trials in adults and healthy children 6 months to 9 years of age [90-92]. An additional Phase I/IIa trial is being conducted in healthy 6 – 24-month-old children and 2-month-old infants [93]. This candidate uses bovine/human PIV 3 as a vector to express RSV F-protein [94,95]. The bovine PIV 3 vaccine has been evaluated in clinical studies in 1 – 3 months old children and found to be safe, immunogenic and non-transmissible in the day care setting [96].

Further enhancement of existing monoclonal antibodies is under development by MedImmune. A Phase II trial is underway to study the pharmacokinetics, safety and tolerability of a liquid formulation of palivizumab in children born at or after 35 weeks gestation [97]. Another potential development is MEDI-557 which is a third generation monoclonal antibody derived from motavizumab with an extended half-life. The antibody has a triple mutation in the Fc portion of motavizumab, which results in an increase in binding, similar release and improved serum half-life in cynomolgus monkeys [98]. The compound is currently in a Phase I clinical trial in healthy adults [99]. A monoclonal antibody with a prolonged half-life would probably reduce the number of doses necessary to provide coverage during the RSV season. This could provide some cost savings, particularly in the cost of administration.

Motivizumab is also being evaluated for the treatment of RSV illness. A Phase II study was completed in non-hospitalized

Table 3. Emerging vaccines and drugs in active clinical trials.

Compound	Company	Class	Route	Phase	Ref.
Motivizumab	MedImmune	Monoclonal antibody against RSV F protein	Injection, Intramuscular	III	[100]
MEDI-559	MedImmune	Live attenuated vaccine against RSV	Intranasal	I/IIa	[89]
MEDI-534	MedImmune	Live attenuated vaccine against RSV and PIV3	Intranasal	I/IIa	[90-96]
Palivizumab	MedImmune	Monoclonal antibody against RSV F protein	Oral, liquid	II	[97]
MEDI-557	MedImmune	Monoclonal antibody targeting RSV F protein with extended half life	Intravenous	I	[98,99]
ALN-RSV01	Alnylam	siRNA	Intranasal	II	[101-104]
BTA9981	Biota	Fusion inhibitor	Oral	I	[106,107]
RSV604/A-60444	Novartis, Arrow	Benzodiazepine	Oral	II	[108-110]

children up to 12 months old with upper respiratory tract infection from RSV disease. Children received one dose of 30 mg of motavizumab/kg to determine effect on viral load and motavizumab levels in the upper respiratory tract [100]. Results of the research have not been published yet, however MedImmune is continuing to pursue motivizumab as a treatment agent [87].

3.2 Antiviral drugs

New antiviral drugs are also in development. The first class in development is siRNAs which work by targeting specific mRNA resulting in mRNA degradation and reduced viral protein production [101]. ALN-RSV01 is an intranasally administered siRNA targeting RSV. A Phase II study was conducted in healthy adults who received the medication for 2 days before inoculation and 3 days after exposure. A significantly lower proportion of treated subjects were infected compared with those that received placebo and there was a trend toward lower viral load in treated subjects [102]. A subsequent Phase II study is being conducted in adult lung transplant patients with documented RSV infection [103]. Initial results show that the incidence of new or progressive bronchiolitis obliterans syndrome is significantly reduced in recipients of ALN-RSV01 at day 90 [104].

The second class of antivirals is RSV fusion inhibitors that target F glycoprotein and prevent virus entry into the host cell [105,106]. BTA9981 is the only fusion inhibitor in clinical trials at this time with a Phase I trial underway in healthy adult patients [107]. Lastly, an oral benzodiazepine RSV604 (also known as A-60444) has anti-RSV activity through inhibition of RNA polymerase in both RSVA and RSVB antigenic subgroups [108]. A Phase I trial was completed in healthy adults as well as a Phase II trial in adult recipients of bone marrow transplants with RSV infection [109,110].

4. Conclusion

RSV-related lower respiratory tract disease is a source of significant morbidity and mortality throughout the world. Palivizumab remains the only drug to reduce morbidity from RSV among premature infants, infants with chronic

lung disease and those with hemodynamically significant heart disease. However, prophylaxis in other vulnerable populations has not shown a clear benefit. Prevention of subsequent development of asthma through treatment with palivizumab has also not been established. Development of a vaccine or anti-viral drug would potentially benefit a wider population including full term infants, immunocompromised patients, the elderly and infants in developing nations.

5. Expert opinion

Palivizumab has a clear role in reducing severity of RSV disease in premature infants less than 32 weeks of gestation, those with chronic lung disease and those with congenital heart disease. This drug has been shown to be safe and well-tolerated. Additional expansion of usage is limited by the paucity of evidence of efficacy in other populations. This is in part due to low numbers of eligible patients resulting in small studies of limited power. Cost of the drug also limits its usage in other vulnerable populations. Furthermore, no reduction in mortality has been demonstrated. Expansion of its usage would probably be driven by availability at a lower cost. Palivizumab is not likely to be replaced by motivizumab as the latter is currently out of development for prophylaxis. A liquid formulation of palivizumab may reduce cost. Similarly, the development of a monoclonal antibody with a longer half-life would probably be a lower cost option since it would require fewer doses to provide similar concentrations of antibody.

A reduction in global incidence and severity of RSV-related disease across the life span will require a multi-pronged strategy. The most inexpensive approach is the standard practice of good hand hygiene and avoidance of sick contacts. This is particularly effective in first-born infants and immunosuppressed patients. Vaccine development remains the best option for preventing RSV disease, however developing an effective vaccine is challenging on many levels. In particular young infants require a delicate balance between adequate attenuation and immunogenicity that is effective during the most vulnerable window in the first 6 months of

life. Indirect protection may be provided through vaccination of siblings and family members; however, the natural history of re-infection throughout the lifespan reflects a lack of sustained immunity after exposure. The length of protection from RSV infection afforded by a live, attenuated vaccine is uncertain and the frequency of vaccination would need to be determined. Highly attenuated live vaccines would need to demonstrate a lack of return to virulence in vulnerable populations, particularly in the developing world.

Another approach is an effective antiviral, for which there are some promising drugs in development. In order to use these drugs effectively patients would need to be identified as having RSV disease and administration would need to occur in a time frame that reduced severity and length of disease. This may prove to be challenging in infants who may not be identified until the peak of disease on day 4 or 5 of illness. The exact mechanism of RSV-related disease

is not fully understood and it is probably related, at least in part, to inflammation in the nose and the lung. Reduction of viral load is one important component of treatment, however, it may be necessary to counter the inflammatory process as well. A drug that reduces the viral load may have limited efficacy if significant inflammation has already occurred, thus underscoring the importance of timing of drug delivery.

Palivizumab remains the only drug therapy to reduce severity of disease. Current usage is likely to continue until a replacement is identified, a vaccine is developed, or an effective antiviral is produced.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Affiliation

Kristin A Shadman[†] MD & Ellen R Wald MD
[†]Author for correspondence
 University of Wisconsin School of Medicine and Public Health, Department of Pediatrics, 600 Highland Avenue, Box 4108, Madison, WI 53792, USA
 Tel: +1 608 262 6667; Fax: +1 608 265 3397;
 E-mail: kshadman@pediatrics.wisc.edu