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Learning Objectives

After studying the literature presented in this issue, participants should be able to:

- Employ the current guideline recommendations, issued by the American Academy of Pediatrics (AAP), in the treatment of high-risk infants who present with respiratory syncytial virus (RSV) bronchiolitis.
- Identify patients at high risk for RSV in your practice who are eligible for appropriate prophylactic treatment.
- Describe the current status of the development of anti-RSV therapies, including the results of the Phase 3 pivotal trial comparing motavizumab to palivizumab prophylaxis in infants at high risk for serious RSV disease.

Target Audience

This educational activity is designed for pediatricians, primary care physicians, pediatric and family nurse practitioners, neonatologists, infectious disease specialists, allergists, pulmonologists, immunologists, and other healthcare professionals involved in the care and management of pediatric respiratory patients.

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The following summaries are based on presentations made at the recent PRCI Satellite Symposium, Managing RSV Infection in Pediatric Patients: What Pediatricians Need to Know, presented on October 29, 2007, in San Francisco, CA.

Review of the AAP Guidelines for the Management of RSV Bronchiolitis

Bronchiolitis is the number one cause of all infant hospitalizations. Sound management of bronchiolitis is thus very important in the care of infants. Dr Caroline Hall, Professor of Pediatrics and Medicine at the University of Rochester School of Medicine and Dentistry, reviewed the Clinical Practice Guidelines, Diagnosis and Management of Bronchiolitis recommended by the American Academy of Pediatrics (AAP).¹

The guidelines address the diagnosis, therapy, and prophylaxis of bronchiolitis.

They cover supportive care, treatments with bronchodilators, corticosteroids, antivirals and antibiotics, and prevention with palivizumab, as well as infection control. The guidelines are not intended as the sole source of information on the management of bronchiolitis or to replace clinical judgment.

The guidelines address infants 1 month to 2 years of age who are first-time wheezers and who do not have underlying conditions that affect immunity or cardiopulmonary function. The guidelines do not address children with recurrent wheezing.

The AAP guidelines include the evidence-based strength of each recommendation or

evidence-based level (EL) by integrating an evidence-quality appraisal with an assessment of the anticipated balance between benefits and harms.² The major recommendations of the AAP guidelines for the management of bronchiolitis are addressed here.

The guidelines recommend that the diagnosis of bronchiolitis be clinical and that lab testing is unnecessary (EL=B); however, risk factors should be assessed in the diagnosis (EL=B).

Tachypnea >70 is considered good for predicting clinical outcomes for bronchiolitis. Bacterial infection is rare in bronchiolitis; most are coinfections and not superinfections.

Both bronchodilators and corticosteroids are not recommended in the routine management of bronchiolitis (EL=B). Similarly, neither ribavirin

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^a The EL was ranked A, B, C, and D based on the strength of the clinical evidence obtained from different types of studies. EL=A is categorized for well-designed randomized controlled trials (RCTs) or diagnostic studies on relevant population; EL=B for RCTs or diagnostic studies with minor limitations, and overwhelming consistent evidence from observational studies; EL=C for observational studies (case-control and cohort design); EL=D for expert opinions, case records, reasoning from first principles.

Disclosures:

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Review of the AAP Guidelines

(Continued)

nor chest physiotherapy should be used routinely (EL=B). Antibiotics should be used only when there is a specific indication (EL=B).

Supplemental oxygen is only recommended if the oxygen saturation (SpO₂) is persistently <90%, and should be discontinued if SpO₂ is >90% (EL=D). As the child improves, continuous monitoring is not routinely recommended (EL=D).

According to the AAP 2006 updated guidelines, palivizumab prophylaxis is recommended for selected infants <24 months of age with chronic lung disease, infants <35 weeks of gestational age, and infants with congenital heart disease (EL=A). Recommended prophylactic treatment consists of an intramuscular injection of 15 mg/kg palivizumab each month for 5 months starting in November or December (EL=C).

Therapy for bronchiolitis remains controversial. The most controversial aspects of the guidelines are the level of SpO₂ governing oxygen therapy and the fact that laboratory diagnosis is not a requirement.

1. AAP. *Pediatrics*. 2006;118(4):1774-1793.

Pearls for Practice

- The guidelines published by the AAP are designed to streamline and reduce costs in the management of RSV bronchiolitis. Anxious clinicians may have a great deal of difficulty resisting the urge to “do something” for the infant in respiratory distress. The urge should be resisted. All treatments carry some risk and definitely some cost. Supplemental oxygen and fluids are all that is required for successful management of nearly all infants with RSV bronchiolitis.
- The guidelines apply to infants experiencing their first episode of wheezing. Nevertheless, there is little reason to doubt that they are also pertinent for infants and young children with recurrent wheezing precipitated by viral infections. The available evidence is that the various interventions discussed in the guidelines are no more effective in recurrently wheezing infants. In particular, the idea that corticosteroid therapy in these infants will prevent airway remodeling and inhibit the development of asthma has been adequately disproved.

Robert Welliver, MD

Current and Future RSV Prophylaxis Strategies

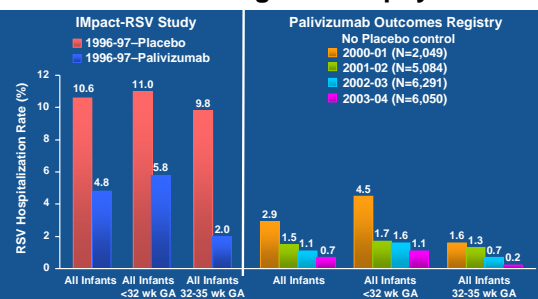
Respiratory syncytial virus (RSV), which was first isolated in 1956, has been considered the most important cause of viral lower respiratory tract infection in infants and children. RSV could be identified in 57% of infants with bronchiolitis and pneumonia. Development of ways to prevent RSV infection has been one of the highest priorities in pediatric respiratory healthcare. Dr Jaime Fergie, Associate Professor of Pediatrics, Texas A&M University College of Medicine, provided an overview of the current and future development for RSV prophylactic treatment, including two monoclonal antibodies, palivizumab and motavizumab.

After the initial failure of the formalin-inactivated RSV vaccine in the late 1960s, focus has been turned to the development of a passive immunoprophylaxis. The first successful attempt at a passive RSV immunoprophylaxis was the use of polyclonal intravenous immunoglobulin (IVIg) obtained from donors with high serum RSV-neutralizing antibody titers. Respiratory

Syncytial Virus Immune Globulin Intravenous (Human) (RSV-IGIV) was approved in 1996 for immunoprophylaxis by the US Food and Drug Administration (FDA). However, RSV-IVIg requires monthly intravenous infusions, each lasting several hours. In 1998, a humanized monoclonal antibody, palivizumab, which is administered intramuscularly, was approved by the FDA for the prevention of RSV infection specifically in high-risk infants and children.

Palivizumab has been successfully used as immunoprophylaxis for 9 years. Two large randomized, multicenter RSV studies on palivizumab, IMpact-RSV¹ and Cardiac Synagis Study Group,² showed the significant impact of palivizumab on RSV prophylaxis in infants, recording significant reductions in RSV hospitalization

Reduced RSV Hospitalizations in All Infants Receiving RSV Prophylaxis



Palivizumab Outcomes Registry Study Group. *Pediatric Pulmonol*. 2003;35:484-489.
Romero JR. *Pediatr Infect Dis J*. 2003;22(2 suppl):S46-S54.
The IMpact-RSV Study Group. *Pediatrics*. 1998;102(3 Pt 1):531-537.

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Current and Future RSV Prophylaxis Strategies

(Continued)

rates, hospital days, days of oxygen use, and intensive care unit admissions as compared with those of placebo. The impact palivizumab had on RSV prophylaxis was also observed in the high-risk premature infants of Alaskan natives.³

The palivizumab outcomes registry^{4,6} covers data collected over four seasons (2000-2001 to 2003-2004) from 19,548 infants receiving palivizumab. Among the 6,049 infants who received prophylaxis during 2003-04, 37% of infants were at a gestational age (GA) of <32 weeks, 79% of infants had a low birth weight of <2.5 kg, 83% of these infants were neonatal intensive care unit (NICU) graduates, and 51% of infants had been exposed to day care. In addition, 1,471 infants (24%) were second-season recipients.

In 2006, the American Academy of Pediatrics (AAP) issued the updated guidelines⁷ for RSV infection and recommended the infant groups considered eligible for RSV prophylaxis. These include:

- Infants <24 months of age with chronic lung disease (CLD) of prematurity and receiving medical treatment within 6 months
- Premature infants with a GA ≤28 weeks in the first RSV season during the first 12 months of life
- Infants with a GA of 29 to 32 weeks, if <6 months of age; infants with a GA of 32 to 35 weeks, if <6 months of age and with two or more risk factors (eg, day care attendance, school-aged siblings, congenital airway abnormalities, low birthweight, family history of wheezing, or asthma)
- Infants at ≤24 months of age with hemodynamically significant congenital heart disease

The AAP updated guidelines⁷ also recommend that properly selected high-risk infants should receive palivizumab 48 to 72 hours before discharge from the NICU. Palivizumab should be given prior to the beginning of the RSV season; however, unpredictability regarding the start of the season poses challenges. Continuous dosing with palivizumab is recommended for RSV-infected infants. Moreover, tobacco smoke is a potential risk factor that can be controlled by the family of an infant at risk for severe RSV. In addition to GA, lists of AAP risk factors and additional risk factors have been shown to cause severe RSV infection.

In addition to palivizumab, a newly-developed humanized IgG-1 monoclonal antibody, motavizumab, which is a derivative of palivizumab

is in development. Motavizumab has demonstrated a more potent neutralizing activity than palivizumab; a 20- to 100-fold increase in activity against RSV was observed in the preclinical studies of motavizumab.⁸ The Phase III trial comparing the safety and relative efficacy of motavizumab versus that of palivizumab in both infants with CLD and premature infants has been completed.⁸ Motavizumab showed noninferiority in RSV hospitalization compared with that of palivizumab ($P<0.01$). Furthermore, motavizumab demonstrated superiority in the reduction of RSV-specific outpatient medically attended RSV lower respiratory tract infections when compared with palivizumab, 2% versus 3.9%, respectively ($P<0.01$).

1. The IMPact-RSV Study Group. *Pediatrics*. 1998; 102(3 Pt 1):531-537.
2. Feltes TF et al. *J Pediatr*. 2003;143(4):532-540.
3. Singleton R et al. *Pediatr Infect Dis J*. 2003;22(6): 540-545.
4. Romero JR. *Pediatr Infect Dis J*. 2003;22(2 suppl): 546-554.
5. Palivizumab Outcomes Study Group. *Pediatric Pulmonol*. 2003;35:484-489.
6. Hudak et al. *J Perinatol*. 2002;22:619. Abstract P32.
7. AAP. In: Pickering LK et al, eds. *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006:560-566.
8. Carbonell MC et al. Presented at: The Pediatric Academic Societies, Annual Meeting. May 5-8, 2007; Toronto. Abstract 618220.9.

“Unpredictability regarding the start of the RSV season poses challenges. When the season ends, healthcare professionals should consult local virology and/or hospitalization and pediatric ICU-care data to determine local RSV epidemiology.”

Jaime Fergie, MD

Pearls for Practice

- Palivizumab continues to be effective in the prevention of severe RSV infection for defined high-risk groups. There is currently no evidence to substantiate that circulating RSV strains have enabled escape mutations that are resistant to palivizumab. Continued use should be encouraged. New high-risk groups have been identified, including those with neuromuscular impairment, members of certain racial groups, and those born just before the onset of the RSV season.
- Future studies will, hopefully, determine if motavizumab can be used more effectively or less expensively than palivizumab; to target the optimal time to start and stop palivizumab therapy in equatorial and arctic regions where the RSV season is more prolonged than in temperate climates; and use of prophylaxis in full-term infants born near the onset of the RSV season.

Robert Welliver, MD



RSV Treatment and Vaccines: What's on the Horizon?

Dr John DeVincenzo, Associate Professor of Pediatrics and Molecular Sciences, University of Tennessee School of Medicine, highlighted the approaches and hurdles affecting RSV vaccine development and reviewed various RSV antiviral therapies, including passive antibodies, ribavirin, and future antivirals.

The early failures resulting from RSV vaccine projects presented hurdles and also influenced current approaches to vaccine development. The initial use of formalin-inactivated RSV for vaccination did not prevent RSV infection, but actually worsened the disease.¹ Subsequent studies have focused on live-attenuated vaccine approaches. The attenuated vaccines have never been shown to induce any vaccine-enhanced disease. The concern of this approach is that RSV attenuation cannot be either too much, which may induce insufficient immunity, or too little, which may cause unacceptable respiratory tract side effects. Recombinant vaccines, which use other viruses engineered to carry RSV proteins, have thus been developed (ie, bovine RSV with human RSV protein(s) inserted and sendai virus with human RSV protein(s) inserted). Phase II trials on some of these studies are underway.

The first hurdle in RSV vaccine development

is the fact that natural RSV infection does not produce long-lasting immunity. Thus, an RSV vaccine would have to produce more effective immunity than the natural infection itself. Other vaccine hurdles include the protection of extremely young infants aged <6 months, when RSV produces the

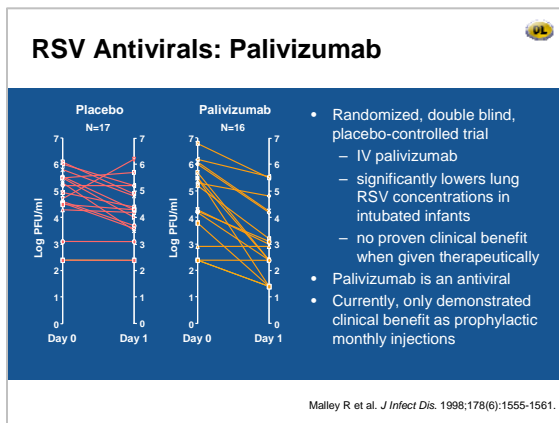
disease burden. The RSV vaccine-induced immunity must be accomplished very early in life (<6 months of age). The pathologic features found in the lung sections of young infants who died of acute RSV disease and RSV infection² showed that RSV caused serious lung disease in these infants by overwhelming viral replication and ineffective host antiviral immune responses. The differences between immunocompetent and immunocompromised patients with RSV are described as follows^{3,4}: the two populations have different viral kinetics in their lungs and, thus, probably have different responses to future antivirals. The effect of corticosteroids on children with RSV was also discussed.

Children who were given therapeutic doses of dexamethasone showed no improvement in the duration of intensive care unit (ICU) stay or hospitalization. However, the pulmonary viral load was altered and showed more viral replication in the early days of the infection for those children with treatment doses of corticosteroids.⁵

Palivizumab is an antiviral which reduces the quantity of RSV virus in the lower respiratory tract of intubated infants. Palivizumab has demonstrated clinical benefits when used as a prophylactic monthly injection; but it is not approved as a therapy for RSV. Ribavirin is the only FDA-approved therapy for RSV. A series of randomized, double-blind clinical trials on ribavirin were reviewed. Ribavirin has shown some modest clinical benefit for reducing RSV; however, it is difficult to deliver and requires a special aerosol device. Additionally, ribavirin is only effective if started very early in the disease. At present, ribavirin has limited use in the United States and Europe for immunocompetent infants and children.

“RSV causes serious disease in infants by rapidly infecting large surface areas of the respiratory epithelium in the absence of a truly effective antiviral immune response. There’s no current vaccine that exists, no current antiviral that exists, although active research in this area is progressing.”

John DeVincenzo, MD



Continued



“It’s a very exciting time to be in RSV research areas because many companies and other research groups are banding together to actually try to create these types of therapeutics and vaccines.”

John DeVincenzo, MD

RSV Treatment and Vaccines: What’s on the Horizon?

(Continued)

Various new RSV antivirals are on the horizon, such as fusion inhibitors,⁶ polymerase inhibitors, and RNA interference approaches. Many have been proven to produce anti-RSV activities in animal models; but none has yet been proven to have an antiviral effect on humans. Since no current vaccine exists and no current antiviral therapy exists, it was concluded that prevention should be the key for controlling RSV infection and a monthly injection of palivizumab is recommended for high-risk infants.

1. Schreiber P et al. *J Vet Med B Infect Dis Vet Public Health*. 2000;47(7):535-550.
2. Welliver TP et al. *J Infect Dis*. 2007;195(8):1126-1136.
3. DeVincenzo J et al. *Int Symp Resp Vir*. 2005.
4. El Saleeby et al. *Clin Infect Dis*. 2004;39(2):e17-e20.
5. Buckingham SC et al. *J Infect Dis*. 2002;185(9):1222-1228.
6. Douglas JL. *Expert Rev Anti Infect Ther*. 2004;2(4):625-639.

Pearls for Practice

- Our approach to the treatment of RSV infection needs revising. The contribution of the cytotoxic lymphocyte response of the host to the pathogenesis of illness has been overestimated in humans. There is good reason to believe that antivirals may improve the outcome of illness in the elderly, in the immunocompromised, and (if given early enough) in infants presenting at the very onset of wheezing; however, this attack should be directed against intracellular virus (the predominant location of RSV), rather than at the virus found in secretions.
- Other measures that could prove beneficial include the use of compounds to improve the macrophage phagocytosis of infected epithelial cells or to accelerate epithelial cell regeneration along the airway.

Robert Welliver, MD

Clinical Insights® in Pediatric Respiratory Care Post-Test (December 2007)

1. According to the AAP 2006 updated guidelines, which of the following is recommended in the routine management of RSV bronchiolitis?
 - a. Bronchodilators
 - b. Corticosteroids
 - c. Palivizumab prophylaxis
 - d. Ribavirin
2. According to the updated AAP guidelines, which infant group is *not* eligible for RSV prophylaxis?
 - a. Infants >24 months of age with chronic lung disease
 - b. Premature infants with GA ≤28 weeks in the first RSV season during the first 12 months of life
 - c. Infants with a GA of 32 to 35 weeks, if >6 months of age with two or more risk factors
 - d. Infants at ≤24 months of age with hemodynamically significant congenital heart disease
3. Which of the following is FDA-approved for the treatment of RSV?
 - a. Motivizumab
 - b. Palivizumab
 - c. Fusion inhibitors
 - d. Ribavirin
 - e. None of the above

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1. c. Palivizumab prophylaxis is recommended for selected infants <24 months of age with chronic lung disease, <35 weeks of gestational age, and those with congenital heart disease. Moreover, intramuscular injection of 15 mg/kg palivizumab each month for 5 months starting in November-December is recommended for prophylactic treatment.
2. a. Infants <24 months of age with chronic lung disease are eligible for RSV prophylaxis, not those >24 months of age.
3. d. Ribavirin is the only FDA-approved therapy for RSV and has shown modest clinical benefit in reducing RSV. At present, ribavirin has limited use in USA and Europe for immunocompetent infants and children, and is effective only if started very early in the disease.

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