Clinical Update on Respiratory Syncytial Virus: What Pharmacists Need to Know

Needs Assessment

Respiratory syncytial virus (RSV), a seasonal virus, is the most common cause of respiratory tract infection in infants and young children. By the age of 2 years, virtually all children have experienced at least one RSV infection; most are mild and self-limited. [Glezen *Am J Child Dis* 1986] Among the vulnerable, however, a moderate-to-severe RSV infection can cause significant morbidity and mortality. RSV infection of the lower respiratory tract is the leading cause of bronchiolitis and pneumonia in infants less than 1 year of age [Leader *Pediatr Infect Dis J* 2002] and of infant viral death. [Thompson *JAMA* 2003]

Clinical options for the control of RSV disease are limited. Ribavirin is the only anti-RSV agent approved for treatment, but concerns about its efficacy and safety limit its use. [Krilov *eMedicine* 2009; Chan-Tack *N Engl J Med* 2009] Other than supportive therapies, management of RSV disease is focused on preventive measures. The humanized monoclonal antibody palivizumab (Synagis®, MedImmune, Inc, Gaithersburg, MD) is the only pharmaceutical product licensed for the prevention of RSV disease in patients at risk. Several products are currently in development for the prevention or treatment of RSV infection.

Strategies for passive immunization with palivizumab continue to be refined. The American Academy of Pediatrics (AAP) recently issued guidelines that revise their criteria for prophylaxis with palivizumab. [Comm Infect Dis *Pediatrics* 2009] On the other hand, a newly published population-based survey identifies candidates for prophylaxis that go beyond AAP guidelines. [Hall *N Engl J Med* 2009]

The debate over who would benefit from immunoprophylaxis appears to be academic. Among even the conservatively defined population of at-risk patients, compliance with AAP guidelines is far less than complete. Several surveys have found that the majority of at-risk patients who develop RSV disease had not received prior prophylaxis with at least one dose of palivizumab. [Mansbach *Ped Emerg Care* 2007; Moynihan *J Pediatr Health Care* 2004]

Pharmacists who collaborate with physicians on the management of RSV disease and evaluation of new products for its treatment or prevention, need to have an in-depth knowledge of RSV disease—how and when RSV is transmitted; clinical features that create RSV vulnerability and why; how, when, and to whom to administer RSV prophylaxis; and how to evaluate potential pharmaceuticals for the prevention or treatment RSV infections.

ASiM has conducted a thorough needs assessment for pharmacists who influence the pharmaceutical management of patients at risk of developing an RSV-associated lower respiratory tract infection, based on a literature review of the most recent evidence-based reports, expert opinions, 2009 AAP treatment guideline update, and physician surveys.

Gap Analysis

Educational Gap	Data Source	Intervention	Measurement Levels (Outcomes)
Pharmacists lack **knowledge** of the acute and chronic burden of RSV disease	*Literature review; Survey data; Expert opinion*	Present evidence-based data on the clinical course of RSV; review the impact of immuno-pathologic damage on the long-term con-sequences of RSV infection; reinforce the need for immuno-prophylaxis in at-risk patients to minimize the morbidity and mortality of RSV disease	3 (Knowledge)

Educational Gap	Data Source	Intervention	Measurement Levels (Outcomes)
Pharmacists lack **knowledge** of how RSV is transmitted and the timing of RSV season by geographic area	*Literature review; Survey data; CDC reports; Expert opinion*	Present evidence-based data on the infectivity of RSV and CDC-identified geographic variations in RSV season and NREVSS epidemiologic data for timing of current RSV season; reinforce the importance of immunoprophylaxis in at-risk patients for optimal control of RSV disease	3 (Knowledge)
Pharmacists lack **knowledge** of how underlying conditions can increase the risks for and outcomes of severe RSV disease	*Literature review; Survey data; Expert opinion*	Discuss the pathophysiology of clinical conditions that create a vulnerability to clinically significant compromise in respiratory function with RSV infection, which increases the severity of RSV disease	3 (Knowledge)

Educational Gap	Data Source	Intervention	Measurement Levels (Outcomes)
Compliance with AAP guidelines for RSV immunoprophylaxis is poor, perhaps due to lack of **knowledge** of the guidelines, or lack of **competence** in communicating, counseling, and monitoring the merits of RSV prevention in at-risk patients	*AAP revised guidelines; Literature review; Survey data; Expert opinion*	Review recently revised AAP guidelines, specifically identification of at-risk patients and appropriate variations in immunoprophylactic regimens; review data from compliance surveys; discuss interventions that can ensure appropriate and adequate immuno-prophylaxis in at-risk patients	3/4 (Knowledge/ Competence)
Pharmacists lack **knowledge** of pharmaceuticals in development for the prevention or treatment RSV infection	*Literature review; Survey data; Clinical trial data; Expert opinion*	Present clinical trial data for immuno-prophylaxis with motavizumab, and treatment with antisense antiviral agents; discuss limitations of antiviral therapy and RSV vaccines	3 (Knowledge)

RSV = Respiratory syncytial virus.
CDC = Centers for Disease Control and Prevention.
NREVSS = National Respiratory and Enteric Virus Surveillance System.
AAP = American Academy of Pediatrics.

RSV is a highly prevalent virus, and the incidence of RSV infection in the United States may be on the rise [Shay *JAMA* 1999] For most, RSV exposure results in a mild, self-limited upper respiratory tract infection. However 25% to 40% of infected individuals, especially infants and young children who have easily compromised respiratory function, develop lower respiratory tract infection [Olszewska *Expert Opin Emerg Drugs* 2009]; 2% to 3% of these are hospitalized each year with significant RSV disease. [Smyth *Lancet* 2006] In the United States, severe RSV infection is the leading cause of infant hospitalization and viral death. [Leader *Pediatr Infect Dis J* 2002; Thompson *JAMA* 2003] Furthermore, long-term complications may develop as a consequence of immunopathologic damage to heart [Checchia *AJHP* 2008] or lung tissue. [Robinson *AJHP* 2008] ***Pharmacists who collaborate with physicians on the management of RSV disease need to know the acute and chronic burden of lower respiratory tract infection associated with RSV.***

Transmission of RSV follows a seasonal and geographic pattern. The shortest RSV season is in the US Midwest, which typically runs from December to March; the longest is in Florida, which runs from September to April. [Forbes *AJHP* 2008; CDC *MMWR* 2008] In southernmost Florida, RSV season is virtually year round. [Forbes *AJHP* 2008] Infection is caused by exposure to RSV respiratory secretions, which can be shed asymptomatically for up to 7 days prior to symptoms and up to 21 days after symptoms have resolved. [Forbes *AJHP* 2008] ***Pharmacists who collaborate with physicians on the management of RSV disease need to understand how RSV is transmitted and know the timing of RSV season by geographic area.***

Several conditions are associated with an increased risk of developing severe RSV disease with increased morbidity and mortality: [Checchia *AJHP* 2008]

- Prematurity (≤35 weeks gestational age): associated with incomplete airway development and absence of maternal in utero transfer of antibodies
- Chronic heart disease: associated with pulmonary hypertension
- Chronic lung disease: associated with bronchial hyper-responsiveness and reduced lung reserve
- Neuromuscular disease: associated with reduced pulmonary muscle strength and endurance
- Immunodeficiency: associated with decreased host defense

Pharmacists who collaborate with physicians on the management of RSV disease need to understand how underlying conditions can increase the risks for and outcomes of severe RSV disease.

Prevention of RSV disease is currently achieved by passive immunization with palivizumab. The AAP recently updated their recommendations for: [Comm Infect Dis *Pediatrics* 2009]

- Initiation and termination of prophylaxis, according to CDC-reported timing of RSV season [CDC NREVSS 2009]
- Eligibility criteria for high-risk categorization
- Regimen variations by risk categories and age at onset of RSV season

A broader definition of eligibility for prophylaxis comes from an inpatient and outpatient surveillance of acute respiratory infections in children ≤5 years old conducted over five RSV seasons. Only prematurity and young age were independently associated with hospitalization for confirmed RSV infection. The survey found substantial morbidity in both inpatient and outpatient settings; most children with RSV infection were previously healthy. The authors concluded that targeting the high-risk population alone doesn't address the population with the highest burden of RSV disease. [Hall *N Engl J Med* 2009] ***Pharmacists who collaborate with physicians on the management of RSV disease need to be able to identify patients who are candidates for RSV prevention and the appropriate regimen for each candidate.***

Despite the identification of candidates for prophylaxis, there is evidence that many children who meet AAP criteria are not receiving palivizumab as indicated:

- In a multicenter observational study, among children <2 years old who were diagnosed with RSV bronchiolitis who met AAP at-risk criteria, only 49% (N = 35) had received at least one dose of palivizumab. [Mansbach *Ped Emerg Care* 2007]
- In a retrospective, medical record review at a tertiary children's hospital, among children <2 years old hospitalized for RSV infection who met AAP at-risk criteria, only 35% (N = 40) had received palivizumab. [Moynihan *J Pediatr Health Care* 2004]
- In a survey mailed to parents of children eligible for palivizumab, only 78% of eligible children received all doses of palivizumab as directed by AAP guidelines. [Langkamp *Amer J Perinatol* 2001]

- A nationwide Palivizumab Outcome Registry tracking 20,000 infants from 2003 to 2006 found that 42% (N = 2780) of preterm infants discharged during RSV season failed to receive the AAP-mandated first dose of immunoprophylaxis 48 to 72 hours prior to discharge, and many experienced a clinically significant delay before receiving palivizumab as an outpatient. [Speer *Neonatol Today* 2007]

Given the poor compliance with AAP guidelines for immunoprophylaxis, pharmacists play a key role in assisting physicians to identify patients who are candidates for passive immunization to reduce the morbidity and mortality of RSV disease.

A number of pharmaceutical products are in clinical development for the prevention or treatment of RSV disease. Preventive measures for RSV disease rely on passive immunization and vaccines.

- A second humanized monoclonal antibody, motavizumab, offers a greater reduction than palivizumab in the incidence of lower respiratory tract RSV infection and hospitalization. Unlike palivizumab, motavizumab inhibits RSV replication in both the lower respiratory tract and nasal passages. [Olszewska *Expert Opin Emerg Drugs* 2009] The Biologics License Application for motavizumab is currently under review by the FDA.
- Numerous biologically-derived, genetically-engineered, live, attenuated vaccines are in development. Unfortunately, these vaccines tend to induce weak immunity or revert to virulence in the target population. [Olszewska *Expert Opin Emerg Drugs* 2009]

There are 2 antisense, anti-RSV agents in Phase II clinical trials: [Olszewska *Expert Opin Emerg Drugs* 2009]

- ALN-RSV01, which inhibits RSV replication by interrupting the synthesis of viral nucleocapsid protein.
- RSV-604, an oral benzodiazepine that inhibits replication of both RSV A and RSV B. Based on its potency and pharmacokinetic profile, RSV-604 has the potential for once-daily administration.

Unfortunately, the utility of all antiviral agents is limited by the need for administration within 48 hours of infection. [Olszewska *Expert Opin Emerg Drugs* 2009] ***Pharmacists who collaborate with physicians on the management of RSV disease need to be able to evaluate potential pharmaceuticals for the prevention or treatment RSV infections.***

Learning Objectives

After watching this CME webcast presentation, the viewer should be able to

1. Discuss the acute and chronic burden of RSV disease in children and adults in the United States.
2. Describe the transmission of RSV, including seasonal and geographic aspects.
3. Explain how age-related airway anatomy and pathophysiology of underlying conditions lead to RSV disease vulnerability.
4. Discuss the implications of the immune response to RSV on disease progression, long-term complications, severity of reinfection, and potential vaccines.
5. Discuss differences between the licensed indication for prophylaxis with palivizumab, the most recently revised AAP guidelines, and the survey that finds a need for far broader prophylaxis.
6. Describe the regimen for administration of palivizumab to candidates at risk, including reasons for regimen variations.
7. Discuss interventions that can enhance the role of the pharmacist in communicating, counseling, and monitoring the merits of RSV prevention in at-risk patients.
8. Discuss differences between palivizumab and the next generation of passive immunoprophylaxis, motavizumab.
9. Discuss the antiviral agents in development for management of RSV disease.

Intended Audience

- Hospital pharmacists
- Specialty pharmacists
- Managed care medical directors
- Pharmacy directors

Proposed Agenda

I. Introduction: The Burden of RSV Disease

- Epidemiology
- Clinical consequences: acute and chronic; in infants; in elderly (eg, with COPD)

II. Respiratory Syncytial Virus

- Virology of RSV: enveloped RNA virus, subgroup A and B; role of F and G surface glycoproteins

- Transmission: method of transmission; persistence of RSV; timing of individual infectivity; CDC definition for onset of RSV season; RSV season by geographic area; National Respiratory and Enteric Virus Surveillance System annual data for duration of RSV season

III. Clinical Characteristics of Vulnerability to RSV Disease

- Prematurity (airway anatomy, maternal antibodies)
- Age relative to onset of RSV season
- Underlying conditions: chronic heart disease, chronic lung disease; neuromuscular disease, immunodeficiency
- Immunologic response to RSV

IV. Prevention of RSV Disease

- Candidates for passive immunization with palivizumab: FDA labeling; most recent AAP guidelines; survey with broader recommendations
- Passive immunization regimen: standard; by age; by severity of underlying condition; by age at onset of RSV season
- Interventions for communicating identification of at-risk patients, counseling the merits of RSV prevention, and monitoring adherence to adequate immunoprophylaxis
- Pharmacokinetics of palivizumab: no interactions with vaccines; no drug-drug interactions
- Cost-effectiveness of palivizumab: reason for poor compliance with guidelines for use?

V. Emerging Options for RSV Disease Management

- Immunoprophylaxis: motavizumab; differences vs palivizumab in site of action and potency in reducing incidence and severity of RSV disease
- Antisense anti-RSV agents in Phase II trials: ALN-RSV01, RSV-604; limited clinical utility of anti-RSV antiviral agents
- Vaccines: versus both A and B strains; limitations of vaccines (eg, vulnerable population too young to mount an immune response; lack of immune memory with RSV exposure; failure of prior RSV vaccine)

VI. Questions and Answers (if program interactive)

VII. Concluding Remarks

Proposed Faculty

Caroline B. Hall, MD
Professor, Pediatrics and Medicine
Division of Infectious Disease
University of Rochester School of Medicine and Dentistry
Rochester, NY
Area of expertise — virology

Michael L. Forbes, MD
Director, Clinical Research and Outcomes Analysis
Children's Hospital Medical Center
Akron, OH
Area of expertise — pediatric intensive care

Paul A. Checchia, MD
Assoc Professor, Pediatrics
Medical Director, Cardiac Intensive Care Service
Department of Pediatrics
Washington University School of Medicine
St. Louis, MO
Area of expertise — infectious complications of congenital heart disease

All faculty members will be screened for possible conflicts of interest (COI) and the program will be executed in a manner that is consistent with OIG, FDA, ACCME, and ACPE standards and guidelines.

References

Centers for Disease Control and Prevention. Brief report: respiratory syncytial virus activity — United States, July 2007–December 2008. *MMWR Morbidity and Mortality Weekly Report*. 2008;57(50):1355-1358.

Centers for Disease Control and Prevention. The National Respiratory and Enteric Virus Surveillance System (NREVSS). http://www.cdc.gov/surveillance/nrevss/. Updated October 27, 2009. Accessed November 3, 2009.

Chan-Tack KM, Murray JS, Birnkrant DB. Use of ribavirin to treat influenza. *N Engl J Med*. 2009;361(17):1713-1714.

Checchia P. Identification and management of severe respiratory syncytial virus. *Am J Health-Syst Pharm*. 2008;65(suppl 8):S7-S12.

Committee on Infectious Disease. American Academy of Pediatrics Policy statement — modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infection. *Pediatrics*. 2009;124(6):2345-2352. (doi:10.1542/peds.2009-2345).

Forbes M. Strategies for preventing respiratory syncytial virus. *Am J Health-Syst Pharm*. 2008;65(suppl 8):S13-S19.

Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Child Dis*. 1986;140(6):543-546.

Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med*. 2009;360(6):588-598.

Krilov LR. Respiratory syncytial virus (RSV) infection. http://emedicine.medscape.com/article/971488-treatment. Updated July 27, 2009. Accessed October 31, 2009.

Langkamp DL, Hlavin SM. Factors predicting compliance with palivizumab in high-risk infants. *Amer J Perinatol*. 2001;18(6):345-352.

Leader S, Kohlhase K. Respiratory syncytial virus-coded pediatric hospitalizations, 1997 to 1999. *Pediatr Infect Dis J*. 2002;21(7):629-632.

Mansbach J, Kunz S, Acholonu U, Clark S, Camargo Jr CA. Evaluation of compliance with palivizumab recommendations in a multicenter study of young children presenting to the emergency department with bronchiolitis. *Ped Emerg Care*. 2007;23(6):3620267.

Moynihan JA, Kim TY, Young T, Checchia PA. Rate of palivizumab administration in accordance with current recommendations among hospitalized children. *J Pediatr Health Care* 2004;18(5):224-227.

Olszewska W, Openshaw P. Emerging drugs for respiratory syncytial virus infection. *Expert Opin Emerg Drugs*. 2009;14(2):207-217.

Robinson RF. Impact of respiratory syncytial virus in the United States. *Am J Health-Syst Pharm*. 2008;65(suppl 8):S3-S6.

Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA*. 1999;282(15):1440-1446.

Smyth RL, Openshaw PJM. Bronchiolitis. *Lancet*. 2006;368(9532):312-322.

Speer ME, Boron M, McLaurin K, Cohen A, Rankin M, Groothuis J. Palivizumab Outcomes Registry 2000 to 2004: delayed prophylaxis in children at high risk of respiratory syncytial virus (RSV) disease. *Neonatol Today*. 2007;2(4):1-5.

Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA*. 2003;289(2):179-186.