S402- AAP Updated Guidelines for Palivizzumab Prophylaxis

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Disclosure of Relevant Relationship

• Dr. Brady (or spouse/partner) has not had (in the past 12 months) any conflicts of interest to resolve or relevant financial relationship with the manufacturers of products or services that will be discussed in this CME activity or in his presentation.

• Dr. Brady will support this presentation and clinical recommendations with the “best available evidence” from medical literature.

• Dr. Brady does not intend to discuss an unapproved/investigative use of a commercial product/device in this presentation.
AAP Updated Guidance for Palivizumab Prophylaxis

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Updated AAP Guidelines for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of RSV Hospitalization

Issued Jointly by COID and the Bronchiolitis Guidelines Committee

Pediatrics 2014; 134: 415-420
Pediatrics 2014; 134: e620-e638
Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection

abstract

Palivizumab was licensed in June 1998 by the Food and Drug Administration for the reduction of serious lower respiratory tract infection caused by respiratory syncytial virus (RSV) in children at increased risk of severe disease. Since that time, the American Academy of Pediatrics has updated its guidance for the use of palivizumab 4 times as additional data became available to provide a better understanding of infants and young children at greatest risk of hospitalization attributable to RSV infection. The updated recommendations in this policy statement reflect new information regarding the seasonality of RSV circulation, palivizumab pharmacokinetics, the changing incidence of bronchiolitis hospitalizations, the effect of gestational age and other risk factors on RSV hospitalization rates, the mortality of children hospitalized with RSV infection, the effect of prophylaxis on wheezing, and palivizumab-resistant RSV isolates. This policy statement updates and replaces the recommendations found in the 2013 Red Book Pediatrics 2014;134(2):415–420.

Policy statements from the American Academy of Pediatrics (AAP) are designed to provide updated guidance for child health care topics, with an emphasis on evidence-based recommendations whenever possible. Policy statements are reviewed at least every 3 years and updated when appropriate. In following this procedure, the AAP Committee on Infectious Diseases (COD) has undertaken a systematic review of all relevant and earlier peer-reviewed literature relating to the burden of respiratory syncytial virus (RSV) disease in infants and children, focusing on publications that delineate children at greatest risk of serious RSV disease and studies that define pharmacokinetics, safety, and efficacy. Detailed input regaridng this guidance has been solicited from 21 committees, councils, sections, and advisory groups within the American Academy of Pediatrics (AAP).
Clinical Trials Data Supporting Palivizumab FDA Licensure
Palivizumab administration to *preterm infants* during an RSV season has been shown to:

- Reduce RSV hospitalization (55% reduction: 10.6% placebo vs. 4.8% palivizumab)
- Reduce RSV hospital days (41% reduction)
- Reduce days requiring oxygen (40% reduction)

*Pediatrics* 1998; 102: 531-537
Palivizumab administration to children with hemodynamically significant acyanotic congenital heart disease has been shown to:

- Reduce RSV hospitalizations (45% reduction)
- Reduce RSV hospital days (56% reduction)
- Reduce oxygen requirement days (73% reduction)

_J Pediatr_ 2003; 143: 532-540
RSV Prophylaxis

Palivizumab administration to preterm infants during an RSV season did NOT show:

• Reduction in proportion of infants requiring mechanical ventilation
• Reduction in total mechanical ventilation days
• Reduction in hospitalizations in cyanotic CHD
• Reduction in mortality (2 deaths [all cause] in palivizumab arm; 0 deaths placebo)
• Reduction in long-term RSV morbidity

*Pediatrics* 1998; 102: 531-537
*J Pediatr* 2003; 143: 532-540

- INDICATIONS AND USAGE: “Synagis is a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease. Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (less than or equal to 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD).”

- “15 mg per kg of body weight, administered IM prior to commencement of the RSV season and remaining doses administered monthly throughout the RSV season.”
FDA Indications vs. Guidelines

FDA Indications

– Describe safety/efficacy determined in manufacturer’s pre-licensure/post licensure studies
– Place limits on manufacture's marketing
– Are not intended to be clinical guidelines

Clinical Guidelines

- Provide evidence-based recommendations from totality of available information on best practice
- Take into account current epidemiology, efficacy, safety, implementation and cost-effectiveness (not limited to FDA licensure studies)
<table>
<thead>
<tr>
<th>Year</th>
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<tr>
<td>Jan 1996</td>
<td>RespiGam licensed by FDA</td>
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<tr>
<td>Apr 1997</td>
<td>AAP Statement: RSV-IVIG Indications</td>
</tr>
<tr>
<td>Jun 1998</td>
<td>Palivizumab licensed by FDA</td>
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<tr>
<td>Nov 1998</td>
<td>AAP Statement: Indications for use of Palivizumab</td>
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<tr>
<td>Dec 2003</td>
<td>AAP Statement: Revised indications for Palivizumab</td>
</tr>
<tr>
<td>‘06 Red Book</td>
<td>Revised indications</td>
</tr>
<tr>
<td>‘09 Red Book</td>
<td>Revised indications</td>
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<tr>
<td>Dec 2009</td>
<td>AAP Policy Statement: Modified recommendation for use of palivizumab</td>
</tr>
<tr>
<td>‘12 Red Book</td>
<td>No major changes</td>
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Participants in Updated Guidance

- Bronchiolitis Guidelines Committee (AAP)
- Committee on Infectious Disease (AAP)
- 21 Committees, Councils, Sections & Advisory Groups within the AAP
- 8 External Organizations
Internal AAP Review

AAP Committee, Councils and Selections:
Committee on Bioethics (COB)
Committee on Child Health Financing (COCHF)
Committee on Fetus and Newborn (COFN)
Committee on Hospital Care (COHC)
Committee on Medical Liability and Risk Management (COMLRM)
Committee on Native American Child Health (CONACH)
Committee on Practice and Ambulatory Medicine (COPAM)
Committee on State Government Affairs (COSGA)
Council on Children with Disabilities (COCWD)
Council on Community Pediatrics (COCP)
Council on Quality Improvement and Patient Safety (COQIPS)
Section on Administration and Practice Management (SOAPM)
Section on Cardiology and Cardiac Surgery (SOCCS)
Section on Epidemiology (SOEp)
Section on Hospital Medicine (SOHM)
Section on Infectious Disease (SOID)
Section on Pulmonary Medicine
Section on Perinatal Pediatrics (SOPPe)
Medical Home Implementation Project Advisory Committee (MHIPAC)
Private Payer Advocacy Advisory Committee (PPAAC)
External Organization Review

- American College of Chest Physicians (ACCP)
- American College of Emergency Physicians (ACEP)
- American Thoracic Society (ATS)
- Emergency Nurses Association (ENA)
- National Association of Neonatal Nurses (NANN)
- National Medical Association (NMA)
- Society of Hospital Medicine (SOHM)
- National Association of Neonatal Nurse Practitioners (NAPNAP)
AAP Board Approval Process

• Each review group provided comments/suggestions
• The Committee on Infectious Disease and the Bronchiolitis Guidelines Committee had to respond to all comments
• The AAP Board reviewed all comments/suggestions and responses
• The AAP Board required clarifications/changes based on their review
• The final document represents the product of all reviews, responses and final approval of the AAP Board.
Trends in Bronchiolitis Hospitalization, United States, 2000-2009

- Among children <2 yrs, bronchiolitis hospitalizations decreased from 17.9 to 14.6/1000 person years (17% decrease)

- Among infants <1 yr, bronchiolitis hospitalizations decreased from 27.1 to 19.2/1000 person years (29% decrease)

- Nationwide hospital mean charge increased from mean of $6400 to $8500 per case (33% increase)

*Pediatrics 2013;132:28*
RSV Hospitalization Rates In One RSV Season by Gestational Age at Birth

Gestational Age

Hospitalization Rates/1000

<29 29-31 32-34 >35

65 100 100

Impact Trial Pediatrics 1998
RSV Hospitalizations Among 559 Children <24 Mon, 2000-2004

New Vaccine Surveillance Network

- 73% of admissions were Jan, Feb, Mar
- Hospitalization rates by gestation:
  - For all term infants: 5.3/1,000
  - Infants ≥35 wk: 5.1/1,000
  - Infants 32-34 wk: 6.9/1,000
  - Infants 29-31: 6.3/1,000
  - Infants <30 wk (3%): 19.3/1,000
- Late-preterm infants hospitalized at rate not statistically significantly less than term infants

Pediatrics 2013;132:e341
RSV Hospitalization Rates In One RSV Season by Gestational Age at Birth

Hospitalization Rates/1000

Gestational Age

<29 29-31 32-34 >35

19.3 6.3 6.9 5.1

IMpact Trial Pediatrics 1998
Hall et al Pediatrics 2013
Average Rates of RSV Hospitalization for Children <24 m by Gestational Age

<table>
<thead>
<tr>
<th>Rate</th>
<th>Very Preterm 18.7/1000</th>
<th>Early &amp; Late Preterm 4.6/1000</th>
<th>Term 5.3/1000</th>
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</thead>
<tbody>
<tr>
<td>&lt;30 weeks</td>
<td>30</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>30–33 weeks</td>
<td>10</td>
<td>5</td>
<td></td>
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<tr>
<td>34–36 weeks</td>
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<td></td>
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</tr>
<tr>
<td>≥37 weeks</td>
<td>5</td>
<td></td>
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</tbody>
</table>

*Pediatrics; 2013:132:e341*
Percent of Infants Not Hospitalized for RSV Infection Stratified by Gestational Age

Helfrich et al PAS May 2014
Percentage of Infants Not Hospitalized for RSV Infection Stratified by Gestational Age

Helfrich et al PAS May 2014
Preterm Infants with No Chronic Lung Disease (CLD)

- **Updated guidance**
  - In the first year of life, palivizumab prophylaxis is recommended for infants born before 29 weeks, 0 days’ gestation *(B; Strong)*
  - Palivizumab prophylaxis is not recommended for otherwise healthy infants born at or after 29 weeks, 0 days’ gestation *(B; Strong)*

- **Previous guidance**
  - Previously, prophylaxis was recommended for infants with preterm birth before 32 weeks gestation. Infants with certain risk factors born at 32 weeks, 0 days to 34 weeks, 6 days were eligible.
  - Palivizumab prophylaxis is not recommended in the second year of life based on a history of prematurity alone
Preterm Infants with (CLD)

- **Updated guidance**
  - In the first year of life, palivizumab prophylaxis is recommended for preterm infants with chronic lung disease of prematurity defined as <32 weeks, 0 days’ gestation and a requirement for >21% oxygen for at least 28 days after birth *(B; Moderate)*

- **Previous guidance**
  - Previously no definition of chronic lung disease was provided.
Infants With Congenital Heart Disease (CHD)

• Updated guidance
  – Clinicians may administer palivizumab prophylaxis in the first year of life to certain infants with hemodynamically significant heart disease.
  – Consultation with a cardiologist currently is recommended for patients with cyanotic heart disease for decisions about prophylaxis.  
  (B; Moderate)

• Previous guidance
  – Previously prophylaxis was recommended in the second year of life for this cohort.
Infants with Hemodynamically Significant congenital heart disease (CHD)

• Certain children who are 12 months of age or younger with hemodynamically significant CHD may benefit from palivizumab prophylaxis. **Children with hemodynamically significant CHD who are most likely to benefit from immunoprophylaxis include infants with acyanotic heart disease who are receiving medication to control congestive heart failure and infants with moderate to severe pulmonary hypertension.**

• **Decisions regarding palivizumab prophylaxis for infants with cyanotic heart defects should be made in consultation with a pediatric cardiologist.**

• **These recommendations apply to qualifying infants in the first year of life who are born during the RSV season or within 12 months of onset of the RSV season.**

• **A second season of palivizumab prophylaxis for children with CHD is NOT recommended for cyanotic or acyanotic children.**
Anatomic Pulmonary Abnormality and Neuromuscular Disease

• Updated guidance

Children with pulmonary abnormality or neuromuscular disease that impairs the ability to clear secretions from the upper airways may be considered for prophylaxis in the first year of life.

• Previous guidance

Previous recommendation was for two years of prophylaxis.
Prophylaxis for Alaska Native and American Indian Infants

- RSV Surveillance data generated by the State of Alaska may be used to determine onset and end of RSV season.

- Due to increased burden of RSV disease in Alaska Native, Navajo and White Mountain Apache Infants, special consideration for a more liberal eligibility for palivizumab prophylaxis is prudent regardless of gestational age or risk factors.
Immunocompromised Children & RSV Prophylaxis

• Updated guidance

  Children less than 24 months of age who will be profoundly immunocompromised during the RSV season may be considered for prophylaxis.

• Similar to previous recommendation
Cystic Fibrosis

• Update guidance
  – Insufficient data are available to routinely recommend palivizumab prophylaxis for children with cystic fibrosis
  – Palivizumab may be considered for CF patients with chronic lung disease or nutritional deficit in the first year of life
  – Previous guidance
  – Previously, the CF recommendation did not include a recommendation for children with chronic lung disease of nutritional deficit.
Down Syndrome

• Updated guidance
  - Insufficient data are available to routinely recommend Palivizumab prophylaxis for children with Down Syndrome
  - Palivizumab may be considered for children with Down Syndrome who are eligible due to CHD

• Previous guidance
  - Children with Down Syndrome were not addressed specifically previously
RSV Breakthrough Hospitalization & RSV Prophylaxis

• Updated guidance

  Monthly prophylaxis should be discontinued in any child who experiences a breakthrough RSV hospitalization (There is a less than 0.5% risk of second RSV hospitalization in the same season.)

• Previous guidance

  Previously, prophylaxis was recommended to continue in a child who experiences a breakthrough RSV hospitalization.
Prevention of Nosocomial RSV Disease

• No rigorous data exist to support palivizumab use in controlling outbreaks of health care-associated disease, and palivizumab use is not recommended for this purpose. Infants in a neonatal unit who qualify for prophylaxis because of CLD, prematurity or congenital heart disease should receive the first dose 48 to 72 hours before discharge to home or promptly after discharge.

• Adherence to strict infection control practices is the basis for reducing nosocomial RSV disease.
Palivizumab Resistant Isolates

- RSV escape mutants resistant to palivizumab have been isolated from 5% to 10% of children with breakthrough RSV hospitalization while receiving monthly palivizumab prophylaxis.

J Inf Dis 2011; 203: 674
J Inf Dis 2012; 205:655
J Clin Virol 2012; 205:635
Pharmacokinetics of Palivizumab

- Pharmacokinetic data published by the manufacturer of palivizumab demonstrate that after five monthly doses, serum levels of palivizumab are at or above protective levels for most children for a total of at least six months (>24 weeks).

- More than 5 monthly doses are not recommended for any geographic area, with the possible exception of some regions in southwest Alaska.
Simulated Palivizumab Concentration-Time Profiles

AAC 2012;56:4927
RSV Season Onset & Offset
2007-2011 (range & median)

MMWR 2011;60:1203
RSV Seasons in US

Burden of RSV Infection

All States except Florida and Alaska
RSV Seasons in US

- All States except Florida and Alaska
- Florida
Number of Monthly Doses

- **Updated guidance**
  - Clinicians may administer up to a maximum of 5 monthly doses of palivizumab during the RSV season to infants who qualify for prophylaxis in the first year of life (including Florida). Qualifying infants born during the RSV season will require fewer doses. For example, infants born in January would receive their last dose in March.
  - Maximum 5 monthly doses for all states (B; Moderate)

- **Previous guidance**
  - Previously, fewer than 5 monthly doses were recommended for some infants
RSV and Wheezing: Is It The Chicken or the Egg
Association of RSV Infection with Recurrent Wheezing

• Severe RSV disease in infancy has been associated with subsequent wheezing

• There is NO data establishing a causal link. (Subsequent wheezing is a consequence of RSV infection vs. underlying susceptibility to reactive airway disease is unmasked with RSV infection)
Effect of palivizumab prophylaxis on subsequent wheezing

- Prophylaxis is not recommended for primary asthma prevention or to reduce subsequent episodes of wheezing.

- Studies have documented that infants hospitalized with viral lower airway disease are more likely to experience recurrent wheezing when compared to infants who do not experience severe bronchiolitis. However, studies in preterm children receiving palivizumab prophylaxis during the first RSV season have shown only a minimal reduction in the number of subsequent wheezing episodes.
Palivizumab Effect on Subsequent Wheezing

• Three company sponsored studies suggest reductions in recurrent/subsequent wheezing in palivizumab recipients as compared to children not receiving palivizumab.

• The first 2 studies were not randomized or double-blind and actually had some relevant mismatches (e.g. prematurity, birth weight, etc.)

1. J Pediatrics 2007; 151: 34
2. Pediatrics 2013; 132: 84
3. NEJM 2013; 368: 1791
Palivizumab Effect on Subsequent Wheezing

• All three studies showed modest reductions wheezing in palivizumab recipients

• None of the 3 studies attempted to correlate subsequent wheezing with prior RSV infection or current viral URI/LRI

• Two of the studies relied on “parent reported” wheezing, i.e. not medically-attended wheezing
Exploring the Association Between Severe RSV Infection as Asthma: A Registry-based Twin Study

AM J Resp Crit Care Med 2009; 179:1091-1097

- 8,280 twin pairs
- RSV hospitalization and asthma were positively associated
- Causation modeling:
  - Asthma “causes” RSV hospitalization fit the data significantly better even when sex, birth weight and maternal smoking were accounted for
  - Author's conclusion: “RSV severe enough to warrant hospitalization does not cause asthma but is an indication of the genetic predisposition to asthma”
• Birth cohort of 2133 infants < 2 months of age
• Pre-RSV pulmonary function for RSV-hospitalized vs. non-hospitalized RSV positive infants
  – Lung compliance was significantly lower for RSV-hospitalized compared to non-hospitalized
  – Lung resistance was higher for RSV-hospitalized compared to non-hospitalized
Palivizumab: Cost and Cost-Effectiveness
Promoting Population Health through Financial Stewardship

Ubel PA and Jagsi R NEJM 2014; 370: 1280

• “If physicians shirk their duty to act as financial stewards when making medical decisions, the end result will be worse health outcomes for the population at large”
Cost of Palivizumab

• Data from MedImmune (2013) (100mg)
  - Wholesale Acquisition Cost - $2962/vial
  - Estimated Medicaid Cost Net Rebate - $1191/vial
    (Proprietary; Varies State to State)

• Cost to Managed Care Medicaid in Ohio (2014)(100mg)
  - $1694/vial (net rebate)

• Cost to Private Insurers (2014)(100mg)
  - $2962 to $???/vial (median CHA hospital charge is $13,612 – net 70-80% of charge.)
Palivizumab: Number Needed to Treat (NNT) to Prevent One Infection

Based on Impact Trial- NNT=17
   (This includes all groups including those with CLD)

Based on CHD Trial-NNT=50

For children who are premature at ≥ 30 weeks gestation and no CLD-NNT ≈ 100
   (Helfrinch PAS May 2014)

Cost of one season of palivizumab exceeds cost of all vaccines given to infants and children to age 18 years
Cost of Immunoprophylaxis Far Exceeds the Economic Benefit of Preventing Hospitalization, even in Highest Risk Infants

- Cost analysis based on actual costs and observed incidence rates in a Florida Medicaid-eligible cohort of 159,790 children 0 to 2 years in 2004-2005
- Among pre-term infants younger than 6 months of age without other indications, palivizumab cost $302,103 to prevent 1 hospitalization
  - Mean cost of 1 RSV hospitalization $8120
  - Palivizumab would be cost neutral at a dose of $47/dose
- For other subgroups, the cost of RSV prophylaxis ranged from $361,727 to $1.3 million to prevent one hospitalization

Arch Pediatr Adolesc Med 2011;165:498
Monoclonal antibody for reducing the risk of RSV infection in children. Cochrane Database of Systematic Reviews 2013;4, Art. No. CD006602

“Almost all included studies that were sponsored by the industry supported the cost-effectiveness of palivizumab prophylaxis while practically all included studies that were not sponsored by the industry suggested that palivizumab was not cost-effective.”
Concluding Comment

• The AAP acknowledges a slightly elevated risk of RSV hospitalization for moderate premature infants in the first months of life but judges the small baseline incidence coupled with high palivizumab cost to not justify the expenditures.

• While the impact of RSV hospitalization on a family is more than just financial cost, administration of palivizumab to a large number of children to prevent one RSV hospitalization exacts a cost on a number of families each month in terms of time and exposure of an infant to other infectious patients in a physician’s office.
References

1. AAP Policy Statement. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for RSV infection. *Pediatrics* 2014;134(2):415-420


5. AAP COID. Severe RSV disease in preterm infants born at 29 to 35 weeks gestation in the United States. Letter-to-Editor. *Pediatrics* 2014;134:
Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis

abstract

This guideline is a revision of the clinical practice guideline, “Diagnosis and Management of Bronchiolitis,” published by the American Academy of Pediatrics in 2006. The guideline applies to children from 1 through 23 months of age. Other exclusions are noted. Each key action statement indicates level of evidence, benefit-harm relationship, and level of recommendation. Key action statements are as follows: Pediatrics 2014;134:e1474–e1502

DIAGNOSIS

1a. Clinicians should diagnose bronchiolitis and assess disease severity on the basis of history and physical examination (Evidence Quality: B; Recommendation Strength: Strong Recommendation).

1b. Clinicians should assess risk factors for severe disease, such as

KEY WORDS
bronchiolitis, infants, children, respiratory syncytial virus, evidence-based, guideline

ABBREVIATIONS
AAP—American Academy of Pediatrics
AOM—acute otitis media
CI—confidence interval
ED—emergency department
KAS—Key Action Statement