

NYSMPEP Respiratory Syncytial Virus (RSV) Bronchiolitis Module

Key Message 2:

- The 2014 guidance from the American Academy of Pediatrics (AAP) suggests that in the absence of other risk factors, infants born prior to 29 weeks' gestation should receive prophylaxis for respiratory syncytial virus (RSV).
- Pre-term infants aged 12 months at the season onset with chronic lung disease (CLD) of prematurity are considered eligible. Prophylaxis may also be considered in the second year of life in patients requiring medical support during the 6-month period prior to the onset of the second RSV season.
- The AAP also recommends RSV prophylaxis for both term and pre-term infants with hemodynamically significant congenital heart disease (CHD).

Pre-term birth, no other risk factors	Pre-term birth, CLD	Pre-term birth, CHD
Pre-term birth is associated with an increased risk of lower respiratory tract disease due to RSV ¹ ; however, this is not specific to RSV, and not all pre-term infants require RSV prophylaxis ²	In previous guidelines, CLD was ill-defined. Per 2014 AAP guidance, CLD of prematurity entails gestational age <32 weeks and a requirement for >21% oxygen for a minimum of 28 days post-birth ³ Prophylaxis may be considered in children aged <24 months at season onset if requiring chronic steroid therapy, diuretics, or supplemental oxygen within 6 months prior to second season onset	Prophylaxis is only likely to benefit patients in the first year of life ¹ Most likely to benefit: <ul style="list-style-type: none"> • Acyanotic heart disease, receiving medication to control congestive heart failure and requiring cardiac surgery • Moderate-to-severe pulmonary hypertension Unlikely to benefit: <ul style="list-style-type: none"> • Hemodynamically insignificant heart disease • Lesions adequately corrected by surgery and without requirement for congestive heart failure pharmacotherapy

Summary of changes in RSV prophylaxis recommendations from the AAP.^{3,4}

Previous Guidelines (2009)	Recent Guidance (2014)
Pre-term infants with no other risk factors	
<ul style="list-style-type: none"> • GA <29 weeks + chronological age <12 months at season onset^a • GA ≥29 weeks and <32 weeks + chronological age <6 months at season onset or • GA ≥32 weeks and <36 weeks + chronological age <6 months at season onset and 1 of following: <ul style="list-style-type: none"> ○ Attends childcare/daycare ○ Lives in household with ≥1 child aged <5 years 	<ul style="list-style-type: none"> • GA <29 weeks • Chronologic age <12 months at season onset
Pre-term infants and children with CLD	
<ul style="list-style-type: none"> • Chronologic age <24 months at season onset with CLD of prematurity (ill-defined) and requires medical support within 6 months prior to season onset 	<ul style="list-style-type: none"> • GA <32 weeks • Requires >21% oxygen for ≥28 days post-birth • Chronologic age <12 months at season onset or • Chronologic age <24 months at season onset and: <ul style="list-style-type: none"> ○ Meets above criteria for CLD of prematurity ○ Requires medical support during 6 months prior to second season onset

References: 1. Brady MT. *Pediatrics*. 2014;134:e620. 2. Hall CB. *N Engl J Med*. 2009;360:588. 3. Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. *Pediatrics*. 2014;134:415. 4. Bocchini Jr JA. *Pediatrics*. 2009;124:1694. 5. Stevens TP. *Arch Pediatr Adolesc Med*. 2000;154:55. 6. Boyce TG. *J Pediatr*. 2000;137:865. 7. Winterstein AG. *JAMA Pediatr*. 2013;167:1118. 8. IMPACT RSV Study Group. *Pediatrics*. 1998;102:531. 9. Feltes TF. *J Pediatr*. 2003;143:532. 10. Chang RK and Chen AY. *Pediatr Cardiol*. 2010;31:90.

Infants with hemodynamically significant CHD

• Chronologic age <24 months at season onset and hemodynamically significant cyanotic or acyanotic CHD

• Chronologic age <12 months at season onset

^aNew York State Department of Health designates RSV season as October 16 – March 31

Pre-Term Infants with No Other Risk Factors:

The following 3 studies examined the rates of RSV associated hospitalization among pre-term infants without other risk factors and the gestational age groups most likely to be affected. Based on the evidence, pre-term infants of younger gestational age (≤28 weeks) are more likely to be hospitalized with RSV than later born pre-term infants. After the age of 12 months, it appears that this population is no longer at increased risk. In the absence of other risk factors, prophylaxis should be restricted to infants born at fewer than 29 weeks gestation who are <12 months at RSV season onset.

Reference	Study Design	Population	Endpoints	Results	Conclusion
Stevens 2000⁵	Retrospective cohort	n=1,029 infants ≤32 wk GA, followed from birth to 1 year in a regional hospital NICU in New York, 1992-1996	Rate of RSV associated hospitalization	Overall RSV hospitalization rate for GA ≤32 wk: 11.2% Admittance rate, by GA, compared to GA 30 to 32 wk: <ul style="list-style-type: none"> • ≤26 wk: 13.9%, 95% CI 8.6 to 19.1 • 27-28 wk: 9.9%, 95% CI 5.4 to 14.4 • >28-30 wk: 7.5%, 95% CI 4.2 to 10.8 • >30-32 wk: 4.4%, 95% CI 2.5 to 6.3 	Rate of RSV hospitalization increased with decreasing GA.
Boyce 2000⁶	Retrospective cohort	n=80,037 child-yr, excluding influenza season; children aged <3 years in Tennessee Medicaid from 1989-1993	Rate of RSV associated hospitalization	Total of 3,553 RSV hospitalizations IRR for RSV hospitalization, relative to incidence in “low-risk” group of same age: <ul style="list-style-type: none"> • <6 mo (rate 44.1 per 1,000 children) GA ≤28 wk: 2.1, 95% CI 1.4 to 3.1 GA 29 to <33 wk: 1.9, 95% CI 1.4 to 2.4 GA 33 to <36 wk: 1.8, 95% CI 1.5 to 2.1 • 6 to <12 mo (rate 15.0 per 1,000 children) GA ≤28 wk: 3.1, 95% CI 1.7 to 5.2 GA 29 to <33 wk: 3.3, 95% CI 2.3 to 4.7 GA 33 to <36 wk: 2.3, 95% CI 1.7 to 3.0 • 12 to <24 mo (rate 3.7 per 1,000 children) GA ≤28 wk: 8.2, 95% CI 4.4 to 14.2 GA 29 to <33 wk: 2.3, 95% CI 1.1 to 4.4 GA 33 to <36 wk: 2.9, 95% CI 1.9 to 4.3 • 24 to <36 mo (rate 1.0 per 1,000 children) GA ≤28 wk: 0.0, 95% CI 0 to 12.2 GA 29 to <33 wk: 2.2, 95% CI 0.3 to 8.8 GA 33 to <36 wk: 0.9, 95% CI 0.1 to 3.6 	Within the age groups, preterm patients had relatively similar RSV hospitalization rates. Overall, children with prematurity, aged >12 months, had rates no higher than those of low-risk infants.
Winterstein 2013⁷	Retrospective cohort	n=247,566 preterm (GA 32-34 wk) infants aged 1-12 months and term (GA 37-41 wk) infants aged 1 month in Texas and Florida Medicaid claims from 1999-2004	Age at which risk of RSV hospitalization was equal for pre-term and term infants	Total of 5,322 RSV hospitalizations Risk of RSV hospitalization, pre-term vs. term: <ul style="list-style-type: none"> • Florida: OR 2.41, 95% CI 1.85 to 2.31 • Texas: OR 1.94, 95% CI 1.64 to 2.30 Age of similar risk: <ul style="list-style-type: none"> • Florida: 4.2 mo, 95% CI 2.5 to 5.7 • Texas: 4.5 mo, 95% CI 2.8 to 6.4 	Age at which similar risk for RSV hospitalization demonstrated between pre-term and term infants suggests more restrictive age thresholds in RSV prophylaxis recommendations.

References: 1. Brady MT. *Pediatrics*. 2014;134:e620. 2. Hall CB. *N Engl J Med*. 2009;360:588. 3. Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. *Pediatrics*. 2014;134:415. 4. Bocchini Jr JA. *Pediatrics*. 2009;124:1694. 5. Stevens TP. *Arch Pediatr Adolesc Med*. 2000;154:55. 6. Boyce TG. *J Pediatr*. 2000;137:865. 7. Winterstein AG. *JAMA Pediatr*. 2013;167:1118. 8. IMPACT RSV Study Group. *Pediatrics*. 1998;102:531. 9. Feltes TF. *J Pediatr*. 2003;143:532. 10. Chang RK and Chen AY. *Pediatr Cardiol*. 2010;31:90.

Pre-term Infants and Children with CLD or CHD

The following studies focused on the rate of RSV-associated hospitalizations in pre-term infants with CLD and infants with CHD. Pre-term infants with CLD who require support prior to the onset of RSV season tend to be at high risk until age 24 months. Infants with CHD are at increased risk until 12 months of age, and prophylaxis should be restricted in this population to the first year of life. In these cohorts, palivizumab was safe and effective in reducing the incidence of RSV-associated hospitalization.

Reference	Study Design	Population	Endpoints	Results	Conclusion
CLD					
IMPACT-RSV⁸	R, DB, PC, trial	n=1502 children with prematurity (GA <35 wk) or BPD during the 1996 to 1997 RSV season in the US, UK, or Canada	Hospitalization with confirmed RSV infection	Total of 101 hospitalizations Among those with BPD hospitalized for RSV: <ul style="list-style-type: none"> • Placebo: 12.8% • Palivizumab: 7.9% • RR=39%, 95% CI 38 to 73 	Palivizumab prophylaxis is effective for preventing RSV associated hospitalizations in children with BPD.
Boyce 2000⁶	Retrospective cohort	n=80,037 child-yr, excluding influenza season; children aged <3 yr in Tennessee Medicaid from 1989-1993	Rate of RSV hospitalization	Total of 3,553 RSV hospitalizations IRR for RSV hospitalization, relative to incidence in “low-risk” group of same age: <ul style="list-style-type: none"> • <6 mo (rate 44.1 per 1,000 children) BPD: 12.8, 95% CI 9.3 to 17.2 • 6 to <12 mo (rate 15.0 per 1,000 children) BPD: 14.3, 95% CI 9.3 to 21.1 • 12 to <24 mo (3.7 per 1,000 children) BPD: 20.0, 95% CI 11.1 to 33.7 • 24 to <36 mo (1.0 per 1,000 children) BPD: 12.9, 95% CI 1.5 to 51.5 	Children with BPD have high RSV hospitalization rates until age 24 mo.
CHD					
Boyce 2000⁶	Retrospective cohort	n=80,037 child-yr, excluding influenza season; children aged <3 yr in Tennessee Medicaid from 1989-1993	Rate of RSV hospitalization	Total of 3,553 RSV hospitalizations IRR for RSV hospitalization, relative to incidence in “low-risk” group of same age: <ul style="list-style-type: none"> • <6 mo (rate 44.1 per 1,000 children) CHD: 2.7, 95% CI 2.2 to 3.4 • 6 to <12 mo (rate 15.0 per 1,000 children) CHD: 4.2, 95% CI 3.1 to 5.7 • 12 to <24 mo (3.7 per 1,000 children) CHD: 5.0, 95% CI 3.0 to 7.9 • 24 to <36 mo (1.0 per 1,000 children) CHD: 4.9, 95% CI 1.3 to 14.2 	Children with CHD aged >12 months had RSV hospitalization rates no higher than those of low-risk infants.

References: 1. Synagis [package insert]. Gaithersburg, MD: MedImmune, LLC; 2014. 2. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics*. 2014;134:415. 3. Webinar – Updated AAP Guidance for Palivizumab Prophylaxis among Infants and Young Children at Increased Risk of RSV Hospitalization. www.aapredbook.org/site/resources/webinars.xhtml. 4. Modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infection. *Pediatrics*. 2009;124:1694.

Reference	Study Design	Population	Endpoints	Results	Conclusion
CHD (continued)					
Feltes 2003 ⁹	R, DB, PC, trial	n=1,287 (each child participated during 1 season) aged ≤24 months with hemodynamically significant CHD, and had un-operated or partially corrected CHD, in the US, Canada, Poland, UK, Germany, Sweden, and France	Antigen confirmed hospitalization	Total of 97 RSV hospitalizations RSV hospitalization: <ul style="list-style-type: none"> • Placebo: 9.7% (63 hospitalizations) • Palivizumab: 5.3% (34 hospitalizations) • 45% RRR, 95% CI 23 to 67 	Palivizumab prophylaxis is effective for young children with hemodynamically significant CHD.
Chang 2010 ¹⁰	Retrospective cohort	n=53,207 RSV-related hospitalizations among children aged <2 yr in California from 2002-2006	Change in RSV hospitalizations from 2000-2002 (pre-palivizumab era) to 2004-2006 (palivizumab era)	RSV hospitalization from 2000-2006: <ul style="list-style-type: none"> • CHD: 1,596 (3.0%); mortality 0.63% • Hemodynamically significant CHD: 266 (0.5%); mortality 1.90% RSV hospitalization, 2000-2002 vs. 2004-2006: <ul style="list-style-type: none"> • Hemodynamically significant CHD: 0.56% vs. 0.46% (p=NR) 	Palivizumab prophylaxis has led to a reduction in RSV hospitalization among patients with hemodynamically significant CHD.

BPD=bronchopulmonary dysplasia; CHD=congenital heart disease; CI=confidence interval; CLD=chronic lung disease; DB=double-blind; GA=gestational age; IRR=incidence rate ratio; NR=not reported; PC=placebo-controlled; R=randomized; RR=relative risk; RRR=relative risk reduction; RSV=respiratory syncytial virus; UK=United Kingdom; US=United States

References: 1. Brady MT. *Pediatrics*. 2014;134:e620. 2. Hall CB. *N Engl J Med*. 2009;360:588. 3. Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. *Pediatrics*. 2014;134:415. 4. Bocchini Jr JA. *Pediatrics*. 2009;124:1694. 5. Stevens TP. *Arch Pediatr Adolesc Med*. 2000;154:55. 6. Boyce TG. *J Pediatr*. 2000;137:865. 7. Winterstein AG. *JAMA Pediatr*. 2013;167:1118. 8. IMPACT RSV Study Group. *Pediatrics*. 1998;102:531. 9. Feltes TF. *J Pediatr*. 2003;143:532. 10. Chang RK and Chen AY. *Pediatr Cardiol*. 2010;31:90.