

Treating Acute Bronchiolitis Associated with RSV

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Treatment for infants with bronchiolitis caused by respiratory syncytial virus (RSV) includes supplemental oxygen, nasal suctioning, fluids to prevent dehydration, and other supportive therapies. High-risk children who should be hospitalized include those younger than three months and those with a preterm birth, cardiopulmonary disease, immunodeficiency, respiratory distress, or inadequate oxygenation. Inhaled beta₂-agonist bronchodilators, the anticholinergic agent ipratropium bromide, and nebulized epinephrine have not been shown to be effective for treating RSV bronchiolitis. However, the Agency for Healthcare Research and Quality states that nebulized epinephrine and nebulized ipratropium bromide are possibly effective. The appropriate use of corticosteroids remains controversial. They may provide some benefit but meta-analyses of clinical trial results are inconsistent. Prophylaxis with RSV intravenous immune globulin or palivizumab, a human monoclonal antibody, can reduce hospitalization rates in high-risk patients, although difficulties with administering the medications and high costs may preclude their widespread use. The use of common infection-control measures can reduce nosocomial transmission of RSV infections. (*Am Fam Physician* 2004;69:325-30. Copyright© 2004 American Academy of Family Physicians)

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In the United States, bronchiolitis related to respiratory syncytial virus (RSV) is the leading cause of hospitalization in infants younger than one year. While only 1 to 2 percent of infants with this condition are hospitalized, annual hospital costs for RSV infections are quite high.¹ Supportive care, attention to adequate hydration and, possibly, supplemental oxygen are the basis of therapy for RSV infection.² This article reviews current guidelines and some controversies regarding treatment for RSV-related bronchiolitis.

Epidemiology

In northern hemispheres, annual outbreaks of RSV infection typically occur between October and May, with the peak effect falling in January and February. Peak incidence occurs in children younger than 12 months. Three months is the mean age of infants hospitalized with RSV infection. The illness can be prolonged, with a median duration of 12 days in children younger than two years. About 10 percent of children remain ill after four weeks. The RSV case fatality rate is less than 1 percent.³ Repeated infections with different forms of RSV in the same child are common.

Prophylaxis

In infants at high risk for RSV infection, two options for RSV prophylaxis are available:

palivizumab (Synagis) and intravenous RSV immune globulin (RSV-IG [RespiGam]). The American Academy of Pediatrics (AAP) recommends prophylaxis with palivizumab or RSV-IG in select infants and children at risk (Table 1).⁴

Palivizumab is the preferred agent for prophylaxis because it is more conveniently administered. It is a human monoclonal antibody preparation given once a month to high-risk infants by intramuscular injection in a dosage of 15 mg per kg. The first injection is administered just before the RSV season begins, usually in early November. Injections continue once a month and end with the fifth dose in March.

The cost-effectiveness of RSV prophylaxis is uncertain. One analysis⁵ suggests that prophylaxis provides real cost savings, while other reports⁶ estimate much higher costs per case avoided. In the Kansas Medicaid program, a group given RSV-related prophylaxis (RSV-IG and palivizumab) was compared with an untreated control group and showed reduced hospitalization rates, length of stay, and inpatient costs, among other benefits, in the treated group. However, the cost of the medications and their administration was more than six times higher than the financial benefit.⁷

Indications for Hospitalization

Infants with acute bronchiolitis may present with a wide range of clinical symptoms

See page 249 for definitions of strength-of-evidence levels.

TABLE 1

Prophylaxis with Palivizumab or RSV-IG*—Categories of Risk

Infants and children less than two years of age with known CLD who required medical therapy for CLD within six months of the anticipated start of the RSV season.

Preterm infants born at 28 weeks of estimated gestational age or earlier may benefit from prophylaxis during their first RSV season, whenever that occurs during the first year of life, even if CLD is not present.

Preterm infants born at 29 to 32 weeks of estimated gestational age or earlier may benefit from prophylaxis during their first RSV season, whenever that occurs during the first six months of life, even if CLD is not present.

Infants born at 32 to 35 weeks of estimated gestational age must have two of the following risk factors to be candidates for prophylaxis: attendance at a child-care center, school-aged siblings, exposure to environmental pollution, abnormalities of the airways, or severe neuromuscular problems.

RSV-IG = intravenous RSV immune globulin (RespiGam); CLD = chronic lung disease; RSV = respiratory syncytial virus.

*—RSV-IG is contraindicated in children with cyanotic congenital heart disease.

Information from reference 4.

and severity, from mild upper respiratory infections to pulmonary infiltrates and impending respiratory failure. The decision to hospitalize a child with RSV infection largely depends on the child's age, the clinically assessed severity of disease, and other risk factors (Table 2). High-risk infants who should be hospitalized include those younger than three months, those whose gestational age at birth was less than 34 weeks, and those with comorbid cardiopulmonary disease or immunodeficiency.⁴

Outpatient Management

Most children with RSV infection develop mild to moderate symptoms and can be treated at home provided they have close supervision by parents or caregivers who have been informed of what to watch for. Specific signs of a worsening condition that should prompt parents to contact their physician include an increasing respiratory rate (especially more than 60 breaths per minute); onset of labored breathing indicated by use of accessory muscles, retractions, cyanosis, or flared nostrils; fewer wet diapers (may indicate inadequate hydration); or an overall worsening appearance.

Infants who are lethargic and have a generally toxic appearance warrant a clinical examination, because these signs are associated with serious bacterial infections.⁸

Any infant 60 days or younger with a rectal temperature of 38°C (100.4°F) or higher should be examined by a physician and considered for sepsis evaluation. Homemade salt-

water nasal drops (one fourth teaspoon salt in 4 oz water) or a similar commercial product can help mobilize nasal mucus if the drops are applied before suctioning. Frequent handwashing by parents, caregivers, and other household contacts may be health protective for both the ill child and contacts. Visitors should be limited to prevent transmission. Parents and caregivers should avoid exposing the ill child to tobacco smoke and should be counseled about smoke exposure by the physician. There is no evidence to support the use of antibiotics, antihistamines, oral decongestants, or nasal vasoconstrictors in the treatment regimen.⁹

Inpatient Management

The basic management principles for infants hospitalized with acute viral bronchiolitis are oxygen therapy, fluids to prevent dehydration, respiratory support, and parental education.^{9,10}

One evidence-based practice guideline⁹ states that routine laboratory studies for RSV infection, including nasopharyngeal washing to determine the presence of the RSV antigen, are not indicated. However, the rate of serious bacterial infections concurrent with RSV infection in otherwise healthy infants is low (less than 2 percent), so using rapid-detection tests for RSV antigen in high-risk infants 60 days or younger may reduce the frequency of costly evaluations for sepsis.¹¹ Chest radiography is not necessary in the absence of clinical findings or other diagnostic suspicions. Cultures of blood or urine for bacteria are not necessary in uncomplicated bronchiolitis cases.

TABLE 2

Indications for Hospitalization in Bronchiolitis Caused by RSV

Age less than three months
 Gestational age at birth of less than 34 weeks
 Cardiopulmonary disease or immunodeficiencies
 Respiratory rate higher than 70 breaths per minute
 Lethargic appearance
 Wheezing and respiratory distress associated with oxygen saturation below 92 percent on room air
 Hypercarbia
 Atelectasis or consolidation on chest radiography

RSV = respiratory syncytial virus.

TABLE 3

Bronchiolitis Caused by RSV: Summary of AHRQ Treatment Recommendations

Clear evidence for effectiveness
Supportive care
Supplemental oxygen
Possibly effective
Nebulized ipratropium bromide (Atrovent) with or without nebulized albuterol (Proventil)*
Oral or inhaled corticosteroids†
Parenteral dexamethasone‡
Nebulized epinephrine‡
Possibly effective for most severe cases
Helium-oxygen combination
Surfactant
Probably ineffective
Aerosolized ribavirin (Virazole)
Antibiotics (unless patient has a clear focus of bacterial infection)
Nebulized furosemide
RSV-IG (RespiGam)
Inhaled interferon alfa-2a (Roferon-A)
rhDNase

RSV = respiratory syncytial virus; RSV-IG = intravenous RSV immune globulin; AHRQ = Agency for Healthcare Research and Quality.

*—Evidence of modest short-term improvement only.

†—Not recommended by the American Academy of Pediatrics; patients with atopy may benefit most.

‡—A randomized clinical trial¹² published after the AHRQ's evidence report found no benefit with nebulized epinephrine.

Adapted from Agency for Healthcare Research and Quality. Management of bronchiolitis in infants and children. Evidence report/technology assessment: number 69. Rockville, Md.: Agency for Healthcare Research and Quality, 2003.

SUPPLEMENTAL OXYGEN AND SUPPORTIVE CARE

Supplemental oxygen should be administered with a headbox or tent if the patient's oxygen saturation consistently falls below 92 percent on room air. Transfer to an intensive care unit for mechanical ventilation should be considered before the criteria for respiratory failure are met: arterial blood gas with a partial pressure of carbon dioxide (PaCO₂) at or above 55 mm Hg or a partial pressure of oxygen (PaO₂) of 70 mm Hg or less on 60 percent oxygen. In one study,¹² the need for supplemental oxygen at admission had the greatest influence on the score for severity of illness and strongly predicted the length of the hospital stay. Continuous oximetry may provide useful clinical data, but it also may increase length of stay and impede a timely discharge.¹³ There is no evidence to support the use of chest physiotherapy for RSV bronchiolitis. Cool mist and aerosol therapies with saline are not recommended.⁹

Intravenous fluids may be considered when the patient is vomiting or unable to take oral feedings at a level suffi-

Infants who should be hospitalized for RSV infection include those younger than three months, those whose gestational age at birth was less than 34 weeks, and those with comorbid cardiopulmonary disease or immunodeficiency.

cient to prevent dehydration. Nasal suctioning before each feeding and inhalation therapy probably are helpful; normal saline nasal drops may be used before suctioning. Before discharge, parents and other caregivers should be taught proper suctioning techniques for home care.

Weaning the patient from oxygen therapy is reasonable when the oxygen saturation as measured by pulse oximetry (SpO₂) on room air consistently stays above 94 percent.¹⁴ Pulse oximetry may be discontinued when the patient is clinically stable while not receiving supplemental oxygen.

Assessing Efficacy of Treatments

A technical report² published by the Agency for Healthcare Research and Quality (AHRQ) reviews the efficacy of agents for the treatment and prevention of bronchiolitis (Table 3).² The evidence base shows that many clinical trials were small, with statistical power insufficient to permit an accurate assessment about the lack of efficacy of the therapeutic agents being investigated.

Some AHRQ categories for efficacy are contrary to current recommendations from other policy-making organizations. In particular, the AAP does not recommend using corticosteroids for the treatment of RSV symptoms, yet corticosteroids are considered "possibly effective" by the AHRQ. The evidence for drug treatments for RSV is discussed in more detail below.

Evidence for "Possibly Effective" Treatments**NEBULIZED EPINEPHRINE**

The recent AHRQ evidence report states that nebulized epinephrine is "possibly effective." However, a recent randomized trial published after the AHRQ report was released had sufficient statistical power to demonstrate that nebulized epinephrine therapy does not significantly reduce the length of the hospital stay or the time until infants with bronchiolitis are ready for discharge.¹² [Evidence level A, randomized controlled trial (RCT)] If a trial

Nebulized epinephrine therapy does not significantly reduce the length of the hospital stay.

of inhaled epinephrine is considered, this therapy should be discontinued if there is no significant improvement in clinical assessment within 30 minutes after the first treatment.⁹

OTHER BRONCHODILATORS

Recent meta-analyses show that among patients with RSV infections, beta₂-agonist bronchodilators do not reduce hospital admission rates or meaningfully improve oxygen saturation levels among patients with RSV infections, even though short-term clinical scores, in some cases, may improve with treatment.^{15,16} [References 15 and 16—Evidence level A, meta-analyses] The AHRQ report suggests that larger clinical trials are needed to make sound conclusions.

Ipratropium bromide (Atrovent) is an anticholinergic bronchodilator with no proven efficacy for RSV bronchiolitis.¹⁷ [Evidence level A, meta-analyses] Among 321 infants in six research studies, there was no significant difference in length of hospital stay between ipratropium bromide and placebo, and no significant difference between the combination of nebulized ipratropium bromide and a beta₂-agonist compared with a beta₂-agonist alone.^{18–20} However, combined ipratropium bromide and beta₂-agonist therapy did show significantly improved clinical scores at 24 hours compared with placebo, and parents preferred ipratropium bromide over placebo for relief of their children's symptoms at home.¹⁷

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CORTICOSTEROIDS

The evidence for and appropriate use of corticosteroids in the treatment of RSV infection remains controversial. The type of steroid does not seem to make a difference, because there is no difference in benefit from oral prednisolone,^{21,22} intravenous dexamethasone,²³ or budesonide.²⁴ There are some safety concerns about adverse reactions to budesonide delivered via metered-dose inhaler,²⁵ although causal associations are not proved. A recent meta-analysis²⁶ of corticosteroids for bronchiolitis showed small, statistically significant improvements in clinical symptoms, length of stay, and duration of symptoms. However, subset analysis for first-time wheezing did not reach statistical significance, and the practical relevance of the small differences between treatment groups is not clear.

There are methodologic concerns about clinical trials reporting benefits from corticosteroids administered during the acute phase of viral bronchiolitis, including omitting any history of atopy or employing retrospective designs.²⁷ Allergies or asthma may be confounding conditions accounting for the beneficial actions of corticosteroids among study participants misclassified as having RSV. The AAP does not recommend the use of corticosteroids in hospitalized infants with RSV.⁴ The AHRQ suggests that further studies are needed.²

HELIUM-OXYGEN AND SURFACTANT FOR SEVERE DISEASE

In one study²⁸ of short-term helium-oxygen (heliox) combination therapy for acute bronchiolitis, modified asthma scores among 18 infants improved after 20 minutes of therapy. This improvement could be the result of reduced airway resistance and decreased breathing work.²⁹ Infants with the most severe disease at baseline demonstrated the greatest decrease in severity score. In another study,³⁰ heliox given via face mask improved clinical scores, reduced tachycardia and tachypnea, and shortened length of stay in the intensive care unit. However, a study³¹ of heliox given to intubated children with bronchiolitis showed there were no benefits in measures of ventilation or oxygenation.

Administration of surfactant has been reported to improve oxygenation and shorten the duration of ventilatory support and length of stay in the intensive care unit.³² A small randomized study³³ demonstrated benefits from administering surfactant in RSV-positive ventilated infants, showing a more rapid improvement in oxygenation

and ventilation indexes over the first 60 hours of ventilation, which indicates small airway patency and better lung compliance. Infants in the placebo group became progressively worse during the first 30 hours after enrollment.

Larger randomized studies are warranted to investigate long-term outcomes for surfactant and heliox therapy. Therefore, these agents should be considered for use only in children with the most severe illness.

Ineffective Treatments

RIBAVIRIN

Ribavirin (Virazole) is a nucleotide analogue with in vitro activity against influenza A and B, measles, and RSV. Possible benefits include reduced time on ventilator, shortened length of hospital stay, and improved clinical scores.^{34,35}

However, there are methodologic concerns about some RCTs that studied the use of ribavirin in acute RSV bronchiolitis. In one study³⁶ of infants on mechanical ventilation for severe RSV infection, the placebo group received nebulized water, an agent known to cause bronchospasm. Thus, the reported advantage of ribavirin actually may have been caused by adverse effects from the placebo. This theory is supported by the lack of significant differences between the treatment and control groups in a later study³⁷ that used nebulized saline placebo. A meta-analysis concluded there is no evidence to support the use of ribavirin in the treatment of RSV bronchiolitis.³⁸ [Evidence level A, meta-analysis] The AAP generally does not recommend ribavirin treatment for RSV infections.⁴ The AHRQ classifies ribavirin as “probably ineffective.”³²

ANTIBIOTICS AND OTHER AGENTS

Concurrent serious bacterial infections are rare in infants and children hospitalized with RSV bronchiolitis. One large study³⁹ of such infants found that fewer than 2 percent had a concurrent bacterial infection. One study⁴⁰ shows no significant difference in length of hospital stay between RSV cases treated with or without antibiotics. The empiric use of broad-spectrum intravenous antibiotics is therefore unnecessary in children with typical signs and symptoms of RSV bronchiolitis, and may be harmful.

Treatments with other agents such as nebulized furosemide,⁴¹ inhaled interferon alfa-2a (Roferon-A),⁴² or rhDNase⁴³ probably are not efficacious in RSV infections. Likewise, antihistamines, oral decongestants, and nasal vasoconstrictors lack efficacy. Based on limited studies, the

herbal remedy Huang Lian Shang delivered by intravenous infusion appears to be safe and may be useful in reducing wheezing associated with RSV infection.⁴⁴ However, well-designed large studies with standardized preparations are needed before this herbal remedy is adopted.

Infection-Control Measures

Technologic medical care must be accompanied by common-sense infection-control measures to protect patients and providers from RSV nosocomial infections.⁴⁵ Isolating suspected cases, segregating case cohorts, and using dedicated stethoscopes and other instruments or supplies (e.g., pens, clipboards) for each patient can be effective in reducing transmission. Washing hands before entering and after leaving the examination room, and using gloves and masks that cover the nose and eyes are effective means of infection control.⁴⁶ Parents and other caregivers should demonstrate the ability to use these protective measures before the patient is discharged.

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