Respiratory Syncytial Virus Immune Globulin Intravenous: Indications for Use

ABSTRACT. Respiratory syncytial virus immune globulin intravenous (RSV-IGIV) has been approved by the Food and Drug Administration for use in the prevention of severe RSV infections in infants and children younger than 24 months with bronchopulmonary dysplasia or a history of premature birth (≤ 35 weeks of gestation). RSV-IGIV administered monthly during the RSV season resulted in a 41% to 65% reduction in hospitalization rates in two clinical trials; however, RSV-IGIV is costly, and intravenous administration can be logistically demanding. RSV-IGIV should be considered for infants with bronchopulmonary dysplasia who are receiving or have received oxygen therapy in the past 6 months. Infants with gestational ages of 32 weeks or less may also benefit clinically from RSV-IGIV prophylaxis. Immunization with measles-containing vaccines should be delayed for 9 months after the last dose of RSV-IGIV, but no changes need to be made for all other routinely administered vaccines. RSV-IGIV has not been approved for use in children with congenital heart disease, and available data indicate that RSV-IGIV should not be administered to children with cyanotic congenital heart disease because of safety concerns.

Respiratory syncytial virus immune globulin intravenous (RSV-IGIV; RespiGam, Massachusetts Public Health Biologic Laboratories and MedImmune, Inc, Gaithersburg, MD) was licensed by the Food and Drug Administration (FDA) in January 1996 for use in the prevention of severe RSV lower respiratory tract disease in infants and children younger than 24 months with bronchopulmonary dysplasia (BPD) or a history of premature birth (≤35 weeks of gestation). Randomized, controlled clinical trials in these high-risk infants demonstrated the safety and efficacy of monthly RSV-IGIV infusions during the period of peak RSV activity. Given the lack of proven effective antiviral therapy for RSV infections, prevention of disease through the use of passive immunoprophylaxis in selected high-risk infants should be considered.

On the other hand, RSV-IGIV prophylaxis is costly and logistically demanding, and a large number of infants qualify for the FDA-approved indications. The average per-patient cost of RSV-IGIV medication for a full respiratory season is between $4000 and $5000, depending on the weight of the patient. Intravenous access and drug administration in these chronically ill, low birth weight infants require support equipment (eg, infusion pumps) and personnel time, which results in additional expense. Among the approximately 4 million live births in the United States in 1993, 282 600 were born at less than 36 weeks of gestation, and 76 700 were born at less than 32 weeks of gestation. Meissner estimates that BPD develops in approximately 14 000 infants each year. Because RSV-IGIV is approved for use until 24 months of age, several hundred thousand infants each year in the United States may qualify for prophylactic therapy. In addition, IGIV is known to interfere with the immune response to some live-virus vaccines. Important questions for child health care providers to consider include not only the safety and efficacy of RSV-IGIV but also the cost effectiveness and feasibility of this treatment in clinical practice.

The purpose of this statement is to summarize the existing data on RSV-IGIV and to make recommendations concerning appropriate use in clinical practice. Previous statements by the Committee on Infectious Diseases have covered other aspects of RSV disease: epidemiologic characteristics, risk factors for serious illness, laboratory diagnosis, and treatment with ribavirin.

CLINICAL STUDIES

RSV-IGIV Clinical Efficacy

Initial trials of routine, commercially available IGIV to prevent RSV disease in high-risk infants demonstrated only minimal benefit, presumably because only low titers of RSV neutralizing antibodies were achieved in the blood of treated infants. RSV-IGIV is prepared from donors selected for high titers of RSV-neutralizing antibody and has been shown to be protective in several animal models of RSV infection and disease. Results of a multi-institution, randomized, controlled clinical trial with prophylactic RSV-IGIV in 249 infants younger than 48 months with underlying BPD, congenital heart disease (CHD), or prematurity (≤35 weeks of gestation) are shown in Table 1. Patients received monthly RSV-IGIV infusions from mid-November through March or April; at least 75% of the dose was infused at 85% of the visits. Infants receiving the high dose (750 mg/kg) had significantly reduced RSV-associated lower respiratory tract disease severity, frequency of admission to the hospital, and number of days in the hospital or intensive care unit. RSV-neutralizing antibody titers almost always exceeded 1:200, a titer close to the threshold is required for protection in animals. Treatment with RSV-IGIV
was well tolerated. Adverse reactions occurred in only 3% of 580 infusions and consisted of mild decreases in oxygen saturation in eight, fever in six, and mild fluid overload in five patients. Six deaths occurred (three in the high-dose group and three in the low-dose group); none were considered related to RSV-IGIV infusion or to RSV infection by an independent committee established by the investigators. Five of the six deaths occurred in patients with CHD; three of the five deaths were related to complications of cardiac surgery. In summary, monthly RSV-IGIV infusions during the respiratory season resulted in a 65% to 85% reduction in RSV-associated disease severity and hospitalization. Patients benefiting most were young children with BPD who had received oxygen therapy within the last 6 months and infants without BPD who were less than 32 weeks of gestational age at birth and younger than 6 months at the start of the respiratory season.17

Results from a multi-institution, randomized, albumin placebo-controlled trial (the PREVENT study) in 510 infants younger than 24 months with BPD and/or prematurity are shown in Table 2.2 Ninety-five percent of children completed the protocol, and 85% completed four or five infusions. Monthly RSV-IGIV infusions reduced RSV-associated illness frequency and severity by 40% to 60%. Subgroup analysis did not demonstrate evidence of interactions between treatment and age of the patient or underlying disease category. The RSV-IGIV–associated reduction in hospitalization rate was greater for infants and children with BPD than those with prematurity only (49% vs 20%, respectively; Table 2). Moderate to severe adverse events were not more frequent in patients receiving RSV-IGIV than in control patients and consisted of fever, increased respiratory distress, and rash. These adverse events were easily managed medically and did not occur with subsequent infusions. Of additional interest was an RSV-IGIV–associated reduction in: (1) non-RSV respiratory hospitalization, a 50% lower rate \( (P = .002) \) and 42% fewer hospital days \( (P = .004) \), and (2) total and RSV-associated episodes of acute otitis media.18

RSV-IGIV in Patients With CHD

At national meetings in 1996, results were reported from a multi-institution, randomized, RSV-IGIV–versus–no infusion clinical trial in 416 children younger than 48 months with underlying CHD.19 The distribution of patients by cardiac disease category was not equal, because more of the 202 children receiving RSV-IGIV had cyanotic CHD (78 [39%]) than the 214 receiving no infusion (47 [22%]; \( P, .001 \)). In the entire group of patients with CHD, there was no significant reduction of disease associated with RSV-IGIV prophylaxis. However, RSV-IGIV–treated infants younger than 6 months at study entry had a 57% lower hospitalization rate \( (P = .01) \). In RSV-IGIV–treated patients of all ages with acyanotic CHD, a trend occurred toward reduced hospitalization rates and hospital days. In contrast, a trend toward increased hospitalization rates occurred in RSV-IGIV–treated patients with cyanotic CHD. Adverse event rates in patients with acyanotic CHD

TABLE 1. Respiratory Syncytial Virus (RSV) Immune Globulin Intravenous Prophylaxis in High-risk Infants: 249 Patients (41% BPD, 35% CHD, and 24% Preterm)*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control</th>
<th>High Dose†</th>
<th>Percentage of Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>89</td>
<td>81</td>
<td>. . . . . . . . . . . . .</td>
</tr>
<tr>
<td>RSV lower respiratory tract illness</td>
<td></td>
<td></td>
<td>. . . . . . . . . . . . .</td>
</tr>
<tr>
<td>Any</td>
<td>22%</td>
<td>9%</td>
<td>59</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>13%</td>
<td>4%</td>
<td>69</td>
</tr>
<tr>
<td>Respiratory disease score</td>
<td>2.3</td>
<td>1.6</td>
<td>30</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>20%</td>
<td>7%</td>
<td>65</td>
</tr>
<tr>
<td>Total hospital d/100 children</td>
<td>144</td>
<td>53</td>
<td>63</td>
</tr>
<tr>
<td>ICU admission</td>
<td>7%</td>
<td>1%</td>
<td>86</td>
</tr>
<tr>
<td>Total ICU d/100 children</td>
<td>38</td>
<td>1.2</td>
<td>97</td>
</tr>
</tbody>
</table>

* Modified from Groothuis et al.1 BPD indicates bronchopulmonary dysplasia; CHD, congenital heart disease; and ICU, intensive care unit.
† 750-mg/kg infusion; low dose (150 mg/kg) data in 79 patients are not shown.

TABLE 2. Respiratory Syncytial Virus Immune Globulin Intravenous (RSV-IGIV) Prophylaxis Trial: The PREVENT Study*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Albumin</th>
<th>RSV-IGIV</th>
<th>Percentage of Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>260</td>
<td>250</td>
<td>. . . . . . . . . . . . .</td>
</tr>
<tr>
<td>RSV hospitalization (all patients)</td>
<td>13.5%</td>
<td>8%</td>
<td>41% .047</td>
</tr>
<tr>
<td>Patients with BPD</td>
<td>17.4%</td>
<td>8.9%</td>
<td>49% .047</td>
</tr>
<tr>
<td>Premature patients without BPD</td>
<td>8.1%</td>
<td>6.8%</td>
<td>20% .045</td>
</tr>
<tr>
<td>RSV hospital d/100 patients</td>
<td>129</td>
<td>60</td>
<td>53% .045</td>
</tr>
<tr>
<td>RSV hospital d receiving O2/100 patients</td>
<td>85</td>
<td>34</td>
<td>60% .007</td>
</tr>
<tr>
<td>RSV hospital d with moderate or severe lower respiratory tract infection/100 patients</td>
<td>106</td>
<td>49</td>
<td>54% .049</td>
</tr>
<tr>
<td>Hospitalization for any respiratory illness</td>
<td>27%</td>
<td>16%</td>
<td>38% .005</td>
</tr>
<tr>
<td>Any respiratory illness hospital d/100 patients</td>
<td>317</td>
<td>170</td>
<td>46% .005</td>
</tr>
<tr>
<td>Moderate/severe adverse event</td>
<td>1.1%</td>
<td>2.4%</td>
<td>. . . NS</td>
</tr>
</tbody>
</table>

* From Connor and the PREVENT Study Group.2 The data on RSV hospitalization rates in patients with bronchopulmonary dysplasia (BPD) were used with permission. (E. Connor, written communication, November 1996.)
were not different between the RSV-IGIV and no-infusion groups. However, surgically related severe events were more common in the infants with cyanotic CHD receiving RSV-IGIV (22 [28%] of 78) than those receiving no infusion (4 [9%] of 47; \(P = .009\)). None of these surgically related severe events was thought by investigators to be attributable directly to RSV-IGIV infusion. Further investigation will be required before prophylactic use of RSV-IGIV can be considered in infants and young children with cyanotic CHD.

**Cost Effectiveness of RSV-IGIV in Clinical Practice**

A recent cost effectiveness analysis indicated that RSV-IGIV prophylaxis of all high-risk infants (FDA-approved indications) is unlikely to produce net savings in medical resources but does result in a favorable cost per year of life saved.\(^4\) However, data available at this time do not allow accurate comparison of the cost of RSV-IGIV prophylaxis with RSV-associated hospitalization expenses in particular subgroups of patients who would most likely benefit. For example, RSV-IGIV prophylaxis may be cost beneficial through 2 years of age in an infant with a gestational age of 28 weeks with BPD currently receiving oxygen therapy but not in an infant with a gestational age of 34 weeks with no underlying disease. The first infant would have a high risk of respiratory disease-associated hospitalization with a prolonged stay and an increased number of days of hospitalization. The second infant would have a high risk of respiratory disease-associated hospitalization with a prolonged stay and an increased number of days of hospitalization. The first infant would have a high risk of respiratory disease-associated hospitalization with a prolonged stay and an increased number of days of hospitalization. The second infant would have a high risk of respiratory disease-associated hospitalization with a prolonged stay and an increased number of days of hospitalization.

Several studies have provided information on the incidence and severity of RSV-associated hospitalization in high-risk infants. Among 30 children younger than 2 years with BPD followed through a respiratory virus season, 50% were rehospitalized with oxygen therapy but not in an infant with a gestational age of 34 weeks with no underlying disease. The first infant would have a high risk of respiratory disease-associated hospitalization with a prolonged stay and an increased number of days of hospitalization in the intensive care unit, whereas the risk in the second infant would be quite low.

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**TABLE 3.** Respiratory Syncytial Virus Disease Severity in Hospitalized Patients*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Cardiac Disease</th>
<th>Chronic Lung Disease</th>
<th>Gestation &lt;37 wk</th>
<th>No Known Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>57</td>
<td>79</td>
<td>148</td>
<td>372</td>
</tr>
<tr>
<td>Hospital stay, d†</td>
<td>11</td>
<td>10</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>In intensive care unit, %</td>
<td>32</td>
<td>37</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Intensive care unit stay, d†</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Mechanical ventilation, %</td>
<td>19</td>
<td>25</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Ventilation, d†</td>
<td>5</td>
<td>8</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Case fatality ratio, %</td>
<td>5.2</td>
<td>5.1</td>
<td>3.4</td>
<td>0</td>
</tr>
</tbody>
</table>

* Modified from Wang et al.\(^22\) Patients with more than one risk factor are included in each group.
† Median days.
RSV-IGIV has been FDA approved for use in infants and children younger than 24 months with BPD or a history of premature birth (≤35 weeks of gestation). In addition to BPD and prematurity, other factors may influence the decision about the use of RSV-IGIV prophylaxis. These include conditions that predispose to respiratory complications (eg, neurologic disease in very low birth-weight infants), the number of young siblings, child care center attendance, exposure to cigarette smoke in the home, anticipated cardiac surgery, ease of intravenous access, medication- and infusion-related costs, practicality and tolerability of monthly infusions, and the distance to and availability of hospital care for severe respiratory illness. For many infants qualifying for the approved indications, the risk of rehospitalization for serious respiratory illness will be low, and the cost and logistic difficulties associated with RSV-IGIV use may outweigh potential benefits. The effectiveness of RSV-IGIV for children who receive an incomplete single infusion or less than the recommended total monthly infusions has not been assessed.

RECOMMENDATIONS

1. RSV-IGIV prophylaxis should be considered for infants and children younger than 2 years with BPD who are currently receiving or have received oxygen therapy within the 6 months before the anticipated RSV season. Patients with BPD with more severe underlying lung disease may benefit clinically from prophylaxis for two RSV seasons, whereas those with less severe underlying disease may benefit only for the first season. Decisions regarding individual patients may need additional input from neonatologists, intensivists, or pulmonologists.

2. Infants born at 32 weeks of gestation or less without BPD or who do not meet the criteria in recommendation 1 may also benefit from RSV-IGIV prophylaxis. In these infants, major risk factors to consider are gestational age and chronologic age at the start of the RSV season. Infants born at 28 weeks of gestation or less may benefit from prophylaxis for 12 months of age. Infants born at 29 to 32 weeks of gestation may benefit from prophylaxis up to 12 months of age. Decisions regarding each patient should be individualized. Practitioners may wish to use RSV rehospitalization data from their own region to assist in the decision-making process.

3. RSV-IGIV is not FDA approved for patients with CHD. Available data indicate that RSV-IGIV should not be used in those with cyanotic CHD. However, patients with BPD and/or prematurity who meet the criteria in recommendations 1 and 2 and who also have asymptomatic acyanotic CHD (eg, patent ductus arteriosus or ventricular septal defect) may benefit from prophylaxis.

4. RSV-IGIV use, either prophylactically or therapeutically, has not been evaluated in randomized trials in immunocompromised pediatric patients. Although specific recommendations for all immunocompromised patients cannot be made, children with severe immunodeficiencies (eg, severe combined immunodeficiency or severe acquired immunodeficiency syndrome) may benefit from RSV-IGIV. If these infants and children are receiving IGIV monthly, providers may consider substituting RSV-IGIV during the RSV season.

5. RSV is known to be transmitted in the hospital setting and to cause serious disease in high-risk infants. In high-risk hospitalized infants, the major means to prevent RSV disease is strict observance of infection control practices, including the use of rapid means to identify and cohort RSV-infected infants. If an RSV outbreak is documented in a high-risk unit (eg, pediatric intensive care unit), primary emphasis should be placed on proper infection control practices. The need for and efficacy of RSV-IGIV prophylaxis in these situations has not been documented.

6. RSV-IGIV prophylaxis should be initiated before the onset of the RSV season and terminated at the end of the RSV season. In most areas of the United States, the usual time for the beginning of RSV outbreaks is October to December, and termination is March to May, but regional differences occur. The onset of RSV occurs earlier in southern states than in northern states. Practitioners should check with health departments and/or diagnostic virology laboratories in their geographic areas to determine the optimal schedule.

7. In infants and children receiving RSV-IGIV prophylaxis (750-mg/kg dose), immunization with measles-mumps-rubella and varicella vaccines should be deferred for 9 months after the last dose. There are no data on the use of RSV-IGIV and the response to hepatitis B vaccine, but there is no reason to anticipate any interference, because RSV-IGIV does not contain antibodies to hepatitis B surface antigen. See Table 3.30 on page 319 of the 1994 Red Book. RSV-IGIV use should not alter the primary immunization schedule for diphtheria and tetanus toxoids, whole-cell or acellular pertussis, Haemophilus influenzae type b, and poliovirus vaccines (inactivated poliovirus vaccine [IPV] or oral poliovirus vaccine [OPV]). The manufacturer of RSV-IGIV has suggested that an additional dose of vaccine might be needed to assure an adequate immune response to diphtheria and tetanus toxoids, whole-cell or acellular pertussis, H influenzae type b, and OPV (RespiGam package insert), but more information is needed before firm recommendations can be made. At this time the available data do not support the need for any supplemental doses of routinely administered vaccines. Parenterally administered immunoglobulin preparations have little, if any, effect on the replication of OPV in the intestinal tract.
8. A critical aspect of RSV prevention in high-risk infants is education of parents and other care givers about the importance of reducing exposure to and transmission of RSV. Preventive measures include limiting, where feasible, exposure to cigarette smoke and contagious settings (eg, child care centers) and emphasis on hand washing in all settings, including the home, especially during periods when contacts of high-risk children have respiratory infections.

FUTURE DEVELOPMENTS

As indicated in “Cost Effectiveness of RSV-IGIV in Clinical Practice,” accurate information is needed on the cost effectiveness of RSV-IGIV infusion versus hospitalization rates and expenses for the various subgroups of high-risk infants. In addition, recommendations concerning RSV-IGIV use should consider other factors such as parental distress and time lost from work and the association between RSV disease in early life and subsequent recurrent or chronic respiratory illness.

More information is needed about the safety, clinical efficacy, and cost effectiveness of RSV-IGIV prophylaxis in infants with CHD, particularly those with cyanotic lesions, and older children with underlying immune deficiency or immunosuppressive disease.

Although initial and recent preliminary studies of RSV-IGIV treatment of high-risk infants with RSV disease have not demonstrated substantial clinical effectiveness, further evaluation is needed. Other potential uses of RSV-IGIV are also being investigated. Combination therapy with IGIV containing high titers of RSV-neutralizing antibody and aerosolized ribavirin was more beneficial than therapy with ribavirin alone based on historical data in bone marrow transplant recipients with RSV disease. Intranasal or small-particle aerosol therapy with RSV-IGIV has been effective in experimental animals, and aerosolized IGIV seems safe in RSV-infected infants. Finally, prophylaxis and treatment studies in experimental animals with humanized murine monoclonal neutralizing antibodies and neutralizing Fab fragments prepared by recombinant DNA technology are in progress.

Progress with RSV vaccines has been hampered by the severe adverse reactions that occurred in children who received the formalin-inactivated vaccine in trials conducted during the 1960s. Recent investigations have demonstrated an unbalanced humoral and cell-mediated immune response to RSV antigens altered by the formalin treatment. New vaccines being evaluated include: (1) cold-adapted or temperature-sensitive, attenuated, live virus, and (2) protein subunit, often using recombinant DNA technology. Several candidate vaccines are safe and immunogenic in adults and children as young as 12 months. However, problems or obstacles remain, including: (1) immunity from natural infection is not durable, because RSV infections are known to occur in adults and children; (2) young infants respond poorly to glycosylated proteins such as those in RSV vaccines; and (3) the immunodominant RSV protein or epitope of particular RSV antigens, as well as the best in vitro correlate(s) of protective immunity, are not well defined. The approach of immunizing women of child-bearing age to provide passive protection during the first several months of life also is being evaluated. Although the investigations with RSV vaccines are promising, a vaccine for clinical use will not be available in the near future.

Optimal prevention and control of RSV disease may well require several strategies, including antiviral and immunotherapy, active and passive immunoprophylaxis, and infection control measures.
REFERENCES


Respiratory Syncytial Virus Immune Globulin Intravenous: Indications for Use
Committee on Infectious Diseases Committee on Fetus and Newborn

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