CLINICAL BRIEFS

RSV Risk: Understanding RSV-Related Hospitalization Of High-Risk Infants

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RSV Risk: Understanding RSV-Related Hospitalization of High-Risk Infants

Respiratory syncytial virus (RSV) bronchiolitis and RSV pneumonia are the leading causes of hospitalization of infants younger than 1 year of age in the United States. Preterm infants, born at 32 to 35 weeks gestational age or less, are particularly at high risk for severe RSV disease. Early recognition of the risk factors known to predispose to serious RSV lower respiratory tract infection is key to planning an effective RSV disease prevention strategy in high-risk infants.

Overview

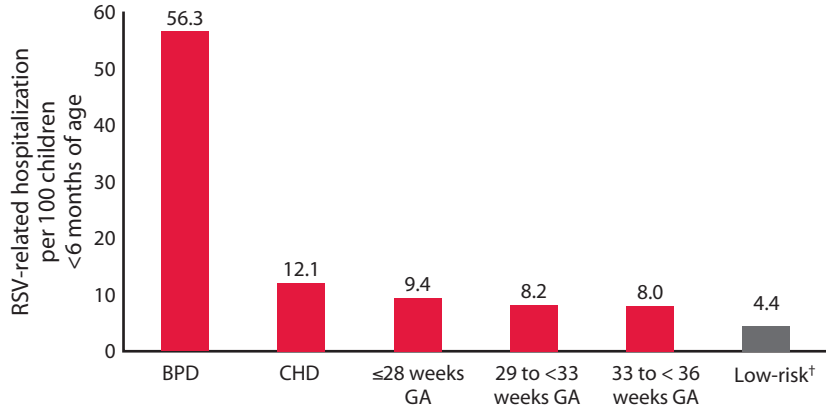
Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia in infants younger than 1 year of age and is the leading cause of infant hospitalization in the United States (Leader 2002). Preterm infants — infants born at 32 to 35 weeks gestational age (GA) or less — are particularly at high risk for RSV-related hospitalization, and rehospitalization is common (McCormick 2002, Resch 2005). Hospitalization rates for RSV lower respiratory tract infection (LRTI) are nearly twice as high for preterm infants as they are for full-term infants (Figure 1), and hospital admission rates as high as 10 percent for RSV LRTI in preterm infants have been reported (Boyce 2000, Law 2004, Liese 2003). Healthcare utilization following RSV-related hospitalization is also greater for preterm infants (Figure 2). Furthermore, preterm births are increasing — in 2006, the number of infants born under 37 completed weeks of gestation increased to 12.8 percent of all births, and since 1990, births at less than 34 weeks of gestation have risen 10 percent (Martin 2008).

Rates of RSV-related hospitalizations are increasing

Estimates of RSV-related hospitalizations by the Institute of Medicine (IOM 1985) suggested that each year approximately 55,000 infants younger than 1 year of age were hospitalized for RSV bronchiolitis or RSV pneumonia. To update national RSV-associated hospitalization estimates, Shay (1999) analyzed U.S. National Hospital Discharge Survey (NHDS) data from 1980 through 1996 and found that annual RSV-related hospitalization rates among children younger than 1 year of age had increased more than 2-fold in the 17-year period, with 57 percent of RSV-associated bronchiolitis hospitalizations occurring among infants younger than 6 months of age. The hospitalization rates for RSV pneumonia rose similarly (Shay 1999). For the 2-year period between 1994 and 1996, up to 81,985 infants younger than 1 year of age were hospitalized for RSV-associated bronchiolitis, with most hospitalizations occurring during the November through April RSV season.

The increase observed in RSV bronchiolitis hospitalizations since 1980 was unexpected, because the rates for hospitalization for other LRTIs due to other pathogens did not rise during the same period. Although Shay (1999) posits that the increased burden of RSV may have resulted from changing child care practices, revised criteria for

FIGURE 1
RSV-related hospitalization of Tennessee Medicaid Infants*



*Retrospective study of enrollees in Tennessee Medicaid, July 1989–June 1993.
†Low-risk defined as all other children born at term.
BPD=bronchopulmonary dysplasia; CHD=chronic heart disease; GA=gestational age.
Source: Boyce 2000

Please see important safety information on page 7 and full prescribing information on pages 10 and 11.

FIGURE 2

Healthcare utilization by 32 to 35 weeks GA infants following RSV-related hospitalization: case control study*

	32–35 weeks GA hospitalized for RSV† n=2,415	32–35 weeks GA controls not hospitalized for RSV n=20,254
Mean (±SD) hospitalizations	2.96 ± 2.81	1.28 ± 1.42
Mean (±SD) hospital stay (days)	14.71 ± 18.69	5.04 ± 7.09

*Follow up: 2.1 years.
†$P<0.001$ for all comparisons with control subjects.
GA= gestational age.
Source: Sampalis 2003

hospitalization or diagnostic coding, or the worsening virulence of RSV strains, none of these factors has yet been proven to have directly influenced prevalence.

Analysis of NHDS data for the years 1997 to 2002 shows that RSV-related hospitalization rates among infants less than 1 year of age increased by an additional 25 percent (McLaurin 2005).

The increasing rate of RSV-related hospitalizations highlights the necessity for the medical community to aggressively pursue interventions to prevent severe RSV disease in high-risk infants. Intervening to mitigate or prevent morbidity from RSV LRTIs depends on an understanding of the natural history of RSV and recognizing the risk factors for vulnerability of high-risk infants to RSV disease.

Epidemiology and natural history of RSV

RSV, an RNA virus of the *Paramyxoviridae* family, is the primary pathogen that causes LRTIs during the first 2 years of life (Wang 1998). In the United States, RSV outbreaks generally occur annually in a seasonal pattern, usually November through April; however, surveillance data indicate that the onset and duration of the RSV season vary greatly throughout the country and, importantly, from locality to locality (Mullins 2003, Panozzo 2007).

RSV is highly infectious and is transmitted via infectious secretions spread by hand contact, followed by self-inoculation to eyes and nose or, less commonly, the mouth (AAP 2009, Hall 2001). The virus also can be picked up from contaminated surfaces, where it can survive for up to 7 hours (Hall 1980).

Prematurity, in the absence of other health conditions, is widely accepted as a major risk category for severe RSV disease in infants (Lanari 2002). Preterm infants are particularly susceptible, because they have decreased maternal antibody transfer — maternal antibody transfer generally occurs during the third trimester (Murphy 1986, Yeung 1968). These infants also have underdeveloped and/or injured lungs, which results in reduced lung capacity (Friedrich 2006, Hall 2001, Langston 1984, Moore 2008).

Risk factors for RSV-related hospitalization of high-risk infants

Approximately two thirds of preterm infants hospitalized for RSV disease are likely to have two or more documented risk factors for RSV disease (MedImmune DOF). The evidence-based appraisal of these risk factors, listed in Table 1 (page 4), is based largely on epidemiologic data and provides a framework for predicting which high-risk infants born at 32 to 35 weeks GA or less warrant closer surveillance for severe RSV disease and the need for palivizumab (Synagis®) immunoprophylaxis (see important safety information on page 7 and full prescribing information on pages 10 and 11). The evidence supporting the factors associated with an increased risk of RSV-related hospitalization of high-risk infants is discussed below.

School-aged siblings. Prospective and retrospective studies indicate that preterm infants born into homes where school-aged siblings reside are at increased risk for severe RSV disease (Carbonell-Estrany 2000, Carbonell-Estrany 2001, Eriksson 2002, Figueras-Aloy 2004, Figueras-Aloy 2008, Law 2004). Carbonell-Estrany (2001) found that infants born at 32 weeks or less GA who had school-aged siblings were 1.64 (95% CI: 1.05–2.55) times as likely to be hospitalized for RSV disease. Figueras-Aloy (2004) found that infants born at 33 to 35 weeks GA who had school-aged siblings were 2.85 (95% CI: 1.88–4.33) times as likely to be hospitalized for RSV disease. Law (2004) found that of 1,832 infants born at 33 to 35 weeks GA, those with preschool-aged siblings were 2.76 (95% CI: 1.51–5.03) times as likely to be hospitalized for RSV disease.

Daycare attendance. Many infants are placed in daycare out of necessity (e.g., parents working). These settings include nurseries and other daycare programs and family and friends' homes. Several studies have suggested that an infant exposed to daycare settings with two or more unrelated children for at least 4 hours per week is at substantially increased risk for severe RSV disease (Anderson 1988, Celedon 1999, Holberg 1993, Law 2004, Marbury 1997). Law (2004) found that infants born at 33 to 35 weeks GA who were placed in daycare were 12.32 (95% CI: 256–59.34) times as likely to be hospitalized for RSV disease.

TABLE 1

Evidence-based risk factors to consider when evaluating infants at high risk for severe RSV disease

Note: This is a sampling of various data that provide support for these risk factors and their association with severe RSV disease. There may be other studies that have not found a similar association.

Risk factor	Odds ratio (95% CI)*
School-aged siblings	**3.84** (1.75–8.43)[1] **2.85** (1.88–4.33)[2] **1.64** (1.05–2.55)[3]
Daycare attendance	**12.32** (2.56–59.34)[4] **2.23** (1.33–3.74)[5] **1.8**** (1.3–2.5)[6] **1.6** (1.0–2.4)[7]
Exposure to environmental air pollutants	No quantitative odds ratio reported in the U.S. (excluding tobacco smoking studies)
Severe neuromuscular disease	**4.94** (2.69–8.94)[8] for PICU admissions
Congenital abnormalities of the airways	No quantitave odds ratio reported in the U.S.

Risk factor	Odds ratio (95% CI)*
Young chronological age (≤12 weeks)	**8.46** (3.09–23.18)[9] **4.88** (2.57–9.29)[4] **3.95** (2.65–5.90)[2] **2.27**† (1.3–4.0)[3]
Crowded living conditions	**4.7**‡ (1.6–14.2)[10] **2.42** (1.23–4.76)[1] **1.93**§ (P<.001)[11] **1.91** (1.19–3.07)[2]
Exposure to environmental tobacco smoke	**5.06** (1.36–18.76)[12] **1.87** (1.07–3.26)[4] **1.63** (1.05–2.56)[3] **1.59** (1.12–2.26)[13] **1.3**§ (1.09–1.56)[14]
Low birth weight (<2,500 grams)	**2.4**‡§ (P<.001)[15] **2.24** (1.53–3.28)[16]
Multiple births	**5.5** (1.43–21.03)[17]
Family history of wheezing or asthma	**2.11** (0.97–4.59)[1] **1.90** (1.19–3.0)[2] **1.74** (1.55–1.96)[18]

*Odds ratios (ORs) are used to measure how strongly a risk factor is associated with an outcome. See «http://intmedweb.wfubmc.edu/ebmreviews/odds.html». ORs and 95% CI>1 indicates a significantly increased likelihood of severe RSV disease when a particular risk factor is present. See «http://slack.ser.man.ac.uk/theory/association_odds.html».
CI= confidence interval; PICU=pediatric intensive care unit; RSV=respiratory syncytial virus.
** rate ratio
† inverse calculation of odds ratio; adapted from Carbonell-Estrany 2001
‡ relative risk
§ no 95% CI

Sources: [1]McConnochie 1986, [2]Figueras-Aloy 2004, [3]Carbonell-Estrany 2001, [4]Law 2004, [5]Holberg 1993, [6]Marbury 1997, [7]Celedon 1999, [8]Wilkesmann 2007, [9]Rossi 2007, [10]Holberg 1991, [11]Anderson 1988, [12]von Linstow 2008, [13]Figueras-Aloy 2008, [14]Stensballe 2006, [15]Lanari 2002, [16]Cilla 2006, [17]Resch, 2005, [18]Carroll 2007

Congenital abnormalities of the airways and severe neuromuscular disease. Premature infants with congenital pulmonary disorders, such as cystic fibrosis, pulmonary malformation, or tracheoesophageal fistula, are more likely to develop severe RSV disease (Arnold 1999, Wang 1995). Panitch (2004) concluded that infants with severe neuromuscular weakness may have similar risk for severe RSV disease compared with other high-risk infants, including infants aged less than 24 months with bronchopulmonary dysplasia (BPD) and those with hemodynamically significant congenital heart disease (CHD). Wilkesmann (2007) found that preterm infants with neuromuscular impairment were 4.94 (95% CI: 2.69–8.94 times as likely to receive intensive care for RSV disease. Wang (1995) found that infants with baseline respiratory disorders had significantly greater risk for RSV-related hospitalization, intensive care unit (ICU) admission, and mechanical ventilation, and infants who required home oxygen supplementation also were more likely to require care for RSV disease in the hospital's ICU.

Exposure to environmental tobacco smoke. A growing body of data indicate that tobacco smoke exposure, due to a mother smoking during pregnancy or smoking by any parent or household member after an infant's birth, may contribute to the risk for RSV-related hospitalization (Boyce 2000, Carbonell-Estrany 2001, DHHS

Please see important safety information on page 7 and full prescribing information on pages 10 and 11.

COMMENTARY

Identifying risk factors for RSV-related hospitalization of high-risk infants

A managed care analysis by Albert Tzeel, MD, MHSA, FACPE
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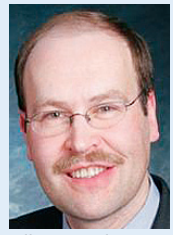
Many people provide advice and, as the saying goes, free advice is generally worth what one pays for it. However, some advice is timeless due to both its simplicity and its accuracy. For example, foreseeing an undesired result is of greater efficacy than addressing that result after the fact.



Albert Tzeel, MD, MHSA, FACPE

Early intervention to avoid the hospitalization of high-risk infants for severe RSV disease begins with the identification of risk factors that may increase the likelihood of an infant's hospitalization. These risk factors are validated in the medical literature and promulgated through medical specialty societies such as the American Academy of Pediatrics. Pediatricians and other healthcare providers who care for preterm infants should be familiar with them.

From a managed care perspective, it is important to ensure that those infants who are appropriate candidates for RSV immunoprophylaxis, based upon their risk factor profile, receive it. To minimize the administration of RSV immunoprophylaxis to "false positives" and to optimize receipt by "true positives," it is incumbent upon managed care organizations (MCOs) to develop processes that address all known risk factors for RSV disease. With the wealth of claims data at their disposal, MCOs should mine those claims to identify those infants at high risk of severe RSV disease. Additional sources of data should include the clinical notes entered into the MCO management system by the case management nurses who follow preterm infants after delivery. Such analyses can lead to the development of a registry of cases for MCO follow-up.

Outreach to the physicians caring for premature infants after hospital discharge with a standardized checklist of the various RSV risk factors will assist in ensuring that those infants with documented risk factors receive RSV immunoprophylaxis. Outreach to the parents with education about RSV disease can serve as a catalyst to engage the infant's healthcare provider as well.

Ultimately, preventing the RSV-associated hospitalization of high-risk infants will help our healthcare system by encouraging responsible management and cost accountability.

2006, Figueras-Aloy 2004, Gürkan 2000, Hall 1984, Holberg 1993, Law 2004, von Linstow 2008). Carbonell-Estrany (2001) found that infants born at 32 weeks GA or less who were exposed to tobacco smoke were 1.63 (95% CI: 1.05–2.56) times as likely to be hospitalized for RSV disease. Hall (1984) found that 76 percent ($P<.01$) of infants hospitalized for RSV disease resided in homes with one or more cigarette smokers (≥5 cigarettes/day).

Multiple births. Birth status may influence the risk for RSV disease. Simoes (1993) studied twins and triplets to determine the effect of multiple births on risk for RSV disease and found an increased incidence (53% vs. 24%, $P=.01$, respectively) and greater severity (hospitalization for RSV pneumonia required in 24% vs. 6%, $P=.05$, respectively) among multiple-birth infants, particularly those with BPD.

Crowded living conditions. RSV disease also occurs more often in infants who live in crowded households (based on living area per person). Figueras-Aloy (2004) found that of infants born at 33 to 35 weeks GA, those in homes with ≥4 additional residents (excluding school-aged siblings) or habitual visitors were 1.91 (95% CI: 1.19–3.07) times as likely to be hospitalized for RSV disease. Law (2004) found that infants born at 33 to 35 weeks GA living with more than 4 other people were 1.79 (95% CI: 1.02–3.16) times as likely to be hospitalized for RSV disease. Other studies have supported the relationship between crowded living, defined as two or more individuals sharing a bedroom and four or more in a home, and an increased risk of RSV disease (Anderson 1988, Holberg 1991).

Young chronological age. Rossi (2007) found that infants younger than 12 weeks at the start of an RSV season were more than 8.46 (95% CI: 3.09-23.18) times as likely to be hospitalized for RSV LRTI. Figueras-Aloy (2004) found that of infants born at 33 to 35 weeks GA,

those infants with a chronological age of 10 weeks or less at the start of an RSV season were 3.95 (95% CI: 2.65–5.90) times as likely to be hospitalized for RSV disease. Law (2004) found that infants born at 33 to 35 weeks GA during the RSV season November through January were 4.88 (95% CI: 2.57–9.29) times as likely to be hospitalized for RSV disease. Other researchers have also found that infants born at 32 to 35 weeks GA and less than 6 months of age during the RSV season are at high risk for hospitalization due to severe RSV disease (Boyce 2000, Heikkinen 2005).

Low birth weight. Lanari (2002) found that birth weight under 2,500 grams (g) and a GA under 36 weeks posed a high risk for severe RSV disease. The investigators noted that bronchiolitis was more frequent in infants 3 months of age or younger than in those 13 to 24 months of age (47.4% vs. 27.4%, respectively, $P<.01$) (Lanari 2002).

Family history of asthma and wheezing. Several investigators have shown that preterm infants whose parents, siblings, grandparents, or extended blood relatives have asthma are at increased risk for severe RSV disease (Figueras-Aloy 2004, McConnochie 1986, Wang 1998). Figueras-Aloy (2004) found that the risk for RSV-related hospitalization was 90 percent greater among infants born at 32 to 35 weeks GA with a family history of asthma compared with those that had no such history. McConnochie (1986) found that a family history of asthma predicted the occurrence of bronchiolitis ($P=.06$) and had even stronger predictive capability when combined with the presence of older siblings ($P<.005$). This additive risk is most likely because siblings are the most frequent carriers of virus to the household.

Multiple risk factors increase the likelihood of RSV-related hospitalization of high-risk infants

Liese (2003) and other investigators have demonstrated that the likelihood of severe RSV disease leading to hospitalization increases proportionately as the number of risk factors increase. Liese's data indicate that the risk for RSV-related hospitalization ranges from 0.4 percent for preterm infants with no risk factors to a high of 53.9 percent in preterm infants with five other risk factors.

The Pediatric Investigators Collaborative Network in Canada (PICNIC) study (Law 2004), which looked at approximately 2,000 preterm infants born during the November to April RSV season, substantiated many of the risk factors discussed in this clinical brief. The investigators reported that a combination of November through January birth, daycare attendance, preschool-age siblings, low birth weight, male gender, two or more smokers in the home, and crowded households were risk factors for hospitalization due to RSV LRTI. In a retrospective cohort study (FLIP-2), Figueras-Aloy (2008) found that the combination of young chronological age at the start of the RSV season, presence of school-aged siblings or daycare attendance, and maternal prenatal smoking significantly increased the risk for RSV LRTI and hospitalization.

Several studies have suggested the development of a risk-factor scoring system to predict RSV-related hospitalizations (e.g., as in Canada and Spain), with each system unique to the country in which it was devised (Paes 2009, Sampalis 2003, Figueras-Aloy 2004). Using the risk factors identified in this clinical brief, it may be possible to develop such a system that fits U.S. epidemiology.

Early recognition of all known risk factors for RSV disease in high-risk infants is key to the appropriate intervention and management of RSV disease and in reducing hospitalizations.

Palivizumab immunoprophylaxis and the 2009 AAP guidelines

Approved by the U.S. Food and Drug Administration in 1998, palivizumab (Synagis®) is an IgG monoclonal antibody with a 20-day half-life that was developed to help protect high-risk infants against severe RSV disease (see important safety information on page 7 and full prescribing information on pages 10 and 11.) Palivizumab is indicated for premature infants born at 35 weeks GA or less, infants with BPD, and children with significant congenital heart disease (CHD). Palivizumab confers passive protection by monthly intramuscular dosing throughout the RSV season (Sáez-Llorens 1998, Synagis 2009, Subramanian 1998). No data exist to suggest that palivizumab will be protective if it is given less frequently than every 30 days during the RSV season (IMpact-RSV 1998).

The safety and efficacy of palivizumab were established in two randomized, double-blind, placebo-controlled, phase 3 registration trials in pediatric patients at high risk of RSV-related hospitalization (IMpact-RSV 1998, Feltes 2003). In both trials, palivizumab was given in a 5-dose regimen throughout the RSV season.

The American Academy of Pediatrics (AAP) recently released its 2009 Red Book recommendations (AAP 2009) for RSV immunoprophylaxis and the use of palivizumab. The AAP recommendations for immunoprophylaxis for infants born at 32 to 35 weeks GA include changes that are inconsistent with the palivizumab phase 3 clinical trial data, the palivizumab prescribing information approved by the FDA, and published clinical evidence to date (Table 2).

One inconsistency is the recommendation to discontinue palivizumab when an infant born at 32 to 35 weeks GA reaches 3 months (90 days) of age irrespective of

TABLE 2

Discrepancies between the AAP 2009 guidelines and the FDA-approved palivizumab package insert for RSV immunoprophylaxis for infants born at 32 to 35 weeks GA

Category	AAP 2009 guidelines	FDA-approved palivizumab package insert
Dosing	Maximum of 3 doses Stop dosing once infant is 3 months (90 days) of age, whenever that occurs during the RSV season	Patients, including those who develop an RSV infection, should continue to receive monthly doses throughout the entire RSV season Five monthly doses were given in the Phase III pivotal trials
Age criteria	Eligibility criteria of <3 months of age at the start of the RSV season or born during the RSV season	Phase III pivotal trial included preterm infants ≤6 months of age at the start of the RSV season
Gestational age eligibility	Eligibility criteria for prophylaxis is defined as 32 weeks and 0 days through 34 weeks and 6 days • 35-week GA infants are excluded	Safety and efficacy were established in infants with a history of premature birth, ≤35 weeks GA
Risk factors	Infant must have one of two risk factors: • Child care attendance • Siblings <5 yrs of age	No risk factors were studied in pivotal trials and none are identified in the FDA-approved package insert

GA=gestational age, RSV=respiratory syncytial virus.

Sources: AAP 2009, Synagis 2009

Please see important safety information page 7 and full prescribing information on pages 10 and 11.

when that occurs during the RSV season. Under this guideline, a significant number of high-risk preterm infants will receive only one or two injections or possibly none. Because the RSV season in the United States typically starts in November and lasts through April, and may begin earlier or persist later in southern states such as Florida (CDC 2006, Mullins 2003, Synagis 2009), such dosing will leave high-risk infants unprotected.

No clinical trials have demonstrated the efficacy and safety of palivizumab if given in less than monthly doses during an RSV season or if discontinued in the midst of an RSV season. On the other hand, comparable data on poor palivizumab compliance (if given less frequently than every 30 days throughout the RSV season) have demonstrated increased hospitalization rates (Frogel 2008).

Another recommendation under the AAP's 2009 guidelines is the inclusion of 32 to 35 weeks GA infants who are less than 3 months old during the RSV season and have only one of two risk factors: Siblings under 5 years of age and child care attendance. As discussed in this clinical brief, many other risk factors for severe RSV disease in high-risk infants, supported by clinical evidence, have been identified.

Important Safety Information

Synagis® (palivizumab) is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease and is administered by intramuscular injection. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD). Synagis has been used in more than 1 million children in the U.S. since its introduction in 1998. The first dose of Synagis should be administered prior to commencement of the RSV season. Patients, including those who develop an RSV infection, should continue to receive monthly doses throughout the season.

Synagis should not be used in pediatric patients with a history of severe prior reaction to Synagis or its components. Cases of anaphylaxis were reported following re-exposure to Synagis and severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure. If a severe hypersensitivity reaction occurs, therapy with Synagis should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on re-administration of Synagis. In post-marketing reports, cases of severe thrombocytopenia

(platelet count <50,000/microliter) have been reported.

In clinical trials, the most common adverse events occurring at least 1% more frequently in Synagis-treated patients than controls were upper respiratory infection, otitis media, fever, and rhinitis. Cyanosis and arrhythmia were seen in children with CHD. There have also been post-marketing reports of injection site reactions.

Please see full prescribing information on pages 10 and 11.

Summary

RSV bronchiolitis and RSV pneumonia are the leading causes of hospitalization of infants younger than 1 year of age in the United States. Preterm infants, born at 35 weeks GA or less, are particularly at high risk of hospitalization for severe RSV disease, and rehospitalizations are common. Early recognition of the risk factors that can lead to severe RSV disease in high-risk infants is key to implementing an effective RSV disease management strategy to reduce hospitalizations of these infants.

The FDA has approved palivizumab as immunoprophylaxis for the prevention of severe RSV LRTI in high-risk infants. Healthcare providers and managed care payers should thoroughly evaluate the clinical evidence published to date when considering immunoprophylaxis and ensure that palivizumab use is consistent with the FDA-approved prescribing information.

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Disclosures:

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SYNAGIS® (PALIVIZUMAB)

for Intramuscular Administration **Rx only**

DESCRIPTION: Synagis (palivizumab) is a humanized monoclonal antibody (IgG1κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Synagis is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor (1) and Cess (2). The human light chain sequence was derived from the constant domain of Cκ and the variable framework regions of the V_L gene K104 with Jκ -4 (3). The murine sequences were derived from a murine monoclonal antibody, Mab 1129 (4), in a process that involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Synagis is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis is supplied as a sterile, preservative-free liquid solution at 100 mg/mL to be administered by intramuscular injection (IM). Thimerosal or other mercury containing salts are not used in the production of Synagis. The solution has a pH of 6.0 and should appear clear or slightly opalescent.

Each 100 mg single-dose vial of Synagis liquid solution contains 100 mg of Synagis, 3.9 mg of histidine, 0.1 mg of glycine, and 0.5 mg of chloride in a volume of 1 mL.

Each 50 mg single-dose vial of Synagis liquid solution contains 50 mg of Synagis, 1.9 mg of histidine, 0.06 mg of glycine, and 0.2 mg of chloride in a volume of 0.5 mL.

CLINICAL PHARMACOLOGY: *Mechanism of Action:* Synagis exhibits neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by Synagis (5). Synagis serum concentrations of ≥ 40 mcg/mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold (5). The *in vivo* neutralizing activity of the active ingredient in Synagis was assessed in a randomized, placebo-controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients, Synagis significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients (6).

Pharmacokinetics: In pediatric patients < 24 months of age without congenital heart disease (CHD), the mean half-life of Synagis was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean ± SD 30 day trough serum drug concentrations of 37 ± 21 mcg/mL after the first injection, 57 ± 41 mcg/mL after the second injection, 68 ± 51 mcg/mL after the third injection and 72 ± 50 mcg/mL after the fourth injection (7). Trough concentrations following the first and fourth Synagis dose were similar in children with CHD and in non-cardiac patients. In pediatric patients given Synagis for a second season, the mean ± SD serum concentrations following the first and fourth injections were 61 ± 17 mcg/mL and 86 ± 31 mcg/mL, respectively.

In 139 pediatric patients ≤ 24 months of age with hemodynamically significant CHD who received Synagis and underwent cardio-pulmonary bypass for open-heart surgery, the mean ± SD serum Synagis concentration was 98 ± 52 mcg/mL before bypass and declined to 41 ± 33 mcg/mL after bypass, a reduction of 58% (see *DOSAGE AND ADMINISTRATION*). The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on Synagis systemic exposure. However, no effects of gender, age, body weight or race on Synagis serum trough concentrations were observed in a clinical study with 639 pediatric patients with CHD (≤ 24 months of age) receiving five monthly intramuscular injections of 15 mg/kg of Synagis.

The pharmacokinetics and safety of Synagis liquid solution and Synagis lyophilized formulation administered IM at 15 mg/kg were studied in a cross-over trial of 153 pediatric patients ≤ 6 months of age with a history of prematurity. The results of this trial indicated that the trough serum concentrations of palivizumab were comparable between the liquid solution and the lyophilized formulation, which was the formulation used in the clinical studies described below.

CLINICAL STUDIES: The safety and efficacy of Synagis were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in pediatric patients at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1,502 patients ≤ 24 months of age with bronchopulmonary dysplasia (BPD) or infants with premature birth (≤ 35 weeks gestation) who were ≤ 6 months of age at study entry (7). Trial 2 was conducted over four consecutive seasons among a total of 1287 patients ≤ 24 months of age with hemodynamically significant congenital heart disease. In both trials participants received 15 mg/kg Synagis or an equivalent volume of placebo IM monthly for five injections and were followed for 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. In Trial 2, 96% of all subjects completed the study and 92% completed all five injections. The incidence of RSV hospitalization is shown in Table 1.

Table 1: Incidence of RSV Hospitalization by Treatment Group

Trial		Placebo	Synagis	Difference Between Groups	Relative Reduction	p-Value
Trial 1 Impact-RSV	N	500	1002			
	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55%	< 0.001
Trial 2 CHD	N	648	639			
	Hospitalization	63 (9.7%)	34 (5.3%)	4.4%	45%	0.003

In Trial 1, the reduction of RSV hospitalization was observed both in patients with BPD (34/266 [12.8%] placebo vs. 39/496 [7.9%] Synagis), and in premature infants without BPD (19/234 [8.1%] placebo vs. 9/506 [1.8%] Synagis). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo versus 15/300 [5.0%] Synagis) and cyanotic children (27/343 [7.9%] placebo versus 19/339 [5.6%] Synagis).

The clinical studies do not suggest that RSV infection was less severe among RSV hospitalized patients who received Synagis compared to those who received placebo.

INDICATIONS AND USAGE: Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD) (see *CLINICAL STUDIES*).

CONTRAINDICATIONS: Synagis should not be used in pediatric patients with a history of a severe prior reaction to Synagis or other components of this product.

WARNINGS: Very rare cases of anaphylaxis (< 1 case per 100,000 patients) have been reported following re-exposure to Synagis (see *ADVERSE REACTIONS, Post-Marketing Experience*). Severe acute hypersensitivity reactions, estimated to be rare, (< 1 case per 1,000 patients) have also been reported on initial exposure or re-exposure to Synagis (see *ADVERSE REACTIONS, Post-Marketing Experience*). If a severe hypersensitivity reaction occurs, therapy with Synagis should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on readministration of Synagis. **If anaphylaxis or severe allergic reactions occur, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.**

PRECAUTIONS: *General:* Synagis is for intramuscular use only. As with any intramuscular injection, Synagis should be given with caution to patients with thrombocytopenia or any coagulation disorder.

The safety and efficacy of Synagis have not been demonstrated for treatment of established RSV disease.

The single-dose vial of Synagis does not contain a preservative. Administration of Synagis should occur immediately after dose withdrawal from the vial. The vial should not be re-entered. Discard any unused portion.

Drug Interactions: No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of patients in the placebo and Synagis groups who received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids were similar and no incremental increase in adverse reactions was observed among patients receiving these agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis, mutagenesis and reproductive toxicity studies have not been performed.

Pregnancy: Pregnancy Category C: Synagis is not indicated for adult usage and animal reproduction studies have not been conducted. It is also not known whether Synagis can cause fetal harm when administered to a pregnant woman or could affect reproductive capacity.

ADVERSE REACTIONS: The most serious adverse reactions occurring with Synagis treatment are anaphylaxis and other acute hypersensitivity reactions (see *WARNINGS*). The adverse reactions most commonly observed in Synagis-treated patients were upper respiratory tract infection, otitis media, fever, rhinitis, rash, diarrhea, cough, vomiting, gastroenteritis, and wheezing. Upper respiratory tract infection, otitis media, fever, and rhinitis occurred at a rate of 1% or greater in the Synagis group compared to placebo (Table 2).

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information does, however, provide a basis for identifying the adverse events that appear to be related to drug use and a basis for approximating rates.

The data described reflect Synagis exposure for 1641 pediatric patients of age 3 days to 24.1 months in Trials 1 and 2. Among these patients, 496 had bronchopulmonary dysplasia, 506 were premature birth infants less than 6 months of age, and 639 had congenital heart disease. Adverse events observed in the 153 patient crossover study comparing the liquid and lyophilized formulations were similar between the two formulations, and similar to the adverse events observed with Synagis in Trials 1 and 2.

Table 2 - Adverse Events Occurring at a Rate of 1% or Greater More Frequently in Patients† Receiving Synagis

Event	Synagis (n=1641) n (%)	Placebo (n=1148) n (%)
Upper respiratory infection	830 (50.6)	544 (47.4)
Otitis media	597 (36.4)	397 (34.6)
Fever	446 (27.1)	289 (25.2)
Rhinitis	439 (26.8)	282 (24.6)
Hernia	68 (4.1)	30 (2.6)
SGOT Increase	49 (3.0)	20 (1.7)

†Cyanosis (Synagis [9.1%]/placebo [6.9%]) and arrhythmia (Synagis [3.1%]/placebo [1.7%]) were reported during Trial 2 in CHD patients.

Immunogenicity

In Trial 1, the incidence of anti-Synagis antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis group. In pediatric patients receiving Synagis for a second season, one of the fifty-six patients had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Synagis in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Synagis with the incidence of antibodies to other products may be misleading.

With any monoclonal antibody, the possibility exists that a liquid solution may be more immunogenic than a lyophilized formulation. The relative immunogenicity rates between the lyophilized formulation, used in Trials 1 and 2 above, and the liquid solution have not yet been established.

Post-Marketing Experience

The following adverse reactions have been identified and reported during post-approval use of Synagis. Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: severe thrombocytopenia (platelet count < 50,000/microliter)

General Disorders and Administration Site Conditions: injection site reactions

Immune System Disorders: severe acute hypersensitivity reactions and anaphylaxis (including dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia and unresponsiveness) have been reported (see *WARNINGS*). None of the reported hypersensitivity reactions were fatal. The relationship between these reactions and the development of antibodies to Synagis is unknown.

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis are similar in character and frequency to those after the initial five doses.

OVERDOSAGE: No data from clinical studies are available on overdosage. No toxicity was observed in rabbits administered a single intramuscular or subcutaneous injection of Synagis at a dose of 50 mg/kg.

DOSAGE AND ADMINISTRATION: The recommended dose of Synagis is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should continue to receive monthly doses throughout the RSV season. The first dose should be administered prior to commencement of the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis serum levels are decreased after cardio-pulmonary bypass (see *CLINICAL PHARMACOLOGY*). Patients undergoing cardio-pulmonary bypass should receive a dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly.

Synagis should be administered in a dose of 15 mg/kg intramuscularly using aseptic technique, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The dose per month = patient weight (kg) x 15 mg/kg ÷ 100 mg/mL of Synagis. Injection volumes over 1 mL should be given as a divided dose.

Administration of Synagis

- **DO NOT DILUTE THE PRODUCT**
- **DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL**
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
- Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the Synagis vial, and wipe the rubber stopper with a disinfectant (e.g., 70% isopropyl alcohol). Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution. Administer immediately after drawing the dose into the syringe.
- Synagis is supplied as a single-dose vial and does not contain preservatives. Do not re-enter the vial after withdrawal of drug; discard unused portion. Only administer one dose per vial.
- To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. DO NOT reuse syringes and needles.

HOW SUPPLIED: Synagis is supplied in single-dose vials as a preservative-free, sterile liquid solution at 100 mg/mL for IM injection.

50 mg vial NDC 60574-4114-1
The 50 mg vial contains 50 mg Synagis in 0.5 mL.

100 mg vial NDC 60574-4113-1
The 100 mg vial contains 100 mg Synagis in 1 mL.

There is no latex in the rubber stopper used for sealing vials of Synagis. Upon receipt and until use, Synagis should be stored between 2°C and 8°C (35.6°F and 46.4°F) in its original container. DO NOT freeze. DO NOT use beyond the expiration date.

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MedImmune

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Information for Patients and Their Caregivers

SYNAGIS® (SĬ-nă-jĭs)

(palivizumab)

Read this Patient Information before your child starts receiving SYNAGIS and before each injection. The information may have changed. This leaflet does not take the place of talking with your child's healthcare provider about your child's condition or treatment.

What is SYNAGIS?

SYNAGIS is a prescription medication that is used to help prevent a serious lung disease caused by Respiratory Syncytial Virus (RSV). Your child is prescribed SYNAGIS because he or she is at high risk for severe lung disease from RSV.

SYNAGIS contains man-made, disease-fighting proteins called antibodies. These antibodies help prevent RSV disease. Children at high risk for severe RSV disease often do not have enough of their own antibodies. SYNAGIS is used in certain groups of children to help prevent severe RSV disease by increasing protective RSV antibodies.

SYNAGIS is not used to treat the symptoms of RSV disease, once a child already has it. It is only used to prevent RSV disease.

SYNAGIS is not for adults.

Who should not receive SYNAGIS?

Your child should not receive SYNAGIS if they have ever had a severe allergic reaction to it or any of its ingredients. Signs and symptoms of a severe allergic reaction could include:

- severe rash, hives or itching skin
- difficult, rapid or irregular breathing
- closing of the throat, difficulty swallowing
- swelling of the lips, tongue, or face
- bluish color of skin, lips or under fingernails
- muscle weakness or floppiness
- unresponsiveness

See the end of this leaflet for a list of ingredients in SYNAGIS.

What should I tell my child's healthcare provider before my child receives SYNAGIS?

Tell your child's healthcare provider about:

- **Any reactions** you believe your child has ever had to SYNAGIS.
- All your child's medical problems, including **any bleeding or bruising problems.** SYNAGIS is given by injection. If your child has a problem with bleeding or bruises easily, an injection could cause a problem.
- **All the medicines your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements.** Especially tell your child's healthcare provider if your child takes a blood thinner medicine.

How is SYNAGIS given?

- SYNAGIS is given as a monthly injection, usually in the thigh (leg) muscle, by your child's healthcare provider. Your child's healthcare provider will prescribe the amount of SYNAGIS that is right for your child (based on their weight).
- Your child's healthcare provider will give you detailed instructions on when SYNAGIS will be given.
    - "RSV season" is a term used to describe the time of year when RSV infections most commonly occur (usually fall through spring). During this time, when RSV is most active, your child will need to receive SYNAGIS shots. Your child's healthcare provider can tell you when the RSV season starts in your area.
    - Your child should receive their **first SYNAGIS shot before the RSV season starts** to help protect them before RSV becomes active. If the season has already started, your child should receive their first SYNAGIS shot as soon as possible to help protect them when exposure to the virus is more likely.
    - **SYNAGIS is needed every 28-30 days during the RSV season.** Each dose of SYNAGIS helps protect your child from severe RSV disease for about a month. **Keep all appointments with your child's healthcare provider.**
- **If your child misses an injection, talk to your healthcare provider and schedule another injection as soon as possible.**
- Your child may still get severe RSV disease after receiving SYNAGIS. Talk to your child's healthcare provider about what symptoms to look for.
- If your child already has an RSV infection and is sick, they still need to get their scheduled SYNAGIS injections to help prevent severe disease from new RSV infections.
- If your child has certain types of heart disease and has corrective surgery, your healthcare provider may need to give your child an additional SYNAGIS injection soon after surgery.

What are the possible side effects of SYNAGIS?

Over one million babies have been given SYNAGIS. Like all medicines, SYNAGIS has been associated with side effects in some patients. Most of the time, the side effects are not serious. If side effects do occur, your child may need medical attention.

Possible, serious side effects include:

- Severe allergic reactions (may occur after any dose of SYNAGIS). See "Who should not take SYNAGIS?" for a list of signs and symptoms.
- Unusual bruising and/or groups of tiny red spots on the skin.

Call your child's healthcare provider or get medical help right away if your child has any of the serious side effects listed above after any dose of SYNAGIS.

Common side effects of SYNAGIS include:

- fever
- cold-like symptoms (upper respiratory infection), including runny nose and ear infection
- rash

Other possible side effects include skin reactions around the area where the shot was given (like redness, swelling, warmth, or discomfort).

In children born with certain types of heart disease, other possible side effects include bluish color of the skin, lips or under fingernails and abnormal heart rhythms.

These are not all the possible side effects of SYNAGIS. Tell your child's healthcare provider about any side effect that bothers your child or that does not go away.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or call MedImmune at 1-877-633-4411.

General Information about SYNAGIS

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets.

This leaflet summarizes important information about SYNAGIS. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about SYNAGIS that is written for health professionals.

For more information, go to www.synagis.com or call 1-877-633-4411.

What are the ingredients in SYNAGIS?

Active Ingredient: palivizumab

Inactive Ingredients: histidine, glycine, and chloride

What is RSV?

Respiratory Syncytial Virus (RSV) is a common virus that is easily spread from person to person. RSV infects nearly all children by their second birthday. In most children, RSV infection is usually no worse than a bad cold. For some children, RSV infection can cause serious lung disease (like pneumonia and bronchiolitis) or breathing problems, and affected children may need to be admitted to the hospital or need emergency care.

Children who are more likely to get severe RSV disease (high risk children) include babies born prematurely (35 weeks or less), or babies born with certain heart or lung problems.

MedImmune

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Gaithersburg, MD 20878

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