Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Economic impact of viral respiratory disease in children

H. Cody Meissner, MD

From the Department of Pediatric Infectious Disease, New England Medical Center, Tufts University School of Medicine, Boston, Massachusetts

The single most important respiratory pathogen in infancy and early childhood is respiratory syncytial virus (RSV). Approximately 40% of primary RSV infections in children result in lower respiratory tract disease. Approximately 1% of RSV-infected children require hospitalization. Especially in high-risk children, primary RSV infection results in significant morbidity and, sometimes, death. This high-risk group includes children with bronchopulmonary dysplasia, children with congenital heart disease, premature infants less than 6 months of age, and children with immunodeficiency diseases. It has been estimated that, in the United States, 14,000 infants with chronic lung disease and 16,400 infants with heart disease will be identified by 12 months of age. More than 91,000 children are hospitalized annually with lower respiratory tract disease caused by RSV, and 4500 deaths occur. In 1985 a report from the Institute of Medicine calculated that the annual hospitalization costs attributable to RSV infection were $300 million. Data collected at the New England Medical Center in 1991 show that the average cost of hospitalization of a child with RSV was $808 each day. Because of difficulty in developing a safe and effective RSV vaccine, attention is now focused on passive immunization using an RSV immune globulin. On the basis of a recently completed multiinstitutional trial, RSV immune globulin appears to be a safe and cost-effective option for prevention of severe RSV disease in high-risk children. (J PEDIATR 1994;124:S17-S21)

Viruses that account for the vast majority of upper and lower respiratory tract infections in infants and children include influenza viruses, parainfluenza viruses, adenoviruses, coronaviruses, rhinovirus, and respiratory syncytial virus; RSV is the single most important respiratory pathogen in infancy and early childhood.[1, 2] Asymptomatic carriage of RSV appears to be an infrequent occurrence. Approximately 60% of primary RSV infections are confined to the upper airways, with symptoms typical of the common cold. Conversely, 40% of primary RSV infections result in lower respiratory tract disease consisting of bronchiolitis and pneumonia.[3] Approximately 1% of children infected with RSV require hospitalization.[4] Children and infants with certain preexisting conditions are at increased risk of hospitalization because of severe RSV infection. Preexisting conditions that increase the risk of hospitalization for severe RSV infection include congenital heart disease, particularly in association with pulmonary artery hypertension, chronic lung disease such as bronchopulmonary dysplasia or cystic fibrosis, and premature birth of infants aged <6 months, particularly those born at <34 weeks of gestation. Also at increased risk of severe RSV infection are infants and children who are immunocompromised, such as those with human immunodeficiency virus infection, organ transplanta-

BPD	Bronchopulmonary dysplasia
CF	Cystic fibrosis
CHD	Congenital heart disease
HIV	Human immunodeficiency virus
LRTI	Lower respiratory tract infection
RSV	Respiratory syncytial virus
RSVIG	RSV immune globulin

Reprint requests: H. Cody Meissner, MD, Department of Pediatric Infectious Disease, New England Medical Center, Tufts University School of Medicine, 750 Washington St., Boston, MA 02111.

Copyright © 1994 by Mosby–Year Book, Inc.
0022-3476/94/$3.00 + 0 **9/0/53626**

tion, or a primary antibody deficiency, and term infants <6 weeks of age.

PEDIATRIC POPULATION WITH CHRONIC LUNG DISEASE

Bronchopulmonary dysplasia is defined as a chronic lung disease of preterm ventilator-supported infants that is characterized by persistent respiratory distress, an oxygen requirement continuing beyond the first month of life, and radiographic abnormalities. A recent study by the National Institute of Child Health and Human Development Neonatal Network estimated that BPD develops in 26% of all low birth weight (<1500 gm) ventilator-supported infants born in the United States, resulting in about 11,000 cases of BPD a year among the 4,200,000 infants born each year in the United States.[5] The number of infants with a birth weight >1500 gm in whom BPD develops may increase this number to a total of approximately 14,000 cases of BPD per year. Among infants and children with BPD, viral LRTI is the most common reason for rehospitalization after initial hospital discharge. A prospective study of the natural history of RSV infection in children with BPD by Groothuis et al.[6] found that 53% of 30 infants in a home oxygen program acquired RSV infection during a single 4-month respiratory virus season. Hospitalization was required for 11 (69%) of the 16 RSV-infected infants. Of the 11 hospitalized infants, 7 were hospitalized for more than 7 days, 4 were admitted to the intensive care unit, and 2 required mechanical ventilation. A recent report from Canada[7] reviewed a 3-year experience in 12 pediatric tertiary care centers with 1504 high-risk infants and children hospitalized with RSV infection. Of 200 pediatric patients hospitalized with chronic lung disease and RSV disease, 80% required supplemental oxygen, 32% required intensive care, and 19% required mechanical ventilation. Seven (3.5%) died within 2 weeks of admission, despite ribavirin therapy. Both of these studies emphasize the potential severity of lower respiratory tract disease caused by RSV infection in infants and young children with preexisting lung disease.

Even infants and children older than 1 year of age with chronic lung disease are at risk of rehospitalization because of RSV infection. Children in this category are typically those with recurrent or recent oxygen requirement. A recent 3-year study at the University of Colorado[8] found that 22% of 282 pediatric patients hospitalized with RSV disease were older than 12 months of age. Most infants had either BPD or reactive airway disease.

Another group of infants and children with chronic lung disease who may have particularly severe RSV disease are those with CF. Although bacterial infections constitute an important cause of acute pulmonary exacerbations in this population, patients with CF are at increased risk of hospitalization for acute respiratory virus infection. A study by Abman et al.[9] prospectively followed 48 infants in whom CF was diagnosed in a newborn screening program. Of the 48 infants, 27% were hospitalized for acute respiratory distress before reaching 12 months of age. RSV was isolated from 7 of the 12 hospitalized infants during this 12-month period. The mean duration of hospitalization was 22 days, and 3 infants required mechanical ventilator support. At a mean follow-up age of 26 months, the infants with CF who had been hospitalized with RSV had significantly worse chronic respiratory symptoms than patients with CF who were not hospitalized early in life because of RSV infection. Whether severe RSV LRTIs contribute to the rapid progression of chronic changes in the lungs of patients with CF or whether RSV tends to be more severe in certain patients with CF who will have more extensive pulmonary involvement is not known. Either explanation, however, recognizes that RSV infection in a young patient with CF places the infant at increased risk.

PEDIATRIC POPULATION WITH CONGENITAL HEART DISEASE

Infants and children with CHD constitute a second group of patients who are frequently hospitalized because of RSV LRTI. MacDonald et al.[10] evaluated the effect of RSV infection on infants with CHD in a prospective study. Six hundred ninety-nine infants were followed during five respiratory virus seasons. Of 73 infants with CHD, 27 (37%) had RSV infection. RSV-infected infants with CHD required more days of intensive care (63% vs 14%) and were more likely to require mechanical ventilation (22% vs 5%) than a control group of infants with RSV infection and no CHD. The mortality rate was 37% in RSV-infected infants with CHD, in contrast to 1.5% in the control patients. Overall, the mortality rate in infants with CHD without RSV infection was 6.5%, compared with a 37% mortality rate in children with both CHD and RSV infection—which emphasizes the importance of this pathogen as a cause of death in infants with CHD. Although no single anatomic lesion predominated in infants with a fatal outcome, infants with heart disease and pulmonary artery hypertension were at greater risk of fatal outcome.

In the previously mentioned Canadian report,[7] which reviewed the experience at 12 Canadian pediatric tertiary care centers during a 3-year period, 260 of the 1584 high-risk infants and children with RSV infection had CHD. Thirty-three percent of hospitalized RSV-infected infants with CHD required intensive care, and almost 18% required mechanical ventilation. Death within 2 weeks of admission occurred in 3.4% of the cohort with CHD. However, among the 53 infants with CHD and pulmonary artery hypertension, the mortality rate was more than twofold higher

(9.4%). There are several possible explanations for the lower mortality rate in the Canadian experience[7] than in the study by MacDonald et al.[10] Advances in cardiac surgery, intensive-care management, and antiviral therapy during the 10 years between the two studies are likely to have improved the prognosis. Despite the lower mortality rate, infection with RSV continues to pose a significant risk to infants and children with CHD.

The incidence of CHD in the United States ranges from 4 to 8 per 1000 live births. Approximately 4 infants per 1000 will be at risk of severe LRTI caused by RSV because of the nature of their cardiac lesion. On the basis of the 4,100,000 births in the United States in 1991, an estimated 16,400 infants with CHD will be at increased risk of complications and hospitalization caused by RSV infection.[5]

PEDIATRIC POPULATION BORN PREMATURELY

Infants born at <34 weeks of gestation, particularly those who are <6 months of age at the onset of RSV infection, constitute a third group of high-risk infants. A 9-year prospective study at the University of Rochester,[11] in New York State, found that 30% of children hospitalized with RSV LRTI had a history of prematurity. Even in the absence of lung disease, prematurity by itself constitutes a risk factor for hospitalization for RSV infection. This was demonstrated most recently in a report by Cunningham et al.[12] that prospectively compared a cohort of 133 survivors born at <33 weeks of gestation with a matched control group of term infants followed for 2 years to assess rates of rehospitalization for RSV infection. Thirty-six percent of all preterm infants (both with and without BPD) were rehospitalized at least once for respiratory illness, in comparison with 2.5% of 121 socioeconomically matched term infants. Twenty-five percent of the preterm infants without BPD were rehospitalized, compared with 45% of preterm infants with a history of BPD. As noted previously, only 2.5% of term infants were rehospitalized. Thus, in this study, preterm infants with BPD had the greatest risk of rehospitalization, although preterm infants with no history of BPD had a tenfold increase in rehospitalization rates compared with control infants. Infants discharged between September and December were approximately three times more likely to be rehospitalized than infants discharged between May and August, a reflection of the importance of respiratory viruses in precipitating readmission. In the previously described Canadian study,[7] 24% of the 1584 hospitalized high-risk patients had prematurity as their only risk factor. Among those premature pediatric patients who had no chronic lung disease, heart disease, or immunodeficiency, the proportion of infants who were admitted to the intensive care unit and required mechanical ventilation was similar to that in other high-risk groups. Thus the degree of prematurity, a history of BPD, and the season of the year at time of discharge all influence the risk of rehospitalization for acute respiratory virus illness.

Epidemiologic studies have demonstrated that term neonates tend to have less severe RSV disease in the first few weeks of life, when maternal neutralizing antibody titers are highest. Severe RSV illness tends to occur after passively acquired maternal antibody levels have fallen to low levels in term infants. In contrast, premature infants are likely to have a high incidence of RSV infection and severe RSV disease in the neonatal period, reflecting a lower titer of maternal neutralizing antibodies to RSV.[11]

Hospitalized premature infants represent the population at greatest risk of nosocomial RSV infection. In comparison with symptoms in older infants, the symptoms of RSV infection in neonates are often nonspecific and without symptoms of lower respiratory tract disease. The risk of nosocomial RSV disease is a function of length of hospitalization for all groups and not just those with prematurity.[13]

IMMUNOCOMPROMISED PEDIATRIC POPULATION

Infants and children with deficiencies of the immune system compose a fourth group at high risk for severe RSV infection. A prospective 10-year study by Hall et al.[14] assessed the relation between immune status and the severity of RSV infection in infants and children <5 years of age who were hospitalized during the respiratory virus season with RSV infection. Of the 608 pediatric patients with RSV infection, 8% were immunocompromised by chemotherapy, steroid therapy, or primary underlying immunodeficiency. Children immunocompromised by either cancer chemotherapy or primary immunodeficiency disease had more severe RSV disease than children with a normal immune status. These children were more likely to acquire pneumonia and to have a fatal outcome, which makes this group an important one for consideration of RSV prophylaxis. Although children receiving long-term steroid therapy demonstrated significantly greater and more prolonged RSV shedding, they did not appear to have more severe disease than children with a normal immune status.

Patients immunosuppressed for the purpose of organ transplantation represent another group of immunocompromised patients at risk of severe RSV infection. Bone marrow transplant recipients, in particular, are at increased risk of infection by either RSV or adenovirus. Particularly during community epidemics of RSV, infection of the lower respiratory tract by RSV may be associated with interstitial pneumonitis and an increased mortality rate in this transplant population. A report from the University of

Minnesota describes RSV infection in 8 of 74 bone marrow transplant recipients. Four of the eight patients died.[15]

Children with acquired immunodeficiency syndrome constitute another category of immunocompromised patients at increased risk of RSV infection. Some HIV-infected patients may not have more severe illness caused by RSV, as measured by duration of illness, degree of hypoxia, temperature, or respiratory rate, but children with symptomatic HIV infection have prolonged shedding of RSV. In comparison with normal children, who shed RSV for an average of 7 days (range, 1 to 21 days), viral shedding for up to 6 months has been documented in HIV-infected infants.[16] A second study[17] found an increased risk of pneumonia and a 20% mortality rate for RSV infection in HIV-infected children. An interesting feature of RSV infection in HIV-infected children is the reduced likelihood of wheezing. Cell-mediated immunity, specifically the lymphoproliferative response to viral antigens, is believed to be important in the pathogenesis of bronchiolitis and wheezing. Dysfunction of this aspect of the immune response has been postulated as the explanation for the absence of wheezing.

PEDIATRIC POPULATION LESS THAN 6 WEEKS OF AGE

An additional high-risk group includes healthy infants <6 weeks of age who become infected with RSV. A study from the University of Pittsburgh[18] noted that previously well infants <6 weeks of age who were hospitalized with RSV-infection were significantly more likely to require supplemental oxygen, to spend time in the intensive care unit, and to require a longer period of hospitalization than older infants. In this study, 21 infants <6 weeks of age were hospitalized for a mean of 5.6 days, whereas 27 infants between 6 and 12 weeks of age were hospitalized for 3.0 days. Infants with oxygen saturation <90% at the time of admission were at particular risk of prolonged hospitalization. Infants >3 months of age experienced a mean hospital stay of 2.5 days, a typical duration for older, non-high-risk infants with RSV bronchiolitis or pneumonia.

ECONOMIC IMPACT

In 1994, RSV continues to cause severe disease in several high-risk groups. These high-risk infants and children are at increased risk of prolonged hospitalization and respiratory failure. Compared with normal children with RSV infection, this pediatric population is more likely to require supplemental oxygen, intensive care, tracheal intubation, and mechanical ventilation. A 1991 report from Stanford Medical Center[19] described a randomized, double-blind, placebo-controlled study of ribavirin therapy in infants receiving mechanical ventilation for documented RSV-induced respiratory failure. The mean hospital bill for infants receiving ribavirin therapy was $68,067; placebo-treated patients had a mean hospital bill of $77,666 (not significantly different). In a study conducted in 1991,[20] the daily cost for infants hospitalized at the New England Medical Center with RSV infection was $808. A report in 1985 from the Institute of Medicine calculated the annual hospitalization costs for treatment of RSV infection to be $300 million. This figure was based on an estimated 91,000 hospitalizations for treatment of RSV infection in 1985. In a consideration of the total economic impact of RSV, it should noted that many times that number of children are treated as outpatients.

A recently completed multiinstitutional, randomized trial demonstrated the safety and efficacy of a hyperimmune RSV immune globulin in high-risk infants and children with cardiac disease, prematurity, or BPD.[21] An analysis based on this study shows that RSVIG immunoprophylaxis has a favorable cost-effectiveness profile (Hay JW, Ernst RL, Meissner HC: unpublished observations). Although RSVIG prophylaxis may not save medical sector resources, the average cost per year of life saved is between $15,000 and $20,000, a figure that compares favorably with a number of therapies currently used. In the absence of an effective RSV vaccine and without an effective antiviral agent for chemoprophylaxis, passive immunoprophylaxis with RSVIG holds the greatest promise for reducing the morbidity and mortality rates for RSV disease in high-risk patients.

REFERENCES

1. Hellman CA. Respiratory syncytial and parainfluenza viruses. J Infect Dis. 1990;161:402-6.
2. Anderson LJ, Parker RA, Strikas RL. Association between respiratory syncytial virus outbreaks and lower respiratory tract deaths of infants and young children. J Infect Dis 1990;161:640-6.
3. Hall CB. Respiratory syncytial virus. In: Feigen RD, Cherry JC, eds. Textbook of pediatric infectious diseases. Philadelphia: WB Saunders, 1992:1653-75.
4. Kim HW, Arrobio JO, Brandt CD, et al. Epidemiology of respiratory syncytial virus infection in Washington, D.C. I. Importance of the virus in different respiratory tract disease syndromes and temporal distribution of infection. Am J Epidemiol 1973;98:216-25.
5. Hack M, Horbar JD, Malloy MH, Tyson JE, Wright E, Wright L. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Network. Pediatrics 1991;87:587-97.
6. Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. Pediatrics 1988;82:199-203.
7. Navas L, Wang E, de Carvalho V, Robinson J. Improved outcome of respiratory syncytial virus infection in a high-risk hospitalized population of Canadian children. J PEDIATR 1991;121:348-54.
8. Groothuis JR, Salbenblatt CK, Lauer BA. Severe respiratory

syncytial virus infection in older children. Am J Dis Child 1990;144:346-8.
9. Abman SH, Ogle JW, Butler-Simon N, Rumack CM, Accurso FJ. Role of respiratory syncytial virus in early hospitalizations for respiratory distress of young infants with cystic fibrosis. J PEDIATR 1988;113:826-30.
10. MacDonald NE, Hall CB, Suffin SC, Alexson C, Harris PJ, Manning JA. Respiratory syncytial viral infection in infants with congenital heart disease. N Engl J Med 1982;307:397-400.
11. Hall CB, Kopelman AE, Douglas RG, Geiman JM, Meagher MP. Neonatal respiratory syncytial virus infection. N Engl J Med 1979;300:393-6.
12. Cunningham CK, McMillan JA, Gross SJ. Rehospitalization for respiratory illness in infants of less than 32 weeks' gestation. Pediatrics 1991;88:527-32.
13. Hall CB, Geiman JM, Douglas RG, Meagher MP. Control of nosocomial respiratory syncytial viral infections. Pediatrics 1978;62:728-32.
14. Hall CB, Powell KR, MacDonald NE, et al. Respiratory syncytial viral infection in children with compromised immune function. N Engl J Med 1986;315:77-81.
15. Hertz MI, Englund JA, Snover D, Bitterman PB, McGlave PB. Respiratory syncytial virus–induced acute lung injury in adult patients with bone marrow transplants: a clinical approach and review of literature. Medicine 1989;68:269-81.
16. King JC, Burke AR, Clemens JD, et al. Respiratory syncytial virus illnesses in human immunodeficiency virus and noninfected children. Pediatr Infect Dis J 1993;12:733-9.
17. Chandwani S, Borkowsky W, Krasinski K, Lawrence R, Welliver R. Respiratory syncytial virus infection in human immunodeficiency virus–infected children. J PEDIATR 1990; 117:251-4.
18. Green M, Brayer AF, Schenkman KA, Wald ER. Duration of hospitalization in previously well infants with respiratory syncytial virus infection. Pediatr Infect Dis J 1989;8:601-5.
19. Smith DW, Frankel LR, Mathers LH, Tang ATS, Ariagno RL, Prober CG. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. N Engl J Med 1991;325:24-9.
20. Meissner HC, Fulton DR, Groothuis JR, et al. Controlled trial to evaluate protection of high-risk infants against respiratory syncytial virus disease by using standard intravenous immune globulin. Antimicrob Agents Chemother 1993;37:1655-8.
21. Groothuis JR, Simoes EAF, Levin MJ, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. N Engl J Med 1993; 329:1524-30.