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Lower Airway Disease Caused by Respiratory Syncytial Virus

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Abstract. Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract disease in infants and young children. Most infections due to RSV are mild and do not require hospitalization. RSV causes both upper respiratory tract infections as well as lower respiratory tract infections. Infants with underlying disease states like bronchopulmonary dyslasia, congenital heart disease and prematurity appear more prone to develop severe infection and have a higher incidence of hospitalization. The exact pathogenesis of RSV is not well understood. The mortality associated with primary RSV infection in healthy children is estimated to be between .005% to .02%. In hospitalized children the mortality rate is estimated to be from 1% to 3%. Several treatment modalities in the form of bronchodilators, corticosteroids, ribavirin, intravenous immune gammaglobulin and antibiotics are available. Studies have failed to show the true beneficial effect of any of the above treatment modalities. Supportive care is only needed. The best treatment is the supportive care in the form of oxygen and fluids and close monitoring of the vital signs including oxygen saturation. **(Indian J Pediatr 1998; 65 : 355-362)**

Key words : *Respiratory syncytial virus (RSV), Bronchopulmonary dysplasia (BPD), Congenital heart disease (CHD), Intravenous immune gammaglobulin (IVIG).*

Respiratory syncytial virus (RSV)[1,2] is the most important cause of lower respiratory tract disease in infants and young children. Most infections due to RSV are mild and do not require hospitalization. RSV infection resulting in hospitalization involves lower respiratory tract infection and manifests mostly as bronchiolitis[1,3] in young infants. Infants with underlying disease states like bronchopulmonary dysplasia[4] congenital heart disease, and prematurity[5] are more prone to severe infections. Primary RSV infections occur most often between the ages of six weeks and two years. The highest incidence of RSV bronchiolitis and pneumonia is between the ages of two and six months. RSV infection is rare in children less than one month of age.

Respiratory syncytial virus was first isolated in 1955[3,6,7,8] from chimpanzees, and its infectivity in humans was documented one year later. It was named respiratory syncytial virus because of its characteristic ability to induce syncytia in the tissue culture cells. Epidemics[7] of RSV occur each winter, and this virus is seen throughout the world. It has been estimated that in the United States, every year 100,000 children are hospitalized, and about 1500 mortalities per year have been attributed to

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this virus in infants and children.

Agent RSV[8,9] is a polymorphic enveloped cytoplasmic virus containing single-stranded, negative-sence RNA. The RNA is associated with viral proteins, consisting of a nucleocapsid core that is packaged within the lipid envelope. RSV is classified in the genus pneumovirus, which belongs to the family of paramyxoviridae.

EPIDEMIOLOGY

RSV infection has a clear-cut epidemic nature throughout the world. In temperate climates it usually occurs during the fall winter. It usually begins in late fall and peaks in November to March. The epidemic lasts for five to six months and peaks during the third and fourth month. The incidence of primary infection[10] rate is about 69% during the first year of life and 83% during the second year of life. Risk of reinfection is about 33% during the first four years of life. The incidence of primary infection in daycare centres is higher, reaching almost 100% in young infants and 60%-80% in older infants.

TRANSMISSION

RSV infections are transmitted by large droplets, through fomite contamination or by direct contamination with infected secretions. Close contact appears to be necessary for infections to spread from person to person. In a recent study, 40% to 60% of the patients stopped shedding RSV 8-10 days after the onset of illness. Some infants can shed RSV for up to 3-4 weeks or longer. Longer periods of virus shedding have been noted in immunocompromised children and shorter periods in older children.

RISK FACTOR

Several risk factors[11,12] for RSV lower respiratory tract infection have been described. In early months of life, the infections are most common in males. Lower socioeconomic status predisposes these infants to higher incidence of RSV. Breast-feeding for longer than one month has a protective role, especially for those infants of mothers with lower socioeconomic status. The role of atopic predisposition[11] to severe RSV infection is controversial. Many studies[11] have shown that maternal smoking increases the risk of all respiratory virus infections in infants.

PATHOGENESIS

Despite the large number of studies[1,2] on the pathogenesis of RSV infection in humans and experimental animals, the current information is fragmentary and the mechanism of the disease is not well understood. Studies in humans have been difficult to undertake because the infection occurs most frequently in young infants with extremely low mortality. Several facts suggest immunologic injury as a factor in the pathogenesis of bronchiolitis due to RSV. There appears to be a delicate balance between immunopathology and immunoprotection, but the precise mechanism is still unknown.

PATHOLOGY

RSV infects respiratory epithelial cells. In addition, human blood mononuclear cells and human alveolar macrophages have been shown to be infected with RSV. Organ systems outside the respiratory tract do not

become infected in patients with normal immune systems; however, in an immunocompromised patient[13], RSV has been recovered from liver, spleen, and myocardium. There is little to no information about the pathologic changes associated with RSV in mild pneumonia and bronchiolitis. Autopsy studies have revealed lymphocytic peribronchial infiltration in bronchiolitis. There is no cellular infiltration of alveolar tissue. Because RSV is attracted to respiratory epithelium, proliferation and necrosis of the epithelium occurs. As a result, hypersecretion of mucus, round cell infiltration, and edema of the surrounding submucosa takes place. These changes result in the formation of mucus plugs obstructing bronchioles and consequent hyperinflation or collapse of the distal lung tissue. In pneumonia, interstitial alveoli are also infiltrated with mononuclear cells and are thickened. In extensive pneumonia, consolidation by alveolar debris containing protein, macrophages, epithelial cells, and numerous syncytial multinuclear giant cells with eosinophilic cytoplasmic inclusions have been found. Smaller amounts of viral particles and viral antigens were also detected in the lung tissue.

CLINICAL FEATURES

The clinical picture of RSV infection varies according to the age of the patient. The primary RSV infection[1,2] at the age of six weeks to two years is usually symptomatic and involves the lower respiratory tract. Asymptomatic primary RSV infection in children is rare. Subsequent infections in older children are usually less severe. RSV causes both upper respiratory tract as well as lower respiratory tract infection. The common symptoms of upper respiratory tract infection include rhinorrhea, nasal congestion, pharyngitis, and cough. RSV infection causes less fever than other respiratory infections. Soon after the cough develops, the child begins to wheeze audibly. If the disease is mild, the symptoms may not progress beyond this stage. If the illness progresses, then the infant goes on to develop bronchiolitis or pneumonia. Bronchiolitis is characterized by wheezing, dyspnea, respiratory distress, poor feeding, and tachypnea. This may progress to a life-threatening illness associated with central cyanosis, tachypnea, tachycardia, listlessness, and apneic spells[14]. Most of these patients are hypoxic. Hypoxia is the first sign and hypercarbia a late sign. Chest X-rays done on infants show air trapping with hyperexpansion and peribronchial thickening or interstitial pneumonia. Ten to twenty-five per cent of these patients may have segmental consolidations, especially involving the right upper lobe. Pleural effusion is rarely seen. The pathognomic finding of bronchiolitis on chest X-ray is hyperaeration.

In some infants, the course of illness may be akin to pneumonia. In these infants, rhinorrhea and cough are followed by dyspnea, poor feeding, and listlessness. These patients have minimal wheezing and minimal hyperaeration on chest X-ray.

In the great majority of patients with RSV bronchiolitis, the signs and symptoms resolve within a few days. In our own institution (Aggarwal R; RSV Bronchiolitis. Unpublished data.), the average length of stay was five days for high risk infants and three days for low risk infants. Infants under the age of six weeks and those with an underlying illness often need longer hospitalization.

INFECTION IN NEWBORNS

Although RSV infection is rare in the first four weeks of life, epidemics in neonates have been described. It is important to know that in many infants, the RSV infection may be atypical with major manifestations being apnea, lethargy, irritability, and poor feeding. The mechanisms of RSV-associated apnea[14] are not well understood. Possible explanations are stimulation of laryngeal receptors, respiratory muscle fatigue, and abnormal immunological response.

DIAGNOSIS

During an outbreak of RSV, diagnosis can often be assumed on the basis of signs and symptoms of infection and the age of the patient. Definite diagnosis of RSV infection is based on the detection of viral antigens[15,16] in the respiratory secretions. Rapid detection of viral antigens by immunoassays is at present the most suitable single method to demonstrate RSV infections. There are various methods to detect the RSV antigen in the nasopharyngeal secretions with the rapid antigen detection test recommended as a primary test. Detection of virus by cell culture[17] still remains the standard procedure, although it is becoming outdated because of the sensitivity and specificity of the rapid antigen detection test.

MORTALITY

The mortality associated with the primary RSV infection in otherwise healthy children is estimated to be .005% to .02%. In hospitalized children, the mortality rate is estimated to be 1% to 3%. Considerably, higher mortality rates in children with cardiopulmonary abnormalities or immunosuppression have been suggested. A possible significant correlation has been shown to exist between the occurrence of sudden infant death syndrome and RSV infection. At present, however, the role of RSV in SIDS is not fully understood.

TREATMENT

Supportive Care

Supportive care is the backbone of treatment of RSV infection. The majority of patients who are hospitalized are hypoxic, and supplemental oxygen therapy is the cornerstone of the treatment. Pulseoximeter is recommended, and saturations greater than 95% should be maintained. If blood gases are necessary, close follow-up should be done. If the patient shows signs and symptoms of acute respiratory failure demonstrated by pH < 7.25, PCO_2 > 60 mm of Hg, or PaO_2 < 60 mm of Hg in 40% oxygen, or is an infant with prolonged apnea, the patient will need ventilatory support. Intravenous hydration has also been recommended. However, two recent studies[18,19] reported markedly elevated plasma antidiuretic hormone (ADH) levels in children with bronchiolitis. Thus, careful monitoring of body weight in addition to plasma electrolyte concentration is necessary, and in some cases fluid restriction may be indicated[20].

Mist tent and chest physiotherapy were once done as supportive therapy for bronchiolitis. At present, there is evidence that they may do more harm than good. However, frequent aspiration of excessive nasopharyngeal mucus may be necessary in some patients to relieve breathing and

feeding difficulties.

Bronchodilators

The use of bronchodilators[21] in the treatment of bronchiolitis in young infants has been controversial. All the prior studies have suggested little or no beneficial effect from bronchodilators. Several recent studies, however, suggest that bronchodilators may have a beneficial effect in some patients with bronchiolitis. A recent study[20] showed that high dose of nebulized albuterol 0.5 mg/kg may have some beneficial effect.

Corticosteroids

Five early studies on the use of systemic corticosteroids in the treatment of acute bronchiolitis showed no beneficial effect. TAL and co-workers[22] showed, in a small number of patients, that treatment with intramuscular dexamethasone and nebulized salbutamol together, but not separately, had favourable effects on the clinical course of children with acute wheezing associated with upper respiratory tract symptoms. However, these findings could not be confirmed in later studies. Thus, the use of corticosteroids, whether in the systemic or inhaled form, continues to remain controversial with little or no beneficial effect in bronchiolitis.

Ribavirin

Ribavirin is an analog of quanosine and inosine. It has a broad antiviral spectrum and is effective not only against RSV but also *in vitro* against measles, parainfluenza, and influenza viruses. The drug is delivered as an aerosol by a special mist generator 18-20 hours daily for three to five days. Recently, high dose short duration therapy has been started with some promising results. In 1985, the Food and Drug Administration approved the use of Ribavirin for the treatment of infants with severe RSV disease based largely on the results of five double-blind placebo-controlled trials performed in the early 1980s. A number of these studies[23,24,25] have been subsequently criticized, however, for the methodology and criteria for determining therapeutic efficacy. Subsequent placebo control studies[25,26] have failed to demonstrate a difference in the duration of the illness days of tachypnea, hypoxemia, ability to tolerate oral feedings, airway compliance, or airway resistance in infants treated with ribavirin.

In 1987, the American Academy of Pediatrics (AAP) published[23] a recommendation for the use of ribavirin suggesting that it be reserved for (a) infants at high risk for severe or complicated respiratory syncytial viral infection, (b) infants hospitalized with the respiratory syncytial virus and lower respiratory tract disease who are severely ill, and (c) infants hospitalized with lower respiratory tract disease that is not initially severe, but may be at some increased risk of progressing to a more complicated course. These recommendations were based largely on the fact that young infants and those with underlying conditions, such as congenital heart disease (CHD) and bronchopulmonary dysplasia (BPD), typically have the most severe course of illness. However, the ability of ribavirin to alter the course of the disease in these high risk patients is unclear.

In addition to the above guidelines, AAP made further recommendations[24] that mechanically ventilated infants may be

more likely to benefit from ribavirin treatment. In 1991, Smith *et al*,[27] reported that ribavirin therapy was associated with shorter duration of mechanical ventilation, oxygen treatment, and hospitalization stay in 28 critically ill children with RSV. No complications or mortalities occurred in this study and only seven of the 28 patients in the study were considered at high risk. Other authors were unconvinced of the validity of these results, and pointed out that using aerosolized sterile water as placebo therapy rather than half normal or normal saline may have been detrimental in the control patients and, thereby, may have magnified the actual benefits of ribavirin. A subsequent study by Meert, *et al*[28] in 45 mechanically ventilated children with RSV who were treated with ribavirin or aerosolized saline placebo showed that the patients treated with ribavirin had no demonstrable improvement in any of the evaluated physiologic or resource utilization variables compared to those treated with placebo.

Finally, the cost of ribavirin for a three-day course is exorbitant, averaging approximately $5000.

Intravenous Immune Gammaglobulin (IVIG)

Studies[29, 30] on experimental animals and human infants suggest that RSV antibodies given in intravenous immunoglobulins may shorten the course and decrease the severity of RSV infection. Although nasal RSV shedding was reduced in the these patients, there were only modest clinical improvements and no measurable effect on the duration of hospital stay. A recent study by J.R. Groothius and co-workers[31] from the Respiratory Syncytial Virus Immune Globulin study group showed that high dose 750 mg/kg of RSV immune globulin (RSVIG) is safe and highly effective in preventing severe RSV disease when given as monthly infusions to preterm infants. Based on the results of these trials, the FDA licensed RSV-IGIV on January 18, 1996, for the prevention of serious lower respiratory tract infection caused by RSV in children younger than 24 months of age with bronchopulmonary dysplasia or a history of premature birth defined as less than 35 weeks of gestation. The drug was not approved for those infants who had congenital heart disease. Since the approval of this drug, questions have been raised about the true benefit of this drug. In our own centre we found no real benefit in the use of this drug either in preventing a serious RSV infection or decreasing the hospitalization for these preterm infants in which RSV-IGIV was used for prophylaxis. This drug is also expensive and cost benefit analysis remains to be proven. Recent research in monoclonal antibodies against RSV is on in trials and we hope some day the prophylactic measures against RSV will become simpler and less expensive and, thus, more broadly applicable.

Antibiotic Therapy

Antibiotic therapy is given to at least 40%-50% of patients hospitalized with RSV infections. Most often the indications include acute otitis media and possible bacterial type pneumonia. Two randomized studies demonstrated that routine antibiotic therapy has no benefit in the treatment of bronchiolitis. Thus, the routine use of antibiotics is recommended in the treatment of RSV bronchiolitis.

PREVENTION

Universal precautions are the mainstay of preventing the spread of RSV. At present, no safe and effective vaccine against RSV infection is available. Several different kinds of vaccines[32] have been developed and some even tested in clinical trials, but all of them have failed to show their efficacy and safety. Use of RSV immune globulins[30,31] as described above has been recommended recently as the only effective means to prevent severe RSV infection in high risk preterm infants.

CONCLUSION

In summary, infants with RSV bronchiolitis or pneumonia only need supportive care. In our own retrospective study (Aggarwal R; RSV Bronchiolitis. Unpublished data) of 100 infants over five years, there was no change in length of stay or mortality with different treatment modalities. The length of stay depended on the severity of illness and underlying risk factors.

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