Respiratory Syncytial Virus Infection in Children

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Introduction

Respiratory syncytial virus (RSV) is the major cause of viral respiratory tract infections in infants and children [1, 2]. The highly contagious nature of the virus means that essentially all children have been infected with RSV by 2 to 3 years of age. Epidemics principally occur in winter and early spring.

Clinical manifestations range from mild upper respiratory tract infections to severe lower respiratory tract disorders (Table 1). It is estimated that RSV is responsible for 40–70% of cases of bronchiolitis [3], up to 40% of cases of pneumonia [4] and 5% of cases of croup in children under 5 years of age. Apnea may occur in infected infants less than 6 months of age, particularly if they were prematurely born. The clinical course of RSV infection is usually benign, but up to 8% of infected infants will require intensive care treatment for recurrent apnea or respiratory failure [5]. Certain diagnostic subgroups are more likely to show a prolonged and more severe course of RSV infection (Table 2) [6–8]. It is noteworthy that mortality rates are low and in the range of 2–5% even for high risk patients [5, 9–11].

Table 1. Clinical presentation of RSV infection

– Upper respiratory tract infection
– Apnea
– Tracheobronchitis
– Bronchiolitis
– Pneumonia
– ARDS

Table 2. Risk factors for severe RSV disease

Age below 6 weeks
Prematurity
Pulmonary disease
– e. g. bronchopulmonary dysplasia
Congenital heart disease
– especially increased pulmonary blood flow
Neuromuscular disease
Immunosuppression or immunodeficiency

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Pathophysiology

Histopathologically, RSV lower respiratory tract infection is characterized by bronchiolar-inflammation resulting in epithelial necrosis and sloughing into the airway lumen. Tissue edema and increased mucus production result in thick plugs obstructing or occluding the airways, causing areas of atelectasis and hyperinflation. Pneumonia occurs when this process extends into the alveoli.

Despite the frequency with which pediatric intensive care units (PICU) deal with RSV-induced respiratory failure, there is little information on the physiologic pulmonary changes which occur during the acute stage of this disease. With the use of sophisticated lung function testing [12], we have recently demonstrated two characteristic and distinctly different patterns of lower respiratory tract disease in infants with RSV-induced respiratory failure: 1) obstructive small airways disease, and 2) severe restrictive, parenchymal lung disease [13, 14]. In agreement with our observation, Tasker et al. [15] described two different radiological presentations in infants with RSV-induced respiratory failure characterized by diffuse consolidation without hyperinflation or gross hyperinflation without consolidation.

The majority of infants with RSV-triggered respiratory failure suffer from obstructive small airways disease traditionally referred to as bronchiolitis with increased respiratory resistance, reduced maximal expiratory flows and air trapping [13]. This represents the pathophysiologic changes caused by small airway obstruction due to bronchial mucosal edema and peribronchial inflammation. Lung volumes and compliance are slightly reduced which is explained by the presence of atelectatic lung regions. The radiographic changes observed in obstructive disease are entirely consistent with this pathophysiology and include hyperinflation, perihilar infiltrates and atelectasis (Fig. 1).

In contrast, about 25–30% of infants with RSV-induced respiratory failure suffer from severe restrictive parenchymal disease, usually referred to as pneumonia [14].

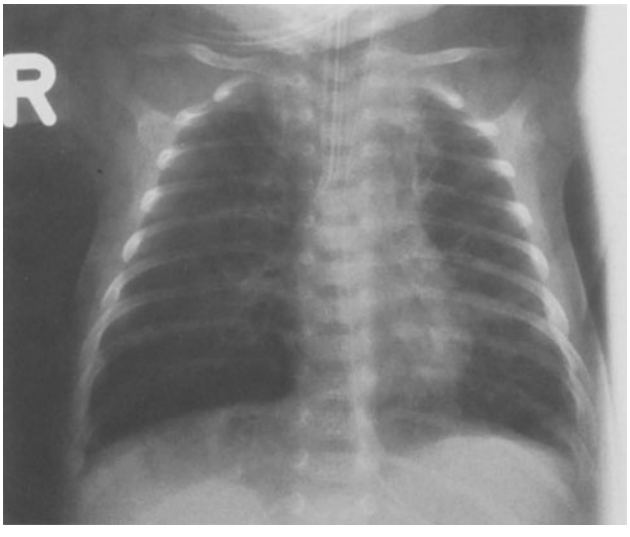

Fig. 1. Chest radiograph of a 4 month-old infant with classic bronchiolitis demonstrates hyperinflation and areas of atelectasis

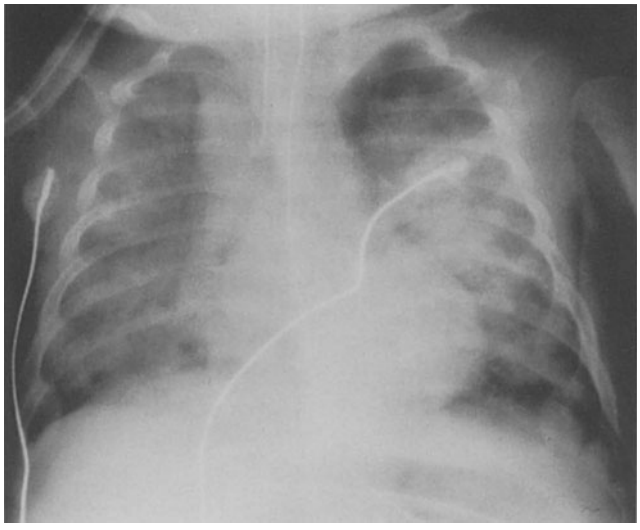

Fig. 2. Chest radiograph of a 5 month-old previously well infant with RSV pneumonia shows bilateral alveolar consolidation

Typically, respiratory compliance and lung volumes are markedly decreased without significant airway obstruction or air trapping. Alveolar consolidation is the main radiographic feature (Fig. 2). We found that these infants also fulfilled the criteria of acute respiratory distress syndrome (ARDS) that were recently recommended by an American-European Consensus Committee: acute disease onset, PaO_2/FiO_2 ratio ≤ 200 mmHg, bilateral infiltrates on chest radiograph, and absence of clinical evidence of left atrial hypertension [16]. In addition, all restrictive (but none of the obstructive) infants had lung injury scores above 2.5 which is again compatible with a diagnosis of ARDS [17, 18]. The lung function results obtained in the patients with restrictive disease are also in agreement with current concepts of respiratory mechanics and lung volume alterations in ARDS [19, 20].

Management

The general principles of the management of infants hospitalized for RSV infection include adequate supportive care (hydration and oxygenation), monitoring (pulse oximetry, transcutaneous CO_2, serial blood gas analyses), and respiratory isolation to prevent nosocomial spread.

Fluid Management

The goal of initial fluid management is the establishment of isovolemia, since these infants may be dehydrated from poor intake or cough-induced vomiting. Intravenous fluid administration is often warranted in spontaneously breathing infants because severe respiratory distress may preclude adequate nursing. Intubated and ventilated children can usually be managed with nasogastric feedings shortly after the

institution of mechanical ventilation. It is important to know that bronchiolitis is assciated with both increased antidiuretic hormone secretion (SIADH) and hyperreninemia with secondary hyperaldosteronism, which leads to water retention [21]. This results in pulmonary and peripheral tissue edema causing further respiratory deterioration. In addition, mechanical forces caused by obstructive breathing and inflammation may contribute to the development of pulmonary edema. Since the usual 20–30% fluid loss from the respiratory tract in infants is avoided when they are ventilated with humidified gases, fluid restriction to about 50–70% of maintenance requirements is recommended in intubated infants after adequate correction of an initial volume deficit. Diuretic therapy is often necessary for appropriate fluid balance.

Respiratory Management

All infants requiring hospitalization for RSV bronchiolitis should be given O_2 to maintain arterial O_2 saturations above 92%. It is important to remember that pulse oximetry does not assess ventilation, and thus a patient with acceptable oxygenation may have a significant degree of hypercarbia and/or acidosis. Criteria for intubation and initiating ventilatory support include continued worsening of respiratory distress by clinical assessment, hypoxia (PaO_2 <60 mmHg in 40% O_2), hypercapnia ($PaCO_2$ $>$ 50–60 mmHg with or without respiratory acidosis), and apnea or bradycardia. The interpretation of $PaCO_2$ values should be related to the degree of tachypnea, since many infants may not develop severe hypercapnia until shortly prior to cardiorespiratory arrest. We favor the use of cuffed endotracheal tubes (internal diameter 0.5 mm smaller than the calculated size for age for uncuffed tubes) to provide optimal and consistent levels of ventilation and oxygenation, especially in a disease-process likely to require relatively high ventilatory pressures [22].

We use pressure-controlled ventilation because of its decelerating flow-pattern allowing a comparatively lower mean airway pressure than volume-controlled ventilation. Most patients need peak inspiratory pressures between 25 to 35 cm H_2O to achieve adequate air movement and ventilation. Infants with obstructive disease have long respiratory system time constants and are best ventilated with slow rates and long inspiration/expiration (I/E) ratios of at least 1/3 to prevent breath-stacking and further hyperinflation. Conversely, patients with restrictive disease may require longer inspiratory times, faster rates and shorter I/E ratios. The cautious application of positive end-expiratory pressure (PEEP) may be helpful to decrease the work of breathing (especially in the presence of intrinsic PEEP) and to improve oxygenation. Neuromuscular blockade and sedation may be necessary to prevent ventilator-patient asynchrony and to facilitate ventilation and oxygenation. Peak inspiratory pressures should be limited at about 40 cm H_2O to prevent severe barotrauma and air leak syndromes (Figs. 3 and 4). Applying the strategy of permissive hypercapnia may help in reducing barotrauma.

Weaning from mechanical ventilation begins with lowering the peak inspiratory pressure if lung compliance has improved, thus allowing adequate tidal volumes at a lower peak inspiratory pressure. The ventilator rate may be reduced gradually if the patient is able to breathe effectively without developing fatigue. Modern flow-trigger

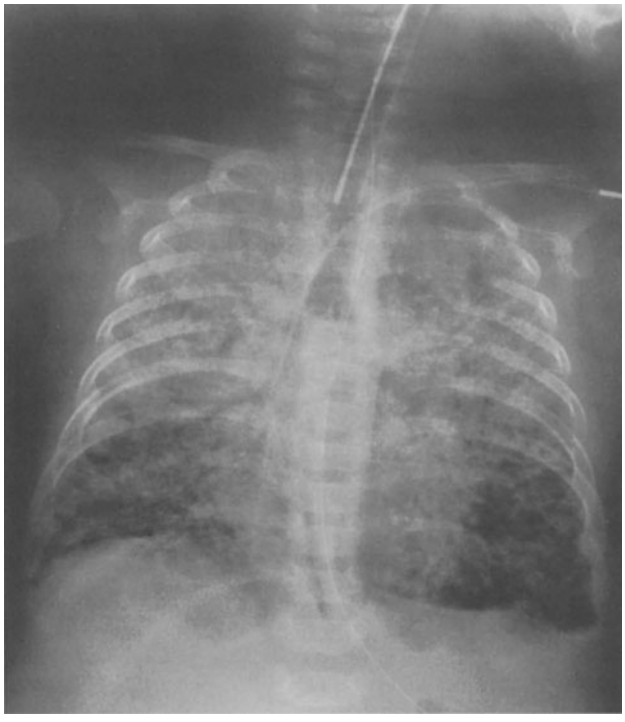

Fig. 3. Chest radiograph of a 4 month-old premature infant with bronchopulmonary dysplasia suffering from severe RSV infection demonstrates hyperinflation and severe interstitial emphysema secondary to the use of unreasonably high peak inspiratory pressures

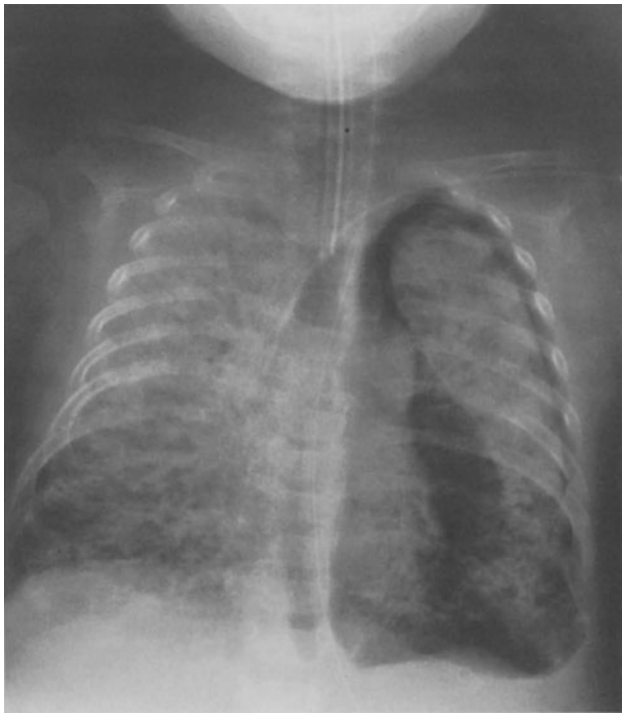

Fig. 4. Chest radiograph of the same infant as in Fig. 3 demonstrates a right pneumothorax as a consequence of severe barotrauma resulting from desperate elevation of the peak inspiratory pressure (over 50 cm H_2O) in response to failure of conventional ventilation

Table 3. Ribavirin and duration of mechanical ventilation (MV) for RSV infection in previously healthy infants

Authors	Reference	N	Ribavirin	MV (days ± SE)
Smith et al	[58]	10	N	10.1 ± 1.8
		11	Y	4.4 ± 1.1
Meert et al	[60]	7	N	2.4 ± 0.5
		10	Y	4.4 ± 1.0
Moler et al	[61]	74	N	5.0 ± 0.5
		33	Y	6.4 ± 0.9
Stretton et al	[5]	11	N	3.9 ± 0.8
Outwater and Crone	[23]	15	N	6.0 ± 1.2
Lebel et al	[24]	62	N	4.4 ± 0.4

mechanisms and PEEP may be helpful to reduce the work of breathing in the weaning phase. The duration of mechanical ventilation of previously healthy infants for uncomplicated RSV infection is in the range of 4–7 days (Table 3) [5, 23, 24]. Infants with underlying risk factors and/or restrictive disease may require a considerably longer duration of mechanical ventilation [14, 15] .

Failure of conventional mechanical ventilation in RSV-induced respiratory failure is an uncommon occurrence [11]. Nevertheless, three retrospective cohort studies have found that extracorporeal membrane oxygenation (ECMO) may provide life-saving support in RSV infected infants in whom conventional mechanical ventilation was believed to have failed [25–27]. It is not possible to determine whether ECMO improved the survival rate for these patients which was 50% in two and 96% in one of the studies. The total number of infants in each study was small, and it remains unclear from the reports whether these infants suffered from restrictive or obstructive pulmonary disease before going on ECMO support. However, there is evidence that RSV-induced respiratory failure represents a relatively benign cause of ARDS in infants [14]. Novel therapies for RSV-induced respiratory failure should, therefore, be reserved to infants in whom conventional therapy has truly failed.

Bronchodilators

Whether infants with acute bronchiolitis should be treated with nebulized salbutamol or other β_2-adrenergic drugs has been debated for more than 20 years. In North America, nebulized salbutamol is used as standard treatment for acute bronchiolitis [28], whereas in Great Britain pediatricians seldom prescribe this drug [29]. Histologically, airway obstruction in acute RSV bronchiolitis is mainly a result of mucus plugs and cellular debris from bronchial inflammation and epithelial necrosis. The contribution of airway smooth muscle constriction (which is treatable) to the airway obstruction is minor in most cases.

Inconsistent results obtained from spontaneously breathing infants, usually in the recovery phase of illness, have fueled the controversy regarding the usefulness of

inhaled bronchodilators in infants in the acute phase of RSV bronchiolitis. Some studies have shown improvements [30–35] in clinical scores and/or lung function, and others found no [36–41] or even adverse [42–44] effects. In most studies, the lung function measurements were done well after the time of severe acute respiratory compromise, during the recovery phase of the disease, because of the need for sedation which could have imperiled sicker, spontaneously breathing infants. Only a few research groups employed methods capable of assessing small airway function. Nevertheless, it is in the acute phase of bronchiolitis that bronchodilators are most frequently applied and would have the greatest potential for benefit.

Recently, we [13] examined the bronchodilator effect of inhaled salbutamol in the acute stage of severe RSV infection in previously healthy children requiring mechanically assisted ventilation in a prospective, non-randomized clinical trial. We found that inhaled salbutamol did not improve respiratory system resistance, small airway function and air trapping in half of our study patients with obstructive disease, and in all infants with restrictive disease. It is difficult to assess the clinical impact of salbutamol treatment on the course of the disease in the other half of infants who demonstrated a bronchodilator response. Although these patients responded with a modest degree of bronchodilatation, in our experience it was small compared with the response usually obtained in asthma (Fig. 5).

There is evidence that combined β- and α-agonists (e.g. epinephrine) are more effective in bronchiolitis than selective β_2-agonists, because of their additional vasoconstrictor effect which decreases bronchial mucosal edema and hence airflow obstruction [45 l . However, one consideration is that all these drugs increase total body oxygen consumption (and hence energy requirement), partly by their direct effect on other organs through β-receptor stimulation, and also indirectly by stimulating minute ventilation and thereby increasing the oxygen costs of breathing in those with respiratory compromise [46]. The potential to increase energy requirements conceivably could cause a longer requirement for assisted ventilation, especially if bronchodilatation is minimal or does not occur. Salbutamol can also worsen

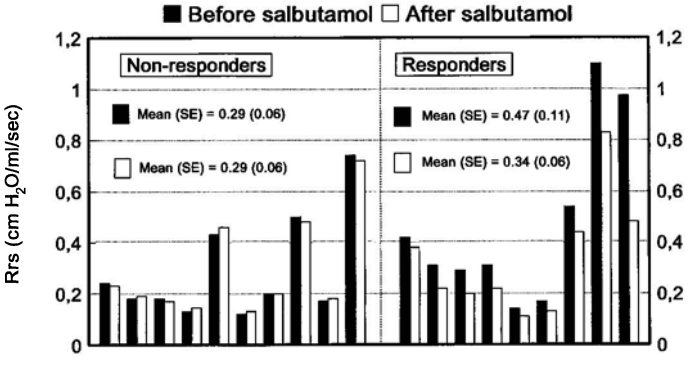

Fig 5. Total respiratory system resistance (Rrs) before and after salbutamol in 19 previously well infants with RSV-induced respiratory failure. 10 infants showed no significant improvement, while 9 infants responded with a statistically significant reduction in Rrs (defined as a change of more than twice the coefficient of variation for repeated baseline measurements. (From [13] with permission)

arterial hypoxemia in already compromised infants on the basis of vasodilatation preceding bronchodilatation, thus worsening ventilation-perfusion mismatch [42, 47].

Bronchodilators require a therapeutic trial to determine their efficacy. In the absence of pulmonary function testing, a clinical response can be assessed in ventilated infants by an increase in arterial oxygen saturation or tension, a decrease in end-tidal or arterial carbon dioxide tension, or an increase in tidal volume or peak inspiratory pressure depending on the ventilation mode. The regular and uncritical use of nebulized bronchodilators in all infants is not recommended.

Nitric Oxide

Inhaled nitric oxide (NO) has become widely used as a selective pulmonary vasodilator in neonatal and pediatric intensive care. Potential beneficial effects of inhaled NO therapy for severe hypoxemic RSV-induced respiratory failure include lowering of pulmonary vascular resistance and subsequent improvement of cardiac function which may decrease pulmonary edema formation. However, there are other physiologic roles for NO in the lung such that both beneficial and detrimental effects could be expected from its administration to RSV-infected infants. Endogenous NO produced by the neuronal NO synthase (NOS) in non-adrenergic, non-cholinergic (NANC) nerves relaxes airway smooth muscles. It is therefore logical to expect that inhaled NO might prove to be a potent bronchodilator. This could be beneficial to infants with obstructive RSV disease. Conversely, NO released from endothelial and inducible NOS dilates bronchial vessels, and increases plasma leakage, mucus secretion and the inflammatory response. Potentially, such effects could aggravate ventilation/perfusion mismatch and further compromise the respiratory status.

We have recently compared the bronchodilator effect of different doses of inhaled NO (20, 40 and 60 ppm) with salbutamol in ventilated infants with obstructive RSV disease [48]. We found that NO produced a significant improvement of the respiratory resistance in only 30% of the infants, whereas salbutamol caused a significant bronchodilatation in 50% of the infants tested. All infants that responded to inhaled NO also responded to the administration of salbutamol. It is noteworthy that the bronchodilator effect of NO was dose-independent and less than that of salbutamol. Our preliminary results suggest that inhaled NO does not provide any additional benefit over the use of salbutamol to improve small airway function in infants with severe obstructive RSV disease.

The use of inhaled NO is currently also under investigation to determine its physiologic effects on oxygenation and hemodynamics in infants with severe hypoxemic respiratory failure. Abman et al. [49] have recently reported improved gas exchange and hemodynamics in 6 infants with RSV-induced hypoxemic respiratory failure. Five of the 6 infants were also suffering from bronchopulmonary dysplasia and all had acute lung injury scores >3, PEEP >5 cmH_2O, and PaO_2 <85 mmHg despite FiO_2 >0.60. Fulfilling these criteria should classify them as ARDS. Unfortunately, it is still unclear whether these infants suffered from acute restrictive disease superimposed on chronic obstructive disease or was merely a worsening of the latter.

From current experience, it seems that inhaled NO may be helpful in selected infants suffering from severe RSV-induced respiratory failure [50, 51], mainly by acting as a pulmonary vasodilator in those with preexisting pulmonary hypertension (e.g. bronchopulmonary dysplasia).

Steroids

The rationale for using corticosteroids in bronchiolitis is its pathophysiological similarity with asthma. However, there are no data to support the use of systemic corticosteroids in the treatment of RSV bronchiolitis, since the majority of studies have failed to show a beneficial effect on the disease course. Most recently, Roosevelt et al. [52] designcd a randomized, double-blind, prospective study and demonstrated that intramuscular dexamethasone had no effect on the duration of O_2 therapy or time to resolution of symptoms in infants with bronchiolitis requiring hospital management [52]. Nevertheless, in many centers, corticosteroids are used for the treatment of acute bronchiolitis. In Canada, the corticosteroid use varied from 6 to 69% among tertiary care centers for inpatient hospital management of infants with no identifiable risk factors [53]. In our own retrospective review [5], we found that the use of steroids in our PICU was confined to the treatment of high risk infants, mainly those with bronchopulmonary dysplasia.

No previous study has examined prospectively the therapeutic value of steroids in those infants who require intubation and assisted ventilation for RSV-induced respiratory failure. The lack of evidence supporting use of steroids in the mildly to moderately afflicted infant would argue for a very judicious approach in ventilated infants, especially during the acute phase of the disease. Corticosteroids are not indicated in uncomplicated bronchiolitis in otherwise normal infants. However, a short-term trial of systemic corticosteroids may he justified in infants with persisting, severe bronchospasm following the acute phase of the disease. Infants with chronic lung disease with an associated high likelihood of bronchial hyperreactivity, such as bronchopulmonary dysplasia, may also benefit from steroid therapy. Further research is needed to document the efficacy of inhaled or systemic steroids in selected infants with severe RSV infection.

Ribavirin

Ribavirin is a nucleotide analog resembling guanosine that interferes with viral protein synthesis. It was introduced in the early 1980's for use in hospitalized children with Severe RSV infection. Early clinical studies of ribavirin in children with mild-to-moderate lower respiratory tract disease demonstrated improvement in severity of illness and O_2 saturation [54–57]. Severely ill infants requiring mechanical ventilation for RSV infection were long excluded from randomization and aggressively treated with the aerosolized drug in the United States.

A randomized, water-placebo-controlled trial in infants requiring mechanical ventilation demonstrated a significant reduction in the number of days of ventilation, hospital stay, and cost per patient [58]. However, the validity of these results

were questioned because aerosolized water has been demonstrated to have adverse effects when administered to infants with reactive airways disease. In addition, the study outcome was not supported by the general clinical experience with ribavirin in PICUs [5, 59], nor by the length of mechanical ventilation which, although much shorter than for their controls, was similar to that reported by other groups without the use of ribavirin (Table 3). Subsequently, Meert et al. [60] used a control aerosol of isotonic saline instead of water and found no reduction in mechanical ventilation days and hospital stay with ribavirin use. This was recently confirmed in a large multicenter trial in previously well infants with severe RSV infection [61].

These results and the high cost of ribavirin therapy prompted the Committee on Infectious Disease of the American Academy of Pediatrics to change recommendations from the previous "should be used" to "may be considered" in infants with underlying risk factors or severe disease [62]. The low mortality of RSV infections suggests the use of expensive therapy with questionable efficacy should be reserved for selected clinical situations. It remains unclear if certain patients, in particular the immunocompromised infants, may benefit from ribavirin therapy.

Conclusion

There are two different, distinctive patterns of lower respiratory tract disease (obstructive versus restrictive) in infants with RSV-induced respiratory failure with characteristic lung function changes and clinical features (Table 4). Intensive care management and ventilation strategy depend on the underlying pathophysiology. The early initiation of ventilation in those infants with severe respiratory distress prevents any of the serious sequelae patients may suffer during prolonged periods of respiratory arrest. Mortality rates for previously healthy infants with RSV infection are extremely low. Mortality rates in patients with preexisting cardiopulmonary disease or immunologic disease may be somewhat higher, but in congenital heart disease less than 8% [63], rather than the 30–37% mortality reported by Hall et al. [561 in 1985. There is evidence that the mortality rate for infants with RSV-induced ARDS is lower than the overall mortality rate reported in clinical and epidemiological studies of pediatric patients with ARDS where causative factors were amalgamated

Table 4. Presentation of severe RSV-induced respiratory failure

	Bronchiolitis	Pneumonia
Radiographic appearance	Hyperinflation/Atelectasis	Alveolar consolidation
Lung function	Obstructive airways disease + moderate restrictive	Restrictive lung disease + mild obstructive
$(A\text{-}a)O_2$ gradient	< 350 torr	> 350 torr
PaO_2/FiO_2	< 200	> 200
Population	70%	30%
Tasker et al. [15]	28/39 patients (no deaths)	11/39 patients (1 death)
Hammer et al [14]	27/37 patients (no deaths)	10/37 patients (1 death)

A: alveolar, *a:* arterial, PaO_2: arterial oxygen pressure, FiO_2: inspired oxygen fraction

[64, 65]. Further studies are needed to demonstrate a clinical benefit of novel therapies such as inhaled nitric oxide, high frequency oscillatory ventilation and ECMO therapy for the rare infant failing modern conventional ventilatory management. Definitely, the most benefit would come from preventive measures of RSV infection such as a vaccination.

References

1. La Via WV, Marks KI, Stutman HR (1992) Respiratory syncytial virus puzzle: Clinical features, pathophysiology, treatment and prevention. J Pediatr 121:503–510
2. Glezen WP, Denny FW (1973) Epidemiology of acute lower respiratory disease in children. N Engl J Med 288:498–505
3. Henderson FW, Clyde WA Jr, Collier AM, et al (1979) The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. J Pediatr 95:183–190
4. Cradock-Watson JE, McQuillin J, Gardner PS (1970) Rapid diagnosis of respiratory syncytial virus infection in children by the immunofluorescent technique. J Clin Pathol 24:308–312
5. Stratton M, Ajizian SJ, Mitchell I, Newth CJL (1992) Intensive care course and outcome of patients infected with respiratory syncytial virus. Pediatr Pulmonol 13:143–150
6. Groothuis JR, Gutierrez KM, Lauer BA (1988) Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. Pediatrics 82:199–203
7. Meert K, Heidemann S, Lieh-Lai M, Sarnaik AP (1989) Clinical characteristics of respiratory syncytial virus infections in healthy versus previously compromised hosts. Pediatr Pulmonol 7:167–170
8. Hall CB, Powell KR, MacDonald NE, et al (1986) Respiratory syncytial viral infection in children with compromised immune function. N Engl J Med 315:77–81
9. Krasinksi K (1985) Severe respiratory syncytial virus infection: Clinical features, nosocomial acquisition and outcome. Pediatr Infect Dis 4:250–257
10. Moler FW, Khan AS, Meliones JN, Custer JR, Palmisano J, Shope TC (1992) Respiratory syncytial virus morbidity and mortality estimates in congenital heart disease patients: A recent experience. Crit Care Med 20:1406–1413
11. Navas L, Wang E, De Carvalho V, Robinson J, and the Pediatric Investigators Collaborative Network on Infections in Canada (1992) Improved outcome of respiratory syncytial virus infection in a high risk hospitalized population of Canadian children. J Pediatr 121:348–354
12. Hammer J, Newth CJL (1995) Infant pulmonary function testing in the Intensive Care Unit. Intensive Care Med 21:744–752
13. Hammer J, Numa A, Newth CJL (1995) Albuterol responsiveness in infants with respiratory failure due to RSV infection. J Pediatr 127:485–490
14. Hammer J, Numa A, Newth CJL (1996) ARDS triggered by RSV infection in infants. Intensive Care Med 22:S168 (Abst)
15. Tasker RC, Kiff K, Gordon I (1996) Severe respiratory syncytial virus-associatcd respiratory failure: Patterns of lower respiratory tract disease in young infants. Intensive Care Med 22:S184 (Abst)
16. Bernard GR, Artigas A, Brigham KL, et al (1994) The American-European Consensus Conference on ARDS. Definition, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824
17. Murray JF, Matthay MA, Luce JM, Flick MR (1988) An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 138:720–723
18. Stretton M, Deakers TW, Newth CJL (1992) Spirometry, lung mechanics and volumes during the acute phase of ARDS in pediatric patients. Am Rev Respir Dis 143:A248 (Abst)
19. Suter PM (1985) Assessment of respiratory mechanics in ARDS. In: Zapol WM, Falke K (eds) Acute respiratory failure. Marcel Dekker, New York, pp 507–519
20. Gattinoni L, Bombino M, Pelosi P, et al (1994) Lung structure and function in different stages of severe acute respiratory distress syndrome. JAMA 271:1772–1779
21. Gozal D, Colin AA, Jaffe M, et al (1990) Water, electrolyte, and endocrine hemostasis in infants with bronchiolitis. Pediatr Res 27:204–209

22. Deakers TW, Reynolds G, Stretton M, Newth CJL (1994) Cuffed endotracheal tubes in pediatric intensive care. J Pediatr 125:57–62
23. Outwater KM, Crone RK (1984) Management of respiratory failure in infants with acute viral bronchiolitis. Am J Dis Child 138:1071–1075
24. Lebel MH, Gauthier M, Lacroix J, Rousseau E, Buithieu M (1989) Respiratory failure and mechanical ventilation in severe bronchiolitis. Arch Dis Child 64:1431–1437
25. Moler FW, Palmisano JM, Green TP, Custer JR (1993) Predictors of outcome of severe respiratory syncytial virus-associated respiratory failure treated with extracorporeal membrane oxygenation. J Pediatr 123:46–52
26. Steinhorn RH, Green TP (1990) Use of extracorporeal membrane oxygenation in the treatment of respiratory syncytial virus bronchiolitis: The national experience, 1983 to 1988. J Pediatr 116:338–342
27. Khan JY, Kerr SJ, Tometzki A, et al (1995) Role of ECMO in the treatment of respiratory syncytial virus bronchiolitis: A collaborative report. Arch Dis Child 73:F91–F94
28. Newcomb RW (1989) Use of adrenergic bronchodilators by pediatric allergists and pulmonologists. Am J Dis Child 143:481–485
29. Goodman TB, Chambers TL (1993) Bronchodilators for bronchiolitis. Lancet 341:1380
30. Schuh S, Canny G, Resiman JJ, et al (1990) Nebulized albuterol in acute bronchiolitis. J Pediatr 117:633–637
31. Klassen TP, Rowe PC, Sutcliffe T, Ross LJ, McDowell IW, Li MM (1991) Randomized trial of salbutamol in acute bronchiolitis. J Pediatr 118:807–811
32. Alario AJ, Lewander WJ, Dennehy P, Seifer R, Mansell AL (1992) The efficacy of nebulized metaproterenol in wheezing infants and young children. Am J Dis Child 146:412–418
33. Soto ME, Sly PD, Uren E, Taussig LM, Landau LI (1985) Bronchodilator response during acute viral bronchiolitis in infancy. Pediatr Pulmonol 2:85–90
34. Tepper RS, Rosenberg D, Eigen H, Reister T (1994) Bronchodilator responsiveness in infants with bronchiolitis. Pediatr Pulmonol 17:81–85
35. Tal A, Sanchez I, Pasterkamp H (1991) Respirosonography in infants with acute bronchiolitis. Am J Dis Child 145:1405–1410
36. Sly PD, Lanteri CJ, Raven JM (1991) Do wheezy infants recovering from bronchiolitis respond to salbutamol? Pediatr Pulmonol 10:36–39
37. Wang EEL, Milner R, Allen U, Maj H (1992) Bronchodilators for treatment of mild bronchiolitis: A factorial randomized trial. Arch Dis Child 67:289–293
38. Sanchez I, De Koster J, Powell RE, Wolstein R, Chernick V (1993) Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with bronchiolitis. J Pediatr 122:145–151
39. Hughes DM, LeSouëf PN, Landau LI (1987) Effect of salbutamol on respiratory mechanics in bronchiolitis. Pediatr Res 22:83–86
40. Stokes GM, Milner AD, Hodges GC, Henry RL, Elphick MC (1983) Nebulised therapy in acute severe bronchiolitis in infancy. Arch Dis Child 58:279–283
41. Rutter N, Milner AD, Hiller EJ (1975) Effect of bronchodilators on respiratory resistance in infants and young children with bronchiolitis and wheezing bronchitis. Arch Dis Child 50:719–722
42. Ho L, Collis G, Landau LI, LeSouëf PN (1991) Effect of salbutamol on oxygen saturation on bronchiolitis. Arch Dis Child 66:1061–1064
43. Prendiville A, Green A, Silverman M (1987) Paradoxical response to nebulised salbutamol in wheezy infants, assessed by partial expiratory flow-volume curves. Thorax 42:86–91
44. O'Callaghan C, Milner AD, Swarbrick A (1986) Paradoxical deterioration in lung function after nebulised salbutamol in wheezy infants. Lancet 2:1424–1425
45. Sanchez I, De Koster J, Powell RE, Wolstein R, Chernick V (1993) Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with bronchiolitis. J Pediatr 122:145–151
46. Newth CJL, Amsler B, Anderson GP, Morley J (1991) The ventilatory and oxygen costs in the anesthetized rhesus monkey of inhaling drugs used in the therapy and diagnosis of asthma. Am Rev Respir Dis 143:766–771
47. Tal A, Pasterkamp H, Leahy F (1984) Arterial oxygen desaturation following salbutamol inhalation in acute asthma. Chest 86:868–869

48. Patel NR, Nichani S, Hammer J, Numa A, Newth CJL (1996) The effect of inhaled nitric oxide on respiratory mechanics in intubated infants with severe RSV bronchiolitis. Am J Respir Crit Care Med 153:A502 (Abst)
49. Abman SH, Griebel JL, Parker DK, Schmidt JM, Swanton D, Kinsella JP (1994) Acute effects of inhaled nitric oxide in children with severe hypoxemic respiratory failure. J Pediatr 124:881–888
50. Leclerc F, Riou Y, Martinot A, et al (1994) Inhaled nitric oxide for a severe respiratory syncytial virus infection in an infant with bronchopulmonary dysplasia. Intensive Care Med 20:511–512
51. Thompson MW, Bates JN, Klein JM (1995) Treatment of respiratory failure in an infant with bronchopulmonary dysplasia with respiratory syncytial virus using inhaled nitric oxide and high frequency ventilation. Acta Paediatr 84:100–102
52. Roosevelt G, Sheehan K, Grupp-Phelan J, Tanz RR, Listernick R (1996) Dexamethasone in bronchiolitis: A randomized, controlled trial. Lancet 348:292–295
53. Law BJ, De Carvalho V and the Pediatric Investigators Collaborative Network on Infections in Canada (1993) Respiratory syncytial virus infections in hospitalized Canadian children: Regional differences in patient populations and management practices. Pediatr Infect Dis J 12:659– 663
54. Hall CB, McBride JT, Walsh EE, et al (1983) Aerosolized ribavirin treatment of infants with respiratory syncytial virus infection. N Engl J Med 308:1443–1447
55. Taber LH, Knight V, Gilbert BE, et al (1983) Ribavirin aerosol treatment of bronchiolitis associated with respiratory syncytial virus infection in infants. Pediatrics 72:613–618
56. Hall CB, McBride JT, Gala CL, Hildreth SW, Schnabel KC (1985) Ribavirin treatment of respiratory syncytial viral infection in infants with underlying cardiopulmonary disease. JAMA 254: 3047–3051
57. Groothuis JR, Woodlin KA, Katz R, et al (1990) Early ribavirin treatment of respiratory syncytial viral infection in high risk children. J Pediatr 117:792–798
58. Smith DW, Frankel LR, Mathers LH, Tang ATS, Ariagno RL, Prober CG (1991) A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. N Engl J Med 325:24–29
59. Mitchell I, Joffe A, Newth CJL (1996) Ribavirin: Red Book Committee recommendations questioned (letter). Pediatrics 95:319–320
60. Meert KL, Sarnaik AP, Gelmini MJ, Lieh-Lai MW (1994) Aerosolized ribavirin in mechanically ventilated children with respiratory syncytial virus lower respiratory tract disease: A prospective, double-blind, randomized trial. Crit Care Med 22:566–572
61. Moler FW, Steinhart CM, Ohmit SE, Stidham GL, and the Pediatric Critical Care Study Group (1996) Effectiveness of ribavirin in otherwise well infants with respiratory syncytial virus-associated respiratory failure. J Pediatr 128:422–428
62. American Academy of Pediatrics (1996) Reassessment of the indications for ribavirin therapy in respiratory syncytial virus infection. Pediatrics 97:137–140
63. Moler FW, Khan AS, Meliones JN, Custer JR, Palmisano J, Shope TC (1991) Respiratory syncytial virus morbidity and mortality estimates in congenital heart disease patients: A recent experience. Crit Care Med 20 :1406–1413
64. Timmons OD, Havnes PL, Fackler JC (1995) Predicting death in pediatric patients with acute respiratory failure. Pediatric Critical Care Study Group. Extracorporeal Life Support Organization. Chest 108:789–797
65. Davis SL, Fuhrman DP, Costarino AT (1993) Adult respiratory distress syndrome in children: Associated disease, clinical course, and predictors of death. J Pediatr 123:35–45