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Bronchiolitis

Origins and Optimal Management

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Summary

There is currently no prospect of an end to the annual epidemics of acute bronchiolitis, which cause considerable morbidity in previously healthy infants and are a major threat to the well-being of infants with underlying cardiac, respiratory or immunological disease. The respiratory syncytial virus remains the major cause of this condition, and prospects of developing a vaccine remain bleak while our understanding of the viral-host interaction remain incomplete.

Treatment of patients with this condition has remained essentially unchanged for more than 30 years. Correction of hypoxia with oxygen, minimal handling to reduce the risk of exhaustion and careful noninvasive monitoring for complications such as apnoea and respiratory failure are the mainstays of management. Mortality in at-risk groups has fallen substantially during the past 10 years. This appears to be due to improved supportive and intensive care. The role of the antiviral agent ribavirin in the improved outcome, if any, is unclear. Other novel therapies have been tried, but none have been shown to significantly alter the natural history of the condition.

The only effective preventive intervention currently available is strict adher-

ence to measures designed to prevent nosocomial infection. This condition is likely to remain a continuing challenge to paediatricians for the foreseeable future.

1. Overview and Definition

The clinical syndrome of acute bronchiolitis is the most common form of lower respiratory tract infection in infancy, with 0.5 to 2% of all infants being admitted to hospital with this condition during the winter following their birth.[1,2] Each winter, during the annual epidemics of respiratory syncytial virus (RSV) infection, paediatric wards are inundated by large numbers of infants with moderate to severe acute bronchiolitis, placing great strains on hospital services.[3] Despite the considerable morbidity associated with the condition and the financial implications of the annual epidemics, there is currently no immediate prospect of preventing them. Surprisingly, despite the frequency and importance of acute bronchiolitis, there are still a number of controversies surrounding the diagnosis and optimal management of this condition.

Many of the controversies regarding management stem from differences in defining the condition. In this article, the clinical entity of acute bronchiolitis is restricted to patients with the following clinical pattern. Initially, infants develop upper respiratory tract symptoms with coryza and cough, followed 2 to 3 days later by lower respiratory tract symptoms. The onset of lower respiratory symptoms is frequently acute, and at presentation the infant is dyspnoeic with a moist, irritating cough. Difficulty feeding and agitation due to hypoxia are common. Wheeze may be present. Tachypnoea, hyperinflation of the chest with downwards displacement of the liver and subcostal recession are typically present. Auscultation reveals widespread crepitations often, but not universally, accompanied by rhonchi.

Limiting the term acute bronchiolitis to patients who fit this pattern, as is the case in the UK, Australia and parts of Europe,[4,5,6] has certain implications for optimal management and may well be important in unravelling the underlying mechanisms. Factors which tend to support the concept that acute bronchiolitis is a distinct clinical entity include the observations that, when using this clinical definition, well over 80% of such cases are caused by RSV;[6,7] atopy does not appear to be a significant risk factor for the acute illness[7-10] and subsequent recurrent respiratory symptoms tend to disappear in early childhood.[9]

In much of North America and parts of Europe, the term bronchiolitis is applied to all infants with expiratory wheeze with evidence of respiratory viral infection such as rhinorrhoea and cough.[11,12] This would include many infants excluded by the above definition and exclude others who would be included. This difference in definition accounts for many of the differences in management observed around the world and is discussed later.

Most episodes of acute respiratory distress in infancy are induced by viruses, and a number of clinical patterns can be associated with these respiratory viral infections. The viruses may induce wheeze in those with atopic asthma or 'wheezy bronchitis', or cause acute bronchiolitis or, less commonly, pneumonia. There is increasing evidence that these are distinct entities which differ in their natural history,[13,14] and probably vary in their response to various therapies.

The similarities in clinical manifestations exhibited by infants who develop any one of these clinical entities may simply be due to the limited repertoire of airway responses. Inflammation within the airways can induce airways obstruction due to secretion of mucus, exudation into airways, mucosal oedema and varying degrees of bronchospasm, irrespective of the underlying immunological process. To include all episodes of acute airways obstruction in which wheeze is associated with an apparent respiratory infection under the same heading of 'bronchiolitis' or 'wheeze associated viral infection' is likely to hinder rather than aid our understanding of these conditions.

1.1 Differential Diagnosis

In the vast majority of infants admitted with the clinical syndrome described above, the causative organism will be RSV. Indeed, some argue that the definition of bronchiolitis should be confined to those with the typical clinical features and evidence of RSV infection.[15] However, it is generally accepted that the same clinical picture can be produced by other viruses including parainfluenza, influenza, adeno- and rhinoviruses. If the illness is severe, unusually prolonged or otherwise atypical it is important to consider other primary diagnoses or associated conditions that may be contributing to the severity of the illness. These would include cystic fibrosis, aspiration, congenital lung abnormalities, chlamydia infection, immunodeficiencies and congenital heart disease, all of which can manifest with many of the features characteristic of acute bronchiolitis.

2. Origins

As noted above, the vast majority of cases are due to RSV. RSV causes annual epidemics[3,16,17] of respiratory disease affecting individuals of all ages.[18,19] It is this ability to infect large segments of the population each winter that is probably the principal reason for the annual influx of infants with bronchiolitis. It is clear that despite recurrent infections, adults develop only transient, partial immunity following infection.[18,19] Consequently, passively acquired protection in infants is generally poor. Most infants will be infected by the virus during their first winter and almost all infants who have lived through 2 annual outbreaks will have been infected by the virus.[12] Of these, most will only develop upper respiratory tract symptoms. A much smaller number will develop mild lower respiratory symptoms and only 1 to 2% will develop moderate to severe bronchiolitis requiring admission.

Individuals are infected regularly throughout life.[18] Consequently, enormous numbers are infected each year. Despite more than 25 years of research, it is still not known how the virus manages to be so successful. There are 2 major groups of RSV, A and B, and these are subdivided into 6 and 3 subgroups, respectively.[20,21] During an epidemic, both groups A and B tend to co-circulate[22] and this heterogeneity may contribute to the annual outbreaks. However, infection with a single strain results in only partial protection against reinfection with the same strain, and this is of short duration.[23] Indeed, half of all adults infected with a single strain will become reinfected within 2 months if rechallenged with the same strain. Hence, the virus appears to have developed strategies by which it prevents the induction of significant protective immunity. It remains far from clear how this is achieved but aspects of the virus host interactions have been discussed in a number of recent reviews.[12,24]

Factors that may be relevant are its ability to infect macrophages and lymphocytes; impairment of interferon production; the induction of interleukin (IL)-1 inhibitors and suppression of intracellular adhesion molecule-1 (ICAM-1) and lymphocyte function–associated antigen-1 (LFA-1). Recent work has suggested that infected macrophages do indeed produce interferon-α (IFNα), and that it is this that has a suppressive effect on T cell proliferation (M. Preston, personal communication). Which, if any, of these proves to be central to the immunosuppression is unclear.

Equally puzzling is why a small proportion of infants infected with the virus should develop acute bronchiolitis. More than 20 years ago workers proposed that specific immunopathological mechanisms were operating in those infants with acute bronchiolitis.[25] A number of hypotheses have been advanced since then.[12,24] These have included that it was caused by an immune-complex process; that it was due to relative deficiency of passively acquired IgG_3; that an RSV-specific IgE response was implicated, and that excessive cytotoxic T cell activity or excessive CD4+ T cell activity is responsible. There is, however, little evidence that the immunological process in the airways of infants with acute bronchiolitis is dif-

ferent from that in the airways of those with upper respiratory tract symptoms only.

It is quite possible that extension of inflammation from the upper to the lower respiratory tract is either a matter of chance or reflects relatively lower levels of protection. Postmortem examination of a small number of infants dying due to RSV infection showed mononuclear cell infiltrates.[26] However, recent work suggests that the dominant inflammatory cell in the airways during all types of RSV infection is the neutrophil and that it is this cell, rather than lymphocytes or mast cells, that is probably responsible for much of the pathology associated with this condition.[27,28]

Neutrophils have previously been implicated in the causation of symptoms in rhinovirus upper respiratory tract infections.[29] These cells release potent stimuli for mucus secretion and will damage respiratory epithelium, so contributing to mucosal oedema and exudation into the airways. The poor response of neutrophils to chemotactic factors in the first month of life[30,31] may explain why bronchiolitis is rare in this age group. RSV infections do occur in these very young infants and can be severe or even fatal,[32] but more often the infection is subclinical, results in nonspecific symptoms or causes apnoea.[32-35]

3. Assessment

At present there is no way of predicting which infants presenting with an upper respiratory tract infection will progress to acute bronchiolitis. However, there are certain groups of children at risk of severe disease should they develop bronchiolitis. In previously healthy infants, the peak incidence of admissions is in those aged 1 to 4 months.[36,37] This is probably due to the low incidence of the condition in younger infants and relatively mild disease in older children, possibly due to growth in the airways. For those admitted to hospital, the severity as judged by the degree of hypoxia,[38] duration of admission[38,39] and the need for ventilation[38,40,41] is increased in younger and smaller infants.

Certain infants are at increased risk of severe disease which may lead to respiratory failure requiring ventilatory support and, in a small proportion, death. These include those with congenital cardiac disease, particularly those with pulmonary hypertension, chronic lung disease with oxygen dependence, immunodeficiencies, cystic fibrosis and those born prematurely.[42-44]

During RSV respiratory infections, the 2 most serious complications are respiratory failure and apnoea. Apnoea is most common in the youngest patients, those born preterm[34,43,45] and those with chronic lung disease.[45] Infants may present with apnoeas and progress to bronchiolitis, show signs of bronchiolitis and develop apnoeas, or have apnoea as the sole sign of RSV infection. RSV infection has been implicated in a number of cases of 'cot death',[46-48] and its ability to precipitate apnoea may be relevant to this observation. A large proportion of infants with RSV infection requiring assisted ventilation do so because of severe recurrent apnoeas rather than respiratory failure.[43] The use of apnoea monitors is therefore important in young infants, those born preterm and those with pre-existing lung disease.

It is well recognised that the clinical assessment of hypoxia is poor.[39,49] Perhaps the most reliable clinical sign is agitation which, if not relieved by supplemental oxygen, can contribute to exhaustion and respiratory failure. Hypercapnia is uncommon in all but the most severely affected infants[39] and hence, with the widespread use of pulse oximetry, blood gas monitoring is rarely required unless mechanical ventilation is being considered. Though these monitors have certain limitations, they play a central role in the assessment of hypoxia and subsequent management of oxygen therapy. Two recent studies found that an infant's oxygen saturation, as judged by pulse oximetry, was the best objective predictor of disease severity.[50,51]

Decisions regarding hospital admission are therefore based upon age, risk factors, clinical assessment and oxygen saturation.

4. Investigations

The most useful investigation is confirmation of RSV or other respiratory viruses using immunofluorescent antibody methods or enzyme-linked immunoabsorbant assays (ELISA).[52,53] Reliable commercial kits are now readily available and widely used. Nasopharyngeal aspirates generally provide suitable samples containing a relatively high yield of virus. A positive result is valuable in supporting the diagnosis and in isolating infants with the virus. However, it should be remembered that all these methods require good quality samples, and a negative result does not exclude RSV infection.

No other investigations are required routinely. Chest x-rays are commonly requested, though there is no evidence that they are of any value in most infants admitted with this condition. The chest radiograph typically shows evidence of hyperinflation and not infrequently demonstrates evidence of collapse/consolidation, especially in the right upper lobe. A recent study found no correlation between the changes on chest x-ray and clinical severity, leading the authors to suggest that this investigation should be limited to those in whom intensive care was being considered, in those who deteriorate unexpectedly and in those with an underlying cardiac or pulmonary disorder.[54]

Because secondary bacterial infection is uncommon in RSV bronchiolitis,[55,56] patchy changes on x-ray are not an indication to use antibiotics in patients with a typical clinical picture and, hence, x-rays seldom alter management.

Electrolyte disturbances are rare except in the most severely ill babies, and there is no indication for the routine assessment of serum electrolytes or full blood counts.

5. Treatment

Careful monitoring and good supportive care remain the cornerstones of management. For those without an underlying immunodeficiency, RSV infections are self-limiting, and management is aimed at providing adequate support until the illness resolves. Monitoring is principally directed towards the detection of apnoea, hypoxia and exhaustion. Supportive care is directed at alleviating hypoxia, providing adequate fluids and preventing exhaustion by relieving hypoxia and minimal handling.

5.1 Oxygen

In the early 1960s, Reynolds and Cook noted that 'oxygen is vitally important in bronchiolitis and there is little evidence that any other treatment is useful'.[57] This is essentially true today. Hypoxia due to ventilation/perfusion mismatching is frequent[39,58] though, as noted above, it is difficult to detect clinically. 30 to 40% warmed and humidified oxygen, delivered via a head box, is sufficient to correct the hypoxia in most cases and rapidly relieves the distress and agitation observed in hypoxic infants.

5.2 Fluids

If uncorrected, the poor intake of fluid due to the respiratory distress and cough can lead to dehydration. This tendency may be compounded by vomiting associated with the bouts of coughing. Hyponatraemia due to inappropriate antidiuretic hormone secretion can occur,[59] usually in the sickest infants and, hence, it is sensible to restrict fluids to about two-thirds of maintenance.

The route of administration varies between units. Some argue that the risks and disadvantages associated with nasogastric feeding are such that any infant requiring supplemental oxygen requires intravenous fluids. The potential problems include increased work of breathing due to obstruction of the upper airway, increased work of breathing due to fluid within the stomach and an increased risk of gastro-oesophageal reflux and aspiration.[60] Other units find that those with mild to moderate illness tolerate a nasogastric tube very well and appear more comfortable with frequent small volume feeds.[61] However, infants will occasionally suddenly deteriorate, apparently due to aspiration and, hence, intravenous fluids are recommended in those more severely affected.

5.3 Ribavirin

Ribavirin is a broad spectrum virustatic drug first synthesised in 1972. Its exact mode of action is unclear. Since the initial enthusiasm that greeted its launch in 1986, concerns have been raised about its cost, safety and efficacy. The drug is administered as an aerosol generated by a small particle aerosol generator (SPAG). The aerosol is usually delivered into a head box for 12 to 18 hours a day, though a recent small study has used higher doses administered for 2 hours 3 times daily.[62] It can be used in ventilator circuits though great care must be taken to prevent valves blocking due to drug crystallising out on them.[63]

Concerns regarding its safety in both treated infants and those caring for them have been expressed since it was first used, but reported adverse effects in patients and their carers are uncommon. In infants, these have been mainly skin rashes and mild bronchospasm.[64] Ribavirin is apparently not incorporated into host cell RNA or DNA, so the potential for unexpected long term adverse effects is believed to be low.

Though the quantities of ribavirin absorbed by hospital personnel appear to be low, concerns regarding possible teratogenic effects have led some units to use stringent precautions to prevent environmental contamination.[65] The risk to hospital personnel appears low provided that simple precautions are taken to minimise exposure, and that pregnant women are not exposed to the aerosol.[42,66]

More contentious is its role in the management of infants with acute bronchiolitis. The results of early studies led some authors to conclude that its role in treating all but the mildest cases was established beyond doubt, and that further studies would be unethical.[67] These studies did not, however, show any impact on parameters such as duration of stay or need for intubation, and they were heavily criticised for a number of reasons.[68-70] Six years later there is still no convincing evidence that ribavirin has any role in the treatment of the vast majority of previously healthy infants.

The American Academy of Pediatrics initially recommended that the use of ribavirin should be 'considered' in those infants at high risk of severe disease (such as those with cardiac disease, chronic lung disease or cystic fibrosis, or those with an immunodeficiency), in severely ill infants or in premature infants.[42] They have subsequently gone further and recommended that it be used for all hospitalised 'at risk' patients and in those who are severely ill, which includes all those with saturations of <90% (presumably in air).[71] These recommendations have again been criticised,[72] and there is still much controversy surrounding the use of the drug for treating such patients. Many centres in the UK and Australia would agree with these criticisms and will rarely use ribavirin.

A large, prospective study using ribavirin early in the course of RSV infections in patients with pre-existing cardiac and respiratory disease concluded that early ribavirin may help reduce morbidity.[73] However, none of those in either the active treatment or placebo groups required ventilation or died, a situation very different from that quoted in historical studies.[74] The authors comment that 'the early and aggressive medical support and meticulous attention to oxygenation may also have played an important role in decreasing the overall morbidity'. The lack of a more impressive effect may have been due to the fact that only a small proportion of infants with RSV infections develop severe bronchiolitis, while the study treated all RSV infections.

A recent retrospective analysis of RSV infection in patients with congenital heart disease found mortality to be very much lower than that reported 10 years ago, and concluded that this was attributable to improvements in management and intensive care rather than to any effect of introducing antiviral therapy.[75] Two other retrospective studies have also found very much lower mortality in a range of high risk groups than reported in previous studies.[43,44] Again, it appeared that improved supportive and intensive care was the major factor rather than the introduction of antiviral therapy.

The American Academy has also recommended using ribavirin for ventilated infants.[71] Again, there is no clear evidence to support this suggestion.[72] One study did show significantly shorter duration of ventilation, supplementary oxygen and hospital stay in those receiving ribavirin.[76] This study has been criticised for using distilled water as the placebo, and it has been suggested that this contributed to the unusually long periods of ventilation observed in the placebo group.[43] Another randomised study found no benefit from using ribavirin to treat ventilated patients.[77]

It would seem reasonable in light of the evidence so far to consider using ribavirin in extremely ill infants as it may hasten the onset of recovery, and have a lower threshold for its use in those at high risk, particularly in those who are immunosuppressed. However, a recent report suggested that RSV infections persisted in a number of immunodeficient patients despite ribavirin.[43] Good supportive care still remains the mainstay of management for all infants.

5.4 Assisted Ventilation

Although the number of infants with acute bronchiolitis requiring ventilation can be minimised by good supportive care, a small proportion of infants admitted to hospital may require ventilation for either recurrent apnoea or respiratory failure. Indications for intubation vary from unit to unit,[12,40,43,78-81] but in general infants are intubated for either recurrent apnoea with significant oxygen desaturations or respiratory failure with persistent acidosis or hypoxia despite high oxygen requirements. Rising carbon dioxide levels of more than 7 to 8 kPa would be viewed by some as an indication for intubation.[12,43,80] Others would tolerate significantly higher levels in the absence of overt exhaustion, acidosis or uncorrected hypoxia.[40,81] Though high peak pressures are often required, the minimum peak pressures required to achieve acceptable oxygenation with an arterial pH >7.28 should be used.[81]

Permissive hypercapnia is preferred to aggressive ventilation designed to normalise carbon dioxide levels. Positive end expiratory pressure, though frequently used, may be detrimental.[82] Slow rates with long expiratory times are generally required in those with respiratory failure.[78,79,81] Patients should be weaned from the ventilator as rapidly as possible.

A number of infants who continued to deteriorate despite mechanical ventilation have been treated with extracorporeal membrane oxygenation (ECMO). Preliminary reports are encouraging.[83] Continuous negative extrathoracic pressure (CNEP) has recently been used for the treatment of infants with severe bronchiolitis and appears to be beneficial (M. Samuels, personal communication). CNEP and intermittent negative extrathoracic pressure (INEP) have also been used for the management of infants with apnoea. The role of both ECMO and negative pressure ventilation is still to be clarified.

5.5 Antibiotics

Secondary bacterial infection appears uncommon in infants with RSV bronchiolitis,[43,55,56] and antibiotics are rarely indicated even in those with patchy changes suggesting pneumonia. The clinical picture together with the rapid confirmation of RSV infection provides reassurance in most mild to moderately unwell infants. Indeed, in one large prospective study, secondary bacterial infection was more common in those given antibiotics than in those who did not receive them. However, dual infections with viruses, chlamydia and bacteria do occur.[56,84,85] It is therefore not unreasonable to start antibiotics in those who are particularly ill or in those with atypical features.

It is increasingly recognised that patients with RSV infections can present with an apparent septicaemia illness.[80,86,87] Antibiotics are given to infants presenting with this type of illness and to those presenting with apnoea. It is also important to bear in mind that coincidental infections outside the respiratory tract do occur.[56]

5.6 Bronchodilators

One of the biggest areas for contention in the management of acute bronchiolitis is in the role of bronchodilators. This largely stems from differences in defining the condition. Clinicians who use the label of acute bronchiolitis as defined in this article find no evidence to support the use of β_2-adrenoceptor agonists in this illness.[6,88-90] Several studies have failed to show any benefit from the use of β_2-agonists,[91,92] while their use may sometimes have a detrimental effects.[93,94] Similarly, there is no convincing evidence that other bronchodilators such as theophylline[95,96] and ipratropium bromide[97,98] are beneficial. These findings are perhaps not surprising in view of the marked mucus production and mucosal inflammation that are contributing to the airways obstruction.

North American and some European authorities frequently argue that there is little doubt that bronchodilators are effective in some patients with bronchiolitis,[12] and sympathomimetic agents and theophylline are used extensively.[87,99] However, most of the studies advanced to support this position used the broader definition of bronchiolitis which includes all wheezy infants.[100-104] These studies generally include many children considerably older than 6 months of age, while it is in this younger age group that those most acutely unwell with acute bronchiolitis are seen. Even using this wider definition, the efficacy of bronchodilators in infants is still debated.[105] In older infants in whom it may be difficult to distinguish 'bronchiolitis' and viral-induced wheeze, a trial of bronchodilators is reasonable, but such infants should receive supplementary oxygen and close monitoring because of the potential for exacerbating ventilation/perfusion mismatching.

5.7 Other Therapies

There is no evidence that 'mist therapy', corticosteroids[106-109] or physiotherapy[110] have any role in the treatment of acute bronchiolitis. Indeed, the excessive handling associated with physiotherapy can be detrimental.[110]

The use of intravenous immunoglobulin in a single study has produced results similar to those obtained when using ribavirin in that treated patients appeared to have a more rapid improvement in oxygenation with a small effect on viral shedding, but it did not reduce the period of hospitalisation.[111] A further study is under way assessing the role of purified human immunoglobulin with high titres of anti-RSV neutralising antibodies.[112]

RSV is said to be both a poor inducer of IFN and to be sensitive to its effects. It was hoped that administration of IFNα would be of benefit in infants with bronchiolitis. However, a clinical trial found no significant benefit when it was used to treat infants with bronchiolitis.[113]

6. Prevention

Prevention of acute RSV bronchiolitis remains a major objective for healthcare in the 1990s. As yet, the only effective measures available are those designed to prevent nosocomial spread within paediatric wards.

6.1 Cross-Infection

It has been known for many years that the virus rapidly spreads through infants on paediatric wards if precautions are not taken,[114,115] and fatalities among infants acquiring the virus while they are inpatients are well recorded.[74] Inhalation of small droplet aerosols generated by coughing and sneezing does not appear to be an important method of transmission. Infection of staff is common through self-inoculation of virus from hands into eyes or the nose[116] and, indeed, infection in members of staff appears to be a major source of nosocomial spread.

The virus is transmitted to infants on the hands of attendant staff or relatives, so simply isolating infants is inadequate in preventing spread. Careful attention to hand washing[117,118] appears to be the most important aspect in the prevention of cross-infection as it will help to reduce both self-inoculation of staff and transmission of virus directly to other patients. More extensive precautions have been advocated by some authors who argue that

isolation and hand washing are ineffective. These include the use of gowns, gloves and even goggles.[119-123] Most of these measures will serve principally to reduce the infection rate among staff and so prevent their passing it on to children, but they will also heighten appreciation of the need for infection control measures.

During epidemics it is important to devise strategies designed specifically to avoid spread to inpatients at highest risk.

6.2 Vaccines

For more than 20 years, much effort has been devoted to producing a vaccine able to prevent much of the respiratory morbidity associated with RSV bronchiolitis. In the 1960s, trials of a formalin-inactivated alum-precipitated vaccine produced alarming results in that not only did the vaccine fail to protect infants but there was also excess morbidity and mortality in the immunised children when they subsequently were infected with the virus.[124,125] This adverse response has yet to be fully explained.

To date, the use of live attenuated virus and temperature-sensitive strains has not provided adequate protection, though there are still hopes that this approach may prove successful. Recent research has included efforts to produce subunit vaccines and the development of recombinant vaccinia and adeno viruses expressing RSV glycoproteins.[112] Such vaccines are being used experimentally in animals, and subunit vaccines have been used in young children,[112] though it is unlikely that they will be used in infants in the near future. One possible alternative strategy is to immunise mothers to overcome the suppressive effect of passively acquired antibodies on the response by infants to vaccines. It is quite possible that effective prevention will not prove possible until we better understand the viral-host interaction.

6.3 Specific Immunoglobulin

A recent multicentre trial appeared to show intravenous immunoglobulin containing high titres of RSV-specific antibodies protected high risk infants from significant lower respiratory tract infection.[126] This was greeted by some as the much needed breakthrough in prevention of severe disease in at-risk groups.[127] However, shortly afterwards, the Blood Products Advisory Committee of the American Food and Drug Administration (FDA) recommended that the product should not be granted a licence. Criticisms of the trial have included problems with randomisation, failure to follow up all the children enrolled and concerns regarding 6 deaths in the active treatment groups compared with none in the placebo group.[128] Though these infants did not die from RSV infection and there was no obvious link between treatment and death, concerns regarding these deaths contributed to caution regarding the possible role of this product. The future, if any, of this approach to the prevention of serious RSV illness in at-risk infants remains to be determined.

A related approach has been to use monoclonal antibodies directed against the relatively conserved F protein. Animal experiments have been encouraging, and studies in infants are being considered.

7. Conclusions

The prevention of acute RSV bronchiolitis in infancy remains a major challenge. The morbidity associated with this condition is considerable, and the financial strains placed on health services is enormous. With improved supportive care, the mortality is now low even in at-risk groups, but the condition still poses a major threat to the health of infants with underlying disease. The basis of treatment remains good supportive care. Antiviral therapy may have a role in a small group of at-risk patients. This condition is likely to challenge clinicians for some time to come.

References

1. Martin AJ, Gardner PS, McQuillin J. Epidemiology of respiratory viral infection among paediatric inpatients over a six year period in North East England. Lancet 1978; 2: 1035-8
2. Glezen WP, Parades A, Allison JE, et al. Risk of respiratory syncytial virus infection for infants from low income families in relationship to age, sex, ethnic group and maternal antibody level. J Pediatr 1981; 98: 708-15

3. Wilcox MH, Williams O, Camp SJ, et al. Characteristics of successive epidemics of respiratory syncytial virus infection. Lancet 1991; 338: 943-4
4. Hubble D, Osborn GR. Acute bronchiolitis in children. BMJ 1941; 1: 107-10
5. Henry R, Milner AD, Stokes GM. Bronchiolitis [letter]. Am J Dis Child 1983; 137: 805
6. Phelan PD, Landau LI, Olinsky A. Respiratory illness in children. Oxford: Blackwell Scientific Publications, 1990; 24-88
7. Gardner PS. How etiological, pathological and clinical diagnoses can be made in a correlated fashion. Pediatr Res 1977; 11: 254-61
8. Sims DG, Gardner PS, Weightman D, et al. Atropy does not predispose to RSV bronchiolitis or post bronchiolitic wheezing. BMJ 1981; 282: 2086-8
9. Pullan CR, Hey EW. Wheezing, asthma and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. BMJ 1982; 284: 1665-9
10. Carlsen KH, Larsen S, Bjerve O, et al. Acute bronchiolitis: predisposing factors and characterisation of infants at risk. Pediatr Pulmonol 1987; 3: 153-60
11. McConnochie KM. Bronchiolitis. What is in a name? Am J Dis Child 1983; 137: 11-3
12. Ruuskanen O, Ogra PL. Respiratory syncytial virus. Curr Prob Pediatr 1993; 50-79
13. Sporik R, Holgate ST, Cogswell JJ. Natural history of asthma in childhood – a birth cohort study. Arch Dis Child 1991; 66: 1050-3
14. Wilson NM. Wheezy bronchitis revisited. Arch Dis Child 1989; 64: 1194-9
15. Landau LI. Bronchiolitis and asthma: are they related? Thorax 1994; 49: 293-6
16. Kim HW, Arrobio JO, Brandt CD, et al. Epidemiology of respiratory syncytial virus infection in Washington DC: 1. Importance of the virus in different respiratory tract disease syndromes and temporal distribution of infection. Am J Epidemiol 1973; 98: 216-25
17. Murphy B, Phelan PD, Jack I, et al. Seasonal pattern of respiratory viral infection in children. Med J Aust 1980; 1: 22-4
18. Hall CB, Geiman JM, Biggar R, et al. Respiratory syncytial virus infections within families. N Engl J Med 1976; 294: 414-9
19. Fleming DM, Cross KW. Respiratory syncytial virus or influenza. Lancet 1993; 342: 1507-10
20. Anderson LJ, Hierholzer JC, Tsou C, et al. Antigenic characterisation of respiratory syncytial virus strains with monoclonal antibodies. J Infect Dis 1985; 151: 626-33
21. Anderson LJ, Hendry, RM, Pierik LT, et al. Multicentre study of strains of respiratory syncytial virus. J Infect Dis 1991; 163: 687-92
22. Hendry RM, Talis AL, Godfrey E, et al. Concurrent circulation of antigenically distinct strains of respiratory syncytial virus during community outbreaks. J Infect Dis 1986; 153: 291-7
23. Hall CB, Walsh EE, Long CE, et al. Immunity to and frequency of reinfection with respiratory syncytial virus. J Inf Dis 1991; 163: 693-8
24. Everard ML, Milner AD. The respiratory syncytial virus and its role in acute bronchiolitis. Eur J Pediatr 1992; 151: 638-51
25. Chanock RM, Kapikian AZ, Mills J, et al. Influence of immunological factors in respiratory syncytial virus disease of the lower respiratory tract. Arch Environ Health 1970; 21: 347-55
26. Aherne W, Bird T, Court SDM, et al. Pathological changes in virus infections of the lower respiratory tract in children. J Clin Pathol 1970; 23: 7-18
27. Everard ML, Swarbrick A, Wrightman M, et al. Analysis of cells obtained by bronchial lavage of infants with respiratory syncytial virus infection. Arch Dis Child 1994; 71: 428-32
28. Everard ML, Fox G, Walls AF, et al. Tryptase and IgE concentrations in the respiratory tract of infants with acute bronchiolitis. Arch Dis Child 1995; 72: 64-9
29. Turner RB. The role of neutrophils in the pathogenesis of rhinovirus infections. Pediatr Infect Dis J 1990; 9: 832-5
30. Carr R, Pumford D, Davies JM. Neutrophil chemotaxis and adhesion in preterm babies. Arch Dis Child 1992; 67: 813-7
31. Dos Santos C, Davidson D. Neutrophil chemotaxis to leukotriene B4 is decreased in the human neonate. Pediatr Res 1993; 33: 242-6
32. Hall CB, Hopelman AE, Douglas RG, et al. Neonatal respiratory syncytial virus infections. N Engl J Med 1979; 300: 393-6
33. Neligan GA, Steiner H, Gardner PS, et al. Respiratory syncytial virus infection of the newborn. BMJ 1970; 3: 146-7
34. Church WR, Anas NG, Hall CB, et al. Respiratory syncytial virus related apnoea in infants. Am J Dis Child 1984; 138: 247-50
35. Pickers DL, Schefft GL, Storch GA, et al. Characterisation of prolonged apnoeic episodes associated with respiratory syncytial virus infection. Pediatr Pulmonol 1989; 6: 195-201
36. Parrott RH, Kim HW, Arrobio JO, et al. Epidemiology of respiratory syncytial virus infection in Washington DC: II. Infection and disease with respect to age, immunologic status, race and sex. Am J Epidemiol 1973: 98: 289-300
37. Report to the Medical Research Council Subcommittee on Respiratory Syncytial Virus Vaccines. Respiratory syncytial virus infection: admissions to hospital in industrial, urban and rural areas. BMJ 1978; 2: 796-8
38. Green M, Brayer AF, Schenkman KA, et al. Duration of hospitalisation in previously well infants with respiratory syncytial virus infection. J Pediatr Infect Dis 1989; 8: 601-5
39. Hall CB, Hall WJ, Speers DM. Clinical and physiological manifestations of bronchiolitis and pneumonia. Am J Dis Child 1979; 133: 798-802
40. Lebel MH, Gauthier M, Lacroix J, et al. Respiratory failure and mechanical ventilation in severe bronchiolitis. Arch Dis Child 1989; 64: 1431-7
41. McMillan JA, Tristram DA, Weiner LB, et al. Prediction of the duration of hospitilization in patients with respiratory syncytial virus infection: use of clinical parameters. Pediatrics 1988; 81: 22-6
42. American Academy of Pediatrics. Use of ribavirin in the treatment of respiratory syncytial virus infection. Pediatrics 1993; 92: 501-4
43. Stretton M, Ajizian SJ, Mitchell I, et al. Intensive care course and outcome of patients infected with respiratory syncytial virus. Pediatr Pulmonol 1992: 13: 143-50
44. Navas L, Wang E, de Carvalho V, et al. Improved outcome of respiratory syncytial virus infection in a high-risk hospitalized population of Canadian children. J Pediatr 1992; 121: 348-54
45. Meert K, Heidemann S, Lieh-Lai M, et al. Clinical characteristics of respiratory syncytial virus infections in healthy versus previously compromised host. Pediatr Pulmonol 1989; 7: 167-70
46. Downham MAPS, Gardner PS, McQuillan J, et al. Role of respiratory viruses in childhood mortality. BMJ 1975; 1: 235-9
47. Williams AL, Uren EC, Bretherton L. Respiratory viruses and sudden infant death. BMJ 1984; 299: 1491-3
48. 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
49. Wang EEL, Milner RA, Navas L, et al. Observer agreement for respiratory signs and oximetry in infants hospitalized with respiratory infections. Am Rev Respir Dis 1992; 145: 106-9
50. Shaw KN, Bell LM, Sherman NH. Outpatient assessment of infants with bronchiolitis. Am J Dis Child 1991; 145: 151-5
51. Mulholland EK, Olinski A, Shann FA. Clinical findings and severity of acute bronchiolitis. Lancet 1990; 335: 1259-61
52. Chonmaitree T, Bessette-Henderson BJ, Hepler RE, et al. Comparison of three rapid diagnostic techniques for detection of respiratory syncytial virus from nasal wash specimens. J Clin Microbiol 1987; 25: 746-7
53. Hughes JH, Mann DR, Hamparian VV. Detection of respiratory syncytial virus in clinical specimens by viral culture, direct and indirect immunofluoresence and enzyme immunoassay. J Clin Microbiol 1988; 26: 588-91
54. Dawson KP, Long A, Kennedy J, et al. The chest radiograph in acute bronchiolitis. J Paediatr Child Health 1990; 26: 209-11
55. Friis B, Andersen P, Brenoe E, et al. Antibiotic treatment of pneumonia and bronchiolitis. Arch Dis Child 1984; 59: 1038-45
56. Hall CB, Powell KR, Schnabel K, et al. The risk of secondary bacterial infection in infants hospitalised with respiratory syncytial virus infection. J Pediatr 1988; 113: 266-71
57. Reynolds EOR, Cook CD. The treatment of bronchiolitis. J Pediatr 1963; 63: 1205-7
58. Reynolds EOR. Arterial blood gas tensions in acute disease of lower respiratory tract in infancy. BMJ 1963; 1: 1192-5
59. van Steensel-Moll HA, Hazelet JA, van der Voort E, et al. Excessive secretion of antidiuretic hormone in infections with respiratory syncytial virus. Arch Dis Child 1990; 65: 1237-9
60. Sporik R. Why block a small hole? The adverse effects of nasogastric tubes. Arch Dis Child 1994; 71: 393-4
61. Milner AD. Why block a small hole? Commentary. Arch Dis Child 1994; 71: 394
62. Englund JA, Piedra PA, Ahn Y-M, et al. High-dose, short-duration ribavirin aerosol therapy compared with standard ribavirin therapy in children with suspected respiratory syncytial virus infection. J Pediatr 1994; 125: 635-41
63. Outwater KM, Meissner C, Peterson MB. Ribavirin administration to infants receiving mechanical ventilation. Am Dis Child 1988; 142: 512-5
64. Janai HK, Marks MI, Zaleska RN, et al. Ribavirin: adverse drug reactions, 1986-1988. Pediatr Infect Dis J 1990; 9: 209-11
65. Fackler JC, Flannery K, Zipkis M, et al. Precautions in the use of ribavirin at the children's hospital. N Engl J Med 1990; 322: 634
66. Infectious Diseases and Immunization Committee, Canadian Paediatric Society. Ribavirin: is there a risk to hospital personnel? Can Med Assoc J 1991; 144: 285-6
67. Conrad DA, Christenson JC, Waner JL, et al. Aerosolized ribavirin treatment of respiratory syncytial virus infection in infants hospitalized during an epidemic. Pediatr Infect Dis J 1987; 6: 152-8
68. Wald ER, Dashefsky B, Green M. *In re* ribavirin: a case of premature adjudication? J Pediatr 1988; 112: 154-8
69. Issacs D, Moxon ER, Harvey D, et al. Ribavirin in respiratory syncytial virus infection: a double blind placebo controlled trial is needed. Arch Dis Child 1988; 63: 986-90
70. Ray CG. Ribavirin: ambivalence about an antiviral agent. Am J Dis Child 1988; 142: 488-9
71. American Academy of Pediatrics Committee on Infectious Disease. Use of ribavirin in the treatment of respiratory syncytial infection. Pediatrics 1993; 92: 501-4
72. Wald ER, Dashefsky B. Ribavirin. Red book committee reccommendations questioned. Pediatrics 1994; 93: 672-3
73. Groothuis JR, Woodin KA, Katz R, et al. Early ribavirin treatment of respiratory syncytial viral infection in high-risk children. J Pediatr 1990; 117: 792-8
74. MacDonald NE, Bresse Hall C, Suffin SC, et al. Respiratory syncytial viral infection in infants with congenital heart disease. N Engl J Med 1982; 307: 397-400
75. Moler FW, Khan AS, Meliones JN, et al. Respiratory syncytial virus morbidity and mortality in congenital heart disease patients: a recent experience. Crit Care Med 1992; 10: 1406-13
76. Smith DW, Frankel LR, Mathers LH, et al. A controlled trial of aerosol ribavirin in infants receiving mechanical ventilation. N Engl J Med 1991; 325: 24-9
77. Meert KL, Sarnik AP, Gelmini MJ, et al. Aerosolised ribavirin in mechanically ventilated children with respiratory syncytial virus lower respiratory tract disease: a prospective double blind trial. Crit Care Med 1994; 22: 566-71
78. Outwater KM, Crone RK. Management of respiratory failure in infants with acute viral bronchiolitis. Am J Dis Child 1984; 138: 1071-5
79. Frankel LR, Lewiston NJ, Smith DW, et al. Clinical observations on mechanical ventilation for respiratory failure in bronchiolitis. Pediatr Pulmonol 1986; 2: 307-11
80. Njoku DB, Kliegman RM. Atypical extrapulmonary presentations of severe RSV infection requiring intensive care. Clin Pediatr 1993; 32: 455-60
81. Rakshi K, Couriel JM. Personal practice: management of acute bronchiolitis. Arch Dis Child 1994; 71: 463-69
82. Smith PJ, Khatib MF, Carlo W. PEEP does not improve pulmonary mechanics in infants with bronchiolitis. Am Rev Respir Dis 1993; 147: 1295-8
83. Steinhorn RH, Green TP. Use of extracorporeal membrane oxygenation in thr treatment of respiratory syncytial virus bronchiolitis: the national experience, 1983-88. J Pediatr 1990; 116: 337-42
84. Tristram DA, Miller RW, McMillan JA, et al. Simultaneous infection with respiratory syncytial virus and other respiratory pathogens. Am J Dis Child 1988: 142: 834-6
85. Ray CG, Minnich LL, Holberg CJ, et al. Respiratory syncytial virus-associated lower respiratory illness: possible influences of other agents. Pediatr Infect Dis J 1993; 12: 15-9
86. Marks MI. Respiratory syncytial virus infection: the expanded clinical spectrum. Clin Pediatr 1993; 32: 461-2
87. La Via WW, Grant SW, Stutman HR, et al. Clinical profile of pediatric patients hospitalised with respiratory syncytial virus infection. Clin Pediatr 1993; 32: 450-4
88. Milner AD, Murray M. Acute bronchiolitis in infancy; treatment and prognosis. Thorax 1989; 44: 1-5
89. Archivist. Salbutamol in bronchiolitis. Arch Dis Child 1991; 66: 1183
90. Goodman RT, Chambers TL. Bronchodilators for bronchiolitis? Lancet 1993; 341: 1380
91. Phelan PD, Williams HE. Sympathomimetic drugs in acute viral bronchiolitis: their effect on pulmonary resistance. Pediatr 1969: 44: 493-7
92. Rutter N, Milner AD, Hiller EJ. Effect of bronchodilators on respiratory resistance in infants and young children with bronchiolitis and wheezy bronchitis. Arch Dis Child 1975; 50: 719-22
93. Ho L, Collis G, Landau LI, et al. Effect of salbutamol on oxygen saturation in bronchiolitis. Arch Dis Child 1991; 66: 1061-4

94. Hughes DM, Le Souef PN, Landau LI. Effect of salbutamol on respiratory mechanics in bronchiolitis. Pediatr Res 1987; 22: 83-6
95. Brooks LJ, Cropp GJA. Theophylline therapy in bronchiolitis: a retrospective study. Am J Dis Child 1981; 135: 934-6
96. Schena JA, Crone RK, Thompson JE. Theophylline therapy in bronchiolitis. Crit Care Med 1984; 12: 225
97. Henry RL, Milner AD, Stokes GM. Ineffectiveness of ipratropium bromide in acute bronchiolitis. Arch Dis Child 1983; 58: 925-6
98. Wang EEL, Milner R, Allen U, et al. Bronchodilators for treatment of mild bronchiolitis: a factorial randomised trial. Arch Dis Child 1992; 67: 289-93
99. Newcombe RW. Use of adrenergic bronchodilators by paediatric allergists and pulmonologists. Am J Dis Child 1989; 143: 481-5
100. Sanchez I, De Koster J, Powell RE, et al. Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics with bronchiolitis. J Pediatr 1993; 122: 145-51
101. Schuh S, Canny G, Reisman JJ, et al. Nebulized albuterol in acute bronchiolitis. J Pediatr 1990; 117: 663-7
102. Alario AJ, Leweander WJ, Dennehy P, et al. The efficacy of nebulised metaproterenol in wheezing infants and young children. Am J Dis Child 1992; 146: 412-8
103. Klassen TP, Rowe PC, Sutcliffe T, et al. Randomized trial of salbutamol in acute bronchiolitis. J Pediatr 1991: 118: 807-11
104. Schweich PJ, Hurt TL, Walkley EI, et al. The use of nebulized albuterol in wheezing infants. Pediat Emerg Care 1992; 8: 184-8
105. Gadomski AM, Lichenstein R, Horton L, et al. Efficacy of albuterol in the management of bronchiolitis. Pediatr 1994; 93: 907-12
106. Connolly JH, Field CMB, Glasgow JFT, et al. A double blind trial of prednisolone in epidemic bronchiolitis due to respiratory syncytial virus. Acta Paediatr Scand 1969; 58: 116
107. Leer JA, Green JL, Hemlich EM, et al. Corticosteriod treatment in bronchiolitis: a controlled collaborative study in 272 infants and children. Am J Dis Child 1969; 117: 495-503
108. Committee on Drugs. Should steroids be used in treating bronchiolitis? Pediatr 1970; 46: 640-2
109. Springer C, Bar-Yishay E, Uwayyed K, et al. Corticosteroids do not affect the clinical or physiological status of infants with bronchiolitis. Pediatr Pulmonol 1990; 9: 181-5
110. Webb MSC, Martin GA, Cartlidge PHJ, et al. Chest physiotherapy in acute bronchiolitis. Arch Dis Child 1985; 60: 1078-9
111. Hemming VG, Rodriquez W, Kim HW, et al. Intravenous immunoglobulin treatment of respiratory syncytial virus infections in infants and young children. Antimicrob Agents Chemother 1987; 31: 1882-6
112. Levin MJ. Treatment and prevention options for respiratory syncytial virus infections. J Pediatr 1994; 124: S22-7
113. Portnoy J, Hicks R, Pacheco F, et al. Pilot study of recombinant interferon Alpha-2a for treatment of infants with bronchiolitis induced by respiratory syncytial virus. Antimicrob Agents Chemother 1988; 32: 589-91
114. Gardner PS, Court SDM, Brocklebank JT, et al. Virus cross infection in paediatric wards. Br Med J 1973; 2: 571-5
115. Hall CB, Douglas Jr GR, Geiman JM, et al. Nosocomial respiratory syncytial virus infections. N Engl J Med 1975; 293: 1343-6
116. Hall CB, Douglas Jr RG. Modes of transmission of respiratory syncytial virus. J Pediatr 1981; 99: 100-3
117. Isaacs D, Dickson H, O'Callaghan CA, et al. Hand washing and cohorting in prevention of hospital acquired infections with respiratory syncytial virus. Arch Dis Child 1991; 66: 227-31
118. O'Callaghan CA. Prevention of nosocomial respiratory syncytial virus infection. Lancet 1993; 341: 182
119. Hall CB, Geiman JM, Douglas Jr GR, et al. Control of nosocomial respiratory syncytial viral infections. Pediatr 1978; 62: 728-31
120. Gala CL, Hall CB, Schnabel KC, et al. The use of eye-nose goggles to control nosocomial respiratory syncytial virus infection. JAMA 1986; 256: 2706-8
121. Leclair JM, Freeman J, Sullivan BF, et al. Prevention of nosocomial respiratory syncytial virus infections through compliance with with glove and gown isolation precautions. N Engl J Med 1987; 317: 329-34
122. Agah R, Cherry JD, Garakian AJ, et al. Respiratory syncytial virus (RSV) infection rate in personnel caring for children with RSV infections. Am J Dis Child 1987; 141: 695-7
123. Madge P, Paton JY, McColl JH, et al. Prospective controlled study of four infection-control procedures to prevent nosocomial infection with respiratory syncytial virus. Lancet 1992; 340: 1079-83
124. Kapikan AZ, Mitchell RH, Chanock RM, et al. An epidemiologic study of altered clinical reactivity to respiratory syncytial virus infection in children previously vaccinated with an inactivated RS virus vaccine. Am J Epidemiol 1969; 89: 405-21
125. Kim HW, Canchola JG, Brandt CD, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol 1969; 89: 422-34
126. Groothius JR, Simoes EAF, Levin JM, 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
127. McIntosh K. Respiratory syncytial virus – successful immunoprophylaxis at last. N Engl J Med 1993; 329: 1572-4
128. Ellenberg SS, Epstein JS, Fratantoni JC, et al. A trial of RSV immune globulin in infants and young children: the FDA's view. N Engl J Med 1994; 331: 203-4

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