



Chapter Respiratory syncytial virus bronchiolitis

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Introduction

Respiratory Syncytial Virus (RSV) bronchiolitis is the leading cause of admission to hospital in children under the age of 1 year in developed countries.¹ RSV is identified as the cause in the overwhelming majority (75%) of cases of bronchiolitis. However, other viruses such as parainfluenza, influenza, adenovirus, and human metapneumovirus may also cause a clinically indistinguishable illness. In the USA it has been estimated that RSV causes 51 000–82 000 admissions annually with 200 to 500 associated deaths.^{2,3}

RSV appears to infect almost all children by the time they are about 2 to 3 years old. Having older siblings or attending day care is associated with earlier primary infection.³ Primary RSV infections are rarely believed to be asymptomatic but very few children require hospitalization. In the developed world, however, admission rates appear to be rising. Over the last 20 years, admission rates have more than doubled to about 3%, although length of admission may have fallen from above 5 days to about 3 days.⁴ Up to 15% of infants hospitalized with bronchiolitis require intensive care and about half of these will require mechanical ventilation. As well as causing misery for children and their families, RSV bronchiolitis accounts for a great deal of healthcare expenditure.⁵ In children who are otherwise well, recovery from severe RSV bronchiolitis is frequently associated with chronic and recurrent wheezing in response to subsequent respiratory virus infection. Pulmonary function abnormalities have been shown to persist for decades following severe bronchiolitis.⁶

Although most children admitted with RSV have previously been well, children with congenital heart disease, chronic lung disease, or immunosuppression are at increased risk of severe disease.⁷

The management of bronchiolitis is primarily supportive and, although there are a number of therapeutic options that may be explored, clear evidence of the beneficial effects of many therapies has been difficult to obtain.

Case history

A 10-month-old female infant presented in January to her local hospital with a 7-day history of cough, mild pyrexia, and wheeze. She has a history of multiple episodes of cough and wheeze, some of which required admission to hospital, that were treated with inhaled bronchodilators – both β_2 agonists and ipratropium bromide – and steroids.

She was born prematurely by cesarean section at 28 weeks' gestation because of maternal placenta praevia. She had a birth weight of 1050 grams. In the neonatal period, she was managed with nasal Continuous Positive Airway Pressure (CPAP) and supplemental oxygen and did not require intubation and ventilation. At 8 weeks of age (36 weeks' post-conceptual age), she was discharged home and required no supplemental oxygen. She had received all

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Chapter 1: Respiratory syncytial virus bronchiolitis

her routine immunizations to date, had no known allergies, and had reached appropriate developmental milestones.

On admission to local hospital:

Examination

Temperature	37.8 °C
Respiratory rate	48 breaths.min ⁻¹
Saturations	88%–92% in air, rising to 96% in 2 litres of oxygen
Chest	Moderate subcostal/intercostal recession widespread expiratory wheeze and fine crackles

Investigations

Chest X-ray	Hyperexpanded with areas of atelectasis in both lung fields
Nasopharyngeal aspirate	Negative for respiratory viruses

On this admission she was treated with oxygen and given a trial of salbutamol and ipratropium bromide inhalers as metered dose inhalers using a spacer device. Both salbutamol and ipratropium bromide were felt to have some therapeutic benefit. She was allowed to continue with normal feeding and appeared to tolerate feeds well.

Over the next 24 hours, there were episodes of increased respiratory distress and rising oxygen requirements. Oral clarithromycin was commenced and feeds were given by nasogastric tube.

By the second day of admission, respiratory distress had worsened and there was an increasing requirement for oxygen. Enteral feeds were discontinued and intravenous fluids (80 ml kg⁻¹ per day of 0.45% saline with 5% dextrose) were started. A capillary blood gas was undertaken which showed: pH = 7.39, pCO₂ = 6.28 kPa, BE = −3.1. Nasal Continuous Positive Airway Pressure (nCPAP) using nasal prongs was started.

A few hours later, she further deteriorated with a respiratory rate above 60 breaths min⁻¹. There was head-bobbing and severe recession. She had become pale, sweaty and was noted to have become lethargic. A repeat capillary gas now showed respiratory acidosis: pH = 7.17, pCO₂ = 9.07 kPa, BE = −3.4. It was decided that she was no longer able to cope and invasive ventilatory support should be instituted.

She was referred to the regional Pediatric Intensive Care Unit (PICU). Prior to transfer she was anesthetized with sevoflurane, fentanyl, and rocuronium and was intubated uneventfully. Sedation, analgesia and muscle relaxation were maintained with morphine, midazolam, and vecuronium. Intermittent positive pressure ventilation was started with settings of 27 cmH₂O PIP and 6 cmH₂O PEEP, to generate a tidal volume of 6–7 ml kg⁻¹. Central venous and arterial access was established. Nebulized salbutamol was administered. There was evidence of partially compensated shock with a tachycardia of 135 b min⁻¹ and peripheral vasoconstriction. A 20 ml kg⁻¹ 0.9% NaCl bolus was given and dopamine started at 8 mcg kg⁻¹ per min to maintain a normal blood pressure. Intravenous cefotaxime was added to her antibiotic regime. The retrieval team transferred her uneventfully to the regional PICU.

Progress on pediatric intensive care unit (Table 1.1)

Respiratory

On admission, she had a strikingly prolonged expiratory phase with wheeze and inspiratory crackles. Since salbutamol had appeared to be associated with improvement at her referring hospital, a salbutamol infusion was commenced beginning at 1 mcg kg⁻¹ per min. Over the following 12 hours, oxygen requirements remained high. After further discussion, a trial of High Frequency Oscillatory Ventilation (HFOV) was commenced. After initiating HFOV there was marked hemodynamic instability, necessitating increased inotropic and vaso-pressor support and it was necessary to return to BIPAP.

A second trial of HFOV on the following day was also abandoned because of hemodynamic instability. On the third day of intensive care, she continued to deteriorate and PEEP had to be increased to 8 cm H₂O. The inspired oxygen fraction to maintain saturations greater than 88% was 0.8–0.9. At this time, the oxygenation index was 19.0 and the Alveolar Arterial Difference in Oxygen (AaDO₂) 520 mmHg. She was placed in a prone position.

The therapeutic options were reconsidered and nitric oxide, steroids, surfactant, and ECMO discussed.

Nitric oxide

It was decided to initiate a therapeutic trial of Nitric Oxide (NO) starting at 5 ppm. There was a concomitant fall in inspired oxygen from 0.95 to 0.65 with a resultant fall in the oxygenation index to 11.8. The NO was increased to 10 ppm with no further associated improvement. Nitric oxide was continued until day 12 at settings between 5 and 12 ppm. Weaning of NO was in accordance with improving ventilation. Ventilatory pressures remained high until the tenth day, when weaning to pressures of 18/6 was possible.

Table 1.1. Findings on admission to PICU

Airway	4.5 uncuffed oral endotracheal tube fixed 11.5 cm at lips
Breathing	BIPAP, Pressures 28/6, rate 24, Inspiratory time = 0.8 seconds FiO ₂ = 70%
Gas	pH = 7.32, pCO ₂ = 6.65 kPa, pO ₂ = 12.22 kPa, BE = −1.3.
Circulation	Pulse = 136 b min ⁻¹ , BP = 88/44 mmHg (MAP = 56) Warm and well perfused; peripheral capillary refill time <2 s Dopamine @ 8 mcg kg ⁻¹ per min Glucose = 2.7 mmol l ⁻¹ , therefore 5 ml kg ⁻¹ 10% dextrose given Urine output = 2 ml kg ⁻¹ per h
Neurology	Pupils small but equal and react briskly to light
Investigations	Hb = 9.4 g dl ⁻¹ , WCC = 11.4 × 10 ⁹ l ⁻¹ , Plts = 294 × 10 ⁹ l ⁻¹ Na = 140 mmol l ⁻¹ , K = 4.1 mmol l ⁻¹ , U = 1.3 mmol l ⁻¹ , Cr = 17 μmol l ⁻¹ , CRP = 45 mg l ⁻¹

Chapter 1: Respiratory syncytial virus bronchiolitis

Extra-corporeal membrane oxygenation (ECMO)

After deciding to initiate a trial of NO, the supra-regional ECMO center was contacted in accordance with our normal local practice. Daily contact was maintained, but she remained adequately oxygenated and did not meet the criteria for ECMO (oxygenation index >25).

Corticosteroids

Despite NO, her clinical condition still gave cause for concern. She remained very unstable, requiring high ventilatory pressures after 5 days of intensive care. It was decided to initiate a therapeutic trial of corticosteroids. Intravenous methylprednisolone (2 mg kg⁻¹ per day) was commenced and continued at high dose for 7 days and then weaned over the following week.

Surfactant

On the ninth day of intensive care, 4 days after starting corticosteroids and 6 days after starting NO, she had a prolonged period of respiratory acidosis and required increasing inspired inflation pressures. After further discussion, it was decided to give a single trial dose of surfactant (Curosurf (Poractant Alfa, Chiesi)). The dose was instilled into the trachea in a weight-appropriate dose in accordance with the manufacturer's instructions. Over the following 6 to 8 hours, no significant improvement in ventilation was felt to have occurred and no further doses were administered.

Cardiovascular and fluids

Dopamine was continued at a rate of 5–10 mcg kg⁻¹ per min for 5 days to maintain adequate blood pressure. No other inotropes were required. The patient was generally hemodynamically stable except for a brief period when high frequency oscillation ventilation was tried.

Fluid and electrolyte balance

Intravenous fluids were initially restricted to 70 ml kg⁻¹ per day. Enteral feeds were commenced on Day 4 and fluid allowance was increased the following day to 100 ml kg⁻¹ per day. Regular furosemide (0.5 mg kg⁻¹ q6) was started on Day 3 to keep the overall fluid balance negative and urine output greater than 1 ml kg⁻¹ per h. This was changed to a continuous furosemide infusion on Day 9, which was continued for 3 days before converting back to intermittent dosing. Serum sodium levels were 140–145 mmol L⁻¹ during the period of difficult ventilation and urea and creatinine levels remained in the normal range.

Microbiology

Initial viral and bacterial investigations were negative, although RSV was isolated on Day 4 of hospitalization. Microbiological culture of a tracheal aspirate grew *Haemophilus influenzae* spp. on one occasion, but all other bacterial and fungal cultures, from sputum and blood, were negative. A 7-day course of cefotaxime was given. Clarithromycin was given for 3 days. The CRP rose to a maximum of 115 on day two of PICU.

Other

She was paralyzed with a continuous infusion of vecuronium for the first 12 days on PICU. She was sedated according to a local protocol with morphine and midazolam, and fentanyl was substituted for morphine from the ninth day of intensive care. Clonidine and chloral

Chapter 1: Respiratory syncytial virus bronchiolitis

hydrate were used from the 12th PICU day onwards to allow weaning of intravenous sedation and manage withdrawal symptoms.

Weaning and discharge

She gradually improved after the 10th day of intensive care and was weaned sufficiently to allow elective extubation on the 16th day after admission. For the next day, she required a small amount of supplemental oxygen, which was steadily reduced and then stopped. She was discharged from the intensive care unit after 17 days and was transferred back to her referring hospital on the following day to complete her recovery.

Discussion

In temperate and continental climates such as most of Europe and North America RSV bronchiolitis occurs in annual epidemics at the coldest point of the year. To date, it is believed that man is the only natural host and that no animal reservoir exists. Nonetheless, it is unclear why there are very few cases at other times of the year or where the virus goes. Recently, some evidence has emerged from animal models that RSV may be able to persist in the lung after primary infection raising the possibility of reactivation.⁸

Most children admitted will be between 3 and 6 months of age during primary RSV infection and the case was slightly older than most. Preterm infants are generally admitted at a younger post presented conceptual age and it has been noted that the peak age of admission corresponds in time with waning passive maternal antibody levels. During the winter months the number of children presenting to pediatric intensive care can be so great that bed availability is stretched and this impacts on the availability of beds for elective or routine procedures. Most transmission is by direct inoculation of the mucous membranes of the eye and nose; both have respiratory epithelium, the mouth does not. Aerosol spread is probably uncommon.⁹ Nosocomial spread is well recognized and RSV has been shown to be able to remain infectious for hours on surfaces and other fomites.¹⁰ For vulnerable infants in hospital, this can represent a real threat.

Presentation of RSV bronchiolitis

Respiratory syncytial virus infection may present in several ways. The first isolates from a child were in a case of croup. However, RSV more commonly presents with symptoms or signs of a coryzal illness or upper respiratory tract infection (URTI), together with evidence of Lower Respiratory Tract Infection (LRTI). In some infants obstruction to airflow is pronounced and wheeze is common. In very young infants apnoea may be a striking feature.

Central, prolonged apnea can be the first sign of RSV infection in young infants in the absence of other respiratory symptoms, the mechanism of which is unclear. It has not been possible to detect viral genome in CSF to confirm direct infection.¹¹ Those under 2 months of age are most likely to present with RSV associated apnea. Apnea at admission increases the risk of recurrent apnea and the need for supportive ventilation significantly increases in children who suffer from recurrent apnea.¹²

Understanding immunity to RSV

RSV is poorly cytopathic *in vitro* and probably causes relatively little direct cell damage during infection. Infection is mainly confined to the respiratory epithelial cells lining the eye, nose, middle ear and lower respiratory tract.

Chapter 1: Respiratory syncytial virus bronchiolitis

In the 1960s a number of vaccine trials were undertaken in children using a formalin-inactivated preparation of the virus. This vaccine was created using the same techniques that had proven so successful in vaccinating against polio. In these studies children showed good serum antibody responses and cell-mediated lymphocyte responses after vaccination. During subsequent natural RSV infection, however, illness appeared to be enhanced.^{13–16} There were increased admissions and some children died with evidence at postmortem of a vigorous inflammatory response in the lung.

In the 1980s and 1990s, with greater understanding of the role of lymphocytes and with animal models, it was possible to show that, during RSV infection, both CD4 helper and CD8 cytotoxic T cells were important in controlling RSV infection. Removing either subset was associated with prolonged shedding of virus but interestingly with reduced illness.^{17,18} Further studies have confirmed that T-cells are essential in controlling primary RSV infection, but are also associated with an inflammatory response that produces the illness we refer to as bronchiolitis. Removing specific cytokines that can be produced by T cells in particular TNF- α has also been shown to ameliorate illness in animal models.¹⁹

Specific T-cell subsets may be primed by different proteins of RSV. In particular the attachment surface “G” protein has been associated with T-helper 2 responses.²⁰ This may have great importance in designing any future vaccine. The RSV genome appears to be somewhat distinct from the other paramyxoviruses and intriguingly the nucleoprotein and polymerase show closer sequence homology to filoviruses like Ebola and Marburg suggesting a possible common ancestor.²¹

Fluid and electrolyte balance

In infants admitted to hospital with bronchiolitis, water overload and hyponatremia may complicate fluid and electrolyte management. RSV bronchiolitis is associated with both increased ADH secretion and hyper-reninemia with secondary hyperaldosteronism.²² These may lead to water retention. In some series hyponatremia has been associated with seizures.²³ Close control of fluid balance and usually fluid restriction are employed by many PICUs.²⁴

Corticosteroids

Corticosteroids have been used in clinical practice for the treatment of many inflammatory diseases for many decades. The predominant mechanism of action is via corticosteroid receptors that are expressed very widely throughout the body.²⁵ Corticosteroids affect multiple steps in immune activation: they inhibit antigen presentation, cytokine production, and lymphocyte proliferation. Lymphocyte, monocyte, and basophil counts decrease in response to corticosteroids, while neutrophil counts increase.²⁶ The striking similarities in some of the clinical features that acute bronchiolitis has with acute asthma has led to the hypothesis that corticosteroids may have a therapeutic role. It is known that acute RSV bronchiolitis is associated with a measurable acute stress response that has similarities to, and differences from, other severe infections such as bacterial sepsis. Cortisol levels are elevated in acute bronchiolitis, but there is no evidence that these levels are higher in children who go on to need intensive care.²⁷

For at least 40 years researchers have been attempting to show whether corticosteroids may be of benefit in acute bronchiolitis.²⁸ Even today there have been advocates for and against. A recent editorial in the *Journal of Pediatrics*²⁹ strongly advocated the early use of corticosteroids following the publication of a randomized control trial of oral prednisolone in the same journal.³⁰ Conversely, in a recent Cochrane review and meta-analysis,³¹ the

Chapter 1: Respiratory syncytial virus bronchiolitis

authors found no benefits in either length of stay or clinical score in infants and young children treated with systemic glucocorticoids as compared with placebo. They also found no significant differences in any of the subanalyses or in return to hospital or readmission rates. Therefore, at present it would seem there is inadequate data to recommend the routine use of steroids in bronchiolitis. The long period of research without demonstrating a clear benefit suggests that, if there is a benefit of corticosteroids, it is unlikely to be clinically very significant.

Surfactant

There are several strands of evidence of the importance of surfactant in bronchiolitis. Knock-out animal models have suggested that surfactant protein A may have a role in clearance of RSV.³² Surfactant protein concentrations may be lower in those with severe bronchiolitis.³³ An association may exist between certain surfactant protein A polymorphisms³⁴ and severe bronchiolitis. RSV infects and causes the apoptosis *in vitro* of type 2 pneumocytes that produce pulmonary surfactant.³⁵

These pieces of data taken together have suggested to some clinicians that there may be a role for the administration of exogenous surfactant in severely ill infants with bronchiolitis. Although reported as individual cases, very few studies have been undertaken using what is still a relatively expensive therapy. Recently, Tibby *et al.* have described a small series of patients in whom some improvement of oxygenation was found after exogenous surfactant in bronchiolitis.³⁶ At present, there is inadequate data to recommend the routine use of surfactant, and cost and potential adverse effects suggest that larger studies will be needed.

Bronchodilators: salbutamol, ipratropium bromide, and adrenaline

For over 30 years clinicians have tried to determine the effectiveness of bronchodilators in bronchiolitis. The consistent finding of airflow obstruction and some similarities in presentation to older children with wheezing has suggested that perhaps bronchospasm may play a role.

A review by Schindler³⁷ commented that, in the 1990, there were 12 randomized control trials, involving many hundreds of infants, examining beta-agonists in bronchiolitis. Nine showed that bronchodilators had no effect and three showed a small transient improvement in the acute clinical score. She also noted that ipratropium bromide had no significant effect.

Two large meta-analyses in 1996³⁸ and 2000³⁹ have concluded that bronchodilator recipients did not show improvement in oxygenation, the rate of hospitalization, or duration of hospitalization. The authors conclude that, at best, bronchodilators produce modest short-term improvement in clinical scores.

Epinephrine has been shown to improve respiratory system resistance but not oxygenation or ventilation. Compared with beta-agonists, adrenaline (epinephrine) was not associated with lower admission rates or/and improved oxygen saturation, although it has been suggested that, soon after treatment, respiratory rate may be lower than after treatment with other bronchodilators. A large recent meta-analysis has concluded that “there is insufficient evidence to support the use of epinephrine for the treatment of bronchiolitis.”⁴⁰

Ribavirin

Ribavirin is a synthetic guanosine analog that inhibits RSV replication during the active replication phase. Introduced into clinical practice in the 1980s after great promise *in vitro*,

Chapter 1: Respiratory syncytial virus bronchiolitis

aerosolized Ribavirin was purported to be associated with improved oxygenation, improved clinical scores, and diminished levels of secretory mediators of inflammation associated with severe wheezing and disease.⁴¹ However, its use was limited initially because of expense and, over the last 20 years, a number of investigators have been unable to convincingly show a beneficial effect on clinical outcome. More studies have been undertaken to determine whether those who had received Ribavirin had better or worse long-term outcomes. No significant differences in outcome following Ribavirin therapy have been demonstrated using outcome measures such as response to methacholine challenge; reported wheezing; severity of recurrent lower respiratory tract illness; oxygen saturation; peak expiratory flow or spirometry,^{42,43} although, in one follow-up study, weighted severity scores suggested a possible long-term beneficial effect.⁴⁴ More recent understandings of the role of the immune response in causing the clinical manifestations of bronchiolitis may indicate why interference with viral replication might have, at most, a limited therapeutic role.

RSV-specific immunoglobulin

It has been noted that the peak incidence of hospitalization with RSV bronchiolitis appears to coincide with the nadir of humoral immunity, as passively acquired maternal antibody wanes. This observation led to studies showing that infants born with higher levels of passive maternal antibody to RSV had a degree of protection against severe RSV bronchiolitis. In the 1990s a preparation of pooled RSV-specific immunoglobulin from donors was developed. Studies suggested that given prophylactically to high-risk infants, the duration and severity of hospitalizations due to RSV may be reduced.

Subsequently, a humanized monoclonal antibody preparation has been produced for use in high risk groups (Palivizumab™, Abbott Laboratories). Data from large randomized controlled studies show some evidence for protection with passive immunization. Some centers have begun to offer Palivizumab to very high-risk infants. However, as Buck *et al.* have suggested,⁴⁵ relatively few children admitted to PICU with RSV bronchiolitis are likely to fall into the groups considered eligible for immunization. The costs of offering this therapy compared with the likely benefits need to be carefully considered.

Despite the potential drawbacks of immunoglobulin from pooled human donations, there may be one group who may still benefit from its use. Progression to pneumonia in pre-engraftment recipients of bone marrow transplants due to RSV is associated with an overall mortality of 60%–80%. There is some evidence that the combination of intravenous immunoglobulin and Ribavirin may significantly reduce mortality in this group.^{10,46}

Nitric oxide

Inhaled nitric oxide (NO) has been used for over a decade in acute lung injury or acute respiratory distress. However, there is little evidence from clinical trials to support its use. It is recognized that, as therapy with NO begins, oxygenation is frequently improved and this is principally due to better matching of ventilation and perfusion. In the context of a child in whom oxygenation cannot be maintained despite maximal ventilation, it is easy to understand why clinicians see a role for its use despite a lack of detailed evidence. Children who are as sick as the child described in this chapter are relatively rare and studies of adequate power hard to achieve. In a recent Cochrane review, inhaled NO had no impact on survival and only transient effects on oxygenation.⁴⁷

Co-infection and the use of antibiotics

Many studies in the developed world have noted that bacterial co-infection during RSV bronchiolitis is unusual. Despite this, in children who require pediatric intensive care, antibiotic use is almost universal.⁴⁸ It is frequently suggested that antibiotics may be being over-used and that measures should be taken to reduce this.⁴⁹ However, diagnosis of co-infection can be delayed, is more common in children requiring intensive care and is associated with a more severe course.⁵⁰ In addition, a recent report has suggested that tracheal colonization with *Haemophilus influenzae* may be associated with a worse PIC course in RSV bronchiolitis.⁵¹ Co-infection with *Bordatella pertussis*⁵² or *Streptococcus pneumoniae*⁵³ are unusual, but not rare, and should be considered. Co-infection with viruses such as human metapneumovirus and human bocavirus have recently been emerging as another potential cause of more severe illness during the bronchiolitis season⁵⁴ and can be diagnosed by PCR.

Summary

The child described happily appears to have completely recovered from a life-threatening episode of bronchiolitis due to RSV infection. Recent epidemiological data regarding bronchiolitis mortality in the United States makes concerning reading. Although childhood deaths associated with any respiratory disease decreased steadily between 1979 and 1997, the number of deaths associated with bronchiolitis among children showed no similar reduction. It was also found that most children dying with bronchiolitis were not concurrently diagnosed with underlying prematurity or pulmonary or cardiac conditions.³

There is evidence of considerable variation in the use of different therapies between institutions but resulting in very little difference in the lengths of stay.⁵⁵ Treatment will therefore remain essentially supportive as we have a great deal still to learn about this illness.

Learning points

- RSV is the dominant respiratory pathogen in infants children needing pediatric intensive care.
- The presentation of RSV bronchiolitis is varied but falls into clinically recognizable patterns.
- The immune response to infection is complex and, although essential in controlling infection, it may be the cause of the clinical illness.
- There may be specific problems related to fluid and sodium balance.
- High-risk groups who may suffer severe illness can be identified and some preventative strategies considered including passive immunization.
- Infection control is important to protect vulnerable infants.
- Proven therapeutic interventions are few and treatment remains essentially supportive.
- Co-infection with viral or bacterial pathogens is associated with more severe illness.
- Long-term pulmonary sequelae occur in the majority of infants following RSV bronchiolitis.

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Chapter 1: Respiratory syncytial virus bronchiolitis

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