REVIEW ARTICLE

Viral bronchiolitis for the clinician

Dominic A Fitzgerald

Department of Respiratory Medicine, The Children's Hospital at Westmead, Westmead, New South Wales, Australia

Abstract: Viral bronchiolitis is common, and about 98–99% of infants are managed in the home. Because about 95% of infants <2 years old are infected with respiratory syncytial virus, however, bronchiolitis is the commonest reason for admission to hospital in the first 6 months of life. It is usually a self-limiting condition lasting around a week in previously well children. About 1% of infants are admitted to hospital, and about 10% of hospitalised infants will require admission to the intensive care unit. Respiratory syncytial virus is isolated from about 70% of infants hospitalised with bronchiolitis. The emphasis of hospital treatment is to ensure adequate hydration and oxygenation. Other than supplemental oxygen, little in the way of pharmacological treatment has been demonstrated to alter the course of the illness or the risk of wheezing in the months following bronchiolitis.

Key words: bronchiolitis; evidence-based management; non-invasive respiratory support; pharmacological treatment; respiratory syncytial virus (RSV); wheezing outcomes.

Introduction

Bronchiolitis is the commonest reason for admission to hospital in the first 6 months of life.[1,2] It describes a clinical syndrome of cough, tachypnoea, feeding difficulties and inspiratory crackles on chest auscultation. Wheezing may be associated but is not an essential feature of the illness. The upper age for bronchiolitis is limited to 12 months of age in the majority of the Australasian and English reports. However, European and North American publications often consider the diagnosis up to the age of 3 years and often define bronchiolitis as a wheezing illness, which leads to difficulties in comparing international studies. While many viruses may give rise to the clinical syndrome of bronchiolitis, respiratory syncytial virus RSV is most frequently implicated in hospitalised cohorts of infants.[1–3] Treatment is predominantly symptomatic, with an emphasis on maintaining adequate hydration and providing supplemental oxygen in moderate to severe cases that are associated with significant hypoxaemia.[3] A range of pharmacological treatments have been advocated in the acute settings, but most have not shown consistent benefit. Bronchiolitis that is severe enough to require hospitalisation is associated with an increased subsequent risk of recurrent wheeze in early to middle childhood, but evidence suggests this is because RSV infection is more severe in children with an underlying predisposition to asthma rather than RSV causing asthma.[1,3,4]

Aetiology

Bronchiolitis is a viral infection. RSV can be detected in about 70% of cases, but other viruses causing an identical clinical picture include rhinoviruses, parainfluenza viruses, human metapneumoviruses, influenza viruses, enteroviruses, human coronaviruses and human bocaviruses.[5,6] RSV infection is near universal (95%) by age 2 years, and 40% of children infected by 12 months of age develop clinical bronchiolitis.[7] RSV can be detected in nasopharyngeal aspirates by immunofluorescence, Enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction or viral culture. RSV detection is useful for cohorting patients in hospital to prevent nosocomial infection and, perhaps, to reduce antibiotic use, but is not essential for the diagnosis of bronchiolitis. It has been suggested that dual viral infections and higher RSV viral load are associated with increased severity, but this has not been a consistent finding.[6,8–10]

Epidemiology

While the majority of children can be managed successfully in the community, 1–2% will require hospital admission and, of these, 6–12% will require admission to the intensive care unit.[11] Maternal antibody is, at best, partially protective, and the

> **Key Points**
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> 1. Bronchiolitis is mild in the great majority of cases and does not require hospital admission.
> 2. The mainstay of therapy is ensuring adequacy of hydration and satisfactory oxygenation, rather than utilising pharmacological treatments.
> 3. For those infants requiring hospitalisation, approximately 10% will require admission to the intensive care unit, where non-invasive respiratory support may avoid the need for endotracheal intubation.

Correspondence: Associate Professor Dominic A Fitzgerald, Department of Respiratory Medicine, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia. Fax: +61 2 9845 3396; email: dominif2@chw.edu.au

disease is most severe in very young babies and in babies with underlying risk factors, notably, prematurity, congenital heart disease, particularly cyanotic, and chronic lung disease, and in children with impaired T-cell immunity.[3]

Pathophysiology

The infecting virus precipitates an inflammatory response in the respiratory epithelium. This gives rise to oedema of the airway wall and an accumulation of mucus and cellular debris within the lumen of the airway.[12] There is impaired mucociliary clearance with cilial damage and airway occlusion. In an era of molecular medicine, work is beginning to emerge on host defence factors, including the innate immunity of the lung with regard to predisposing factors for more severe bronchiolitis.[13] However, there are no consistent signals between relative levels of cytokine activity in the blood and lung fluid and the clinical course of bronchiolitis.

Variable bronchiolar obstruction occurs in bronchiolitis, giving way to patchy hyperinflation and areas of atelectasis, evident on the chest radiograph. The infant has overinflated and stiffer lungs, and breathes at a higher lung volume because of a raised functional residual capacity.[12,14] There is mismatching of ventilation and pulmonary perfusion giving rise to arterial hypoxaemia, and in more severe cases, carbon dioxide retention may be evident.

RSV

The predominant pathogen in bronchiolitis is the RSV. The RSV is responsible for between 50% and 80% of cases of bronchiolitis requiring hospitalisation, but, as stated previously, other viruses are also important causes.[1–4,12,15] RSV is extremely contagious, with almost all children becoming infected by their second birthday.[3,16] Transmission requires close contact, with nasal mucosa being exposed to infected secretions, usually either directly through droplet spread or via fomite spread on hands.[3,17,18] Cross infection in emergency departments and hospital wards remains a considerable challenge.[18] Reinfection with RSV is common through life, although the first infection tends to be the most severe and is more likely to involve the lower respiratory tract.[19,20] It is unclear whether simultaneous infections with two or more viruses will lead to a more severe or protracted bronchiolitic illness.[19–22]

Diagnosis

The diagnosis of bronchiolitis is a clinical one. Most infants present with breathing difficulty in association with a coryzal illness.[3,23] Neonates may have apnoea, but more typically, babies develop rapid, shallow breathing (often at a rate greater than 60 breaths per min in more severe cases), head bobbing, tracheal tug, chest wall hyperinflation with or without intercostal recession and a characteristic cough. Wheeze is not universal, and the most characteristic auscultatory finding is fine crackles.[3,24] In those more severe cases managed in the hospital setting, identification of the infecting agent is not only useful for cohorting patients, but may also be of benefit in predicting a higher risk of wheezing in early to middle childhood.[25]

Differential Diagnosis

In an infant with prolonged symptoms before presentation or atypical features of bronchiolitis, one should consider alternative and/or additional diagnoses, which may include pulmonary aspiration, cardiac failure, bacterial or viral pneumonia, cystic fibrosis, sepsis (with apnoea in very young infants), primary ciliary dyskinesia, tracheomalacia, bronchomalacia, pneumothorax and, finally, in an older child, an inhaled foreign body.[3,23] The initial investigation in atypical cases of bronchiolitis would be a chest radiograph, where one would look for cardiomegaly with congestive cardiac failure or pneumonia. Moreover, the presence of the usual features of hyperinflation, patchy atelectasis and minor perihilar inflammatory changes should provide support for the diagnosis of viral bronchiolitis and obviate the need for unnecessary therapies such as antibiotics.

The diagnosis of bronchiolitis is relevant for children up to the age of 12 months and, generally, is relevant for the first episode of cough, tachypnoea and wheeze (if present). In later infancy and the toddler years, subsequent episodes of cough, tachypnoea and wheeze triggered by viral infections would fall in to the category of viral-induced wheeze or transient early wheezing, rather than recurrent bronchiolitis.[1,3,26] Factors that would favour a diagnosis of transient early wheeze would include exposure to environmental tobacco smoke (both antenatally and post-natally] and reduced lung function.[1,3,26]

Assessment of Severity

A history of preterm delivery, chronic respiratory conditions such as chronic neonatal lung disease or cystic fibrosis, cyanotic congenital heart disease, underlying neurological or neuromuscular conditions, trisomy 21 and immunodeficiency states predicts that the disease will be more severe.[3] The history of the presenting illness would incorporate days of coryzal symptoms, feeding difficulties, an estimate of reduced urine output as a marker of dehydration and any witnessed apnoea in young infants.[3,26]

The physical examination should begin with a period of observation of the child, who should be undressed down to the nappy. Table 1 lists the basic observations and clinical signs to consider. When making an assessment of severity, one must consider the phase of the illness, the risk factors increasing the likelihood of hospital admission (Table 2) and the findings on physical examination. Bronchiolitis may be considered to be mild, moderate or severe when assessed (Table 3).

Should Any Investigations Be Undertaken When Assessing an Infant with Bronchiolitis?

For infants with mild viral bronchiolitis, no routine investigations are necessary.[3,27] For children with moderate to severe bronchiolitis, investigations usually undertaken include:
• Monitoring of patterns of standard clinical parameters of respiratory rate, heart rate and oximetry. This is particularly

Table 1 Clinical signs to consider in the assessment of severity of bronchiolitis[3,7,23,24,26]

Basic observations
  Respiratory rate: >60 breaths per min is tachypnoeic for all infants
  Heart rate: >140 beats per min is tachycardic for all infants
  Temperature: temperature >38.5°C is significantly febrile
  Oxygen saturation (SpO$_2$): <93% is hypoxic
General appearance
  Does the infant appear alert and interactive or lethargic and tired?
Hydration
  Are the mucous membranes moist?
  Is the nappy wet? When was the last wet nappy?
  Is the infant able to take sucking feeds?
Degree of respiratory difficulty
  Are the accessory muscles of respiration being recruited?
  Is he child wheezy?
  Are there fine inspiratory crackles on chest auscultation?
Adequacy of oxygenation
  Is the infant centrally cyanosed?

Table 3 The assessment of severity in bronchiolitis[3,7]

Mild
  Able to feed satisfactorily
  Adequately hydrated
  Minimal respiratory difficulty
  SpO$_2$ ≧ 93%
Moderate
  Feeding compromised
  Level of hydration reduced
  Mild tachypnoea, chest wall recession and nasal flaring
  May appear short of breath when feeding
  Hypoxaemic (SpO$_2$ < 93%) in air, readily corrected with low flow supplemental oxygen
  If a young infant, may have brief apnoeic episodes
Severe
  Unable to take sucking feeds as too breathless
  Marked tachypnoea, chest wall recession, tracheal tug, head bob, nasal flaring and expiratory grunting
  Hypoxaemic and/or centrally cyanosed
  Frequent of prolonged apnoea in young infants
  Appears increasingly tired or fatigued (consider CO$_2$ retention)

Table 2 Factors likely to prompt hospital admission in infants with bronchiolitis[3,23,24]

Known pre-existing lung or structural cardiac disease
Chronological age <6 weeks
Significant preterm delivery (<32 weeks)
History of significant apnoea prior to assessment
Significant dehydration
Moderate or severe breathing difficulty at presentation
Hypoxaemia (SpO$_2$ < 93%) or obvious central cyanosis
Re-presentation within 24 h of initial assessment
Uncertain diagnosis

Outpatient Versus Inpatient Management

The decision to manage the child at home or in hospital is a clinical one, based upon the presenting features and the family circumstances. In cases of mild bronchiolitis, the parents should be reassured, the diagnosis and likely clinical course should be explained, and the child should be offered a review with his/her general practitioner if needed. Infants with moderate to severe bronchiolitis will need admission to hospital for management as they will need supplemental oxygen to overcome hypoxaemia and rehydration with intravenous or possibly nasogastric/transpyloric fluids in less severe cases. An algorithm for the assessment and treatment of bronchiolitis is provided in Table 4.

Non-Pharmacological Management

Hydration

The combination of nasal congestion for obligate nasal breathers, reduced oral intake, lethargy and malaise, insensible water losses from tachypnoea and increased work of breathing predispose to dehydration in bronchiolitis.[3,7] The decision to suspend oral feeding because of concerns about pulmonary aspiration is a clinical one, with the introduction of nasogastric or intravenous fluids in the presence of dehydration and increased respiratory work of breathing evident in moderate to severe bronchiolitis.[3,7] Regular review of hydration status is important.

Nursing issues

Experienced nursing care is an essential component of the care of infants with bronchiolitis, particularly with regard to the recognition of clinical deterioration, which will require intervention.[3] The use of normal saline drops into the nose prior to

useful for young infants at risk of apnoea, and routine oximetry has almost certainly contributed to the considerable reduction in mortality from bronchiolitis.

• A chest radiograph: for localised signs of crepitations or wheeze, cardiac murmur and signs of congestive cardiac failure, and to exclude pneumonia.

• A nasopharyngeal aspirate for RSV immunofluorescence and viral culture.

• A full blood count if pneumonia is suspected clinically or from the appearance of the chest radiograph.

• Blood cultures if baby is severely ill or has a fever >38.5°C: septicaemia occurs in <1% of normal babies with RSV, but is more likely in babies requiring intensive care unit admission and those with underlying conditions.

• In infants with significant dehydration, serum electrolytes, urea and creatinine.

• Blood gas analysis for an infant requiring an FiO$_2$ > 0.40 who is tiring, to assess for pH and carbon dioxide retention. This may be collected as an arterial sample, a free-flowing venous sample or, if unable, a capillary sample.

Table 4 Treatment options for bronchiolitis[3,7,26–28]

Mild

   No investigations

   Manage at home after explanation of course of illness

   Review by general practitioner in 2–3 days

Moderate

   Admit and give supplemental oxygen to maintain $SpO_2 \geq 93\%$

   NPA for viral immunofluorescence and culture

   Maintain hydration with nasogastric or intravenous fluids if significantly dehydrated

   CXR

   Monitor closely for deterioration

   Consider trial of nebulised 3% HS

Severe

   As for moderate bronchiolitis: NPA, CXR, 3% HS and supplemental oxygen

   Nil by mouth and intravenous fluids

   Continuous cardiorespiratory monitoring

   Monitor arterial blood gases (CO_2 retention), renal function and serum electrolytes

   Consider consultation with intensive care or paediatric emergency retrieval service

   Anticipate possible need for non-invasive respiratory support or intubation and ventilation

3% HS, 3% hypertonic saline; CXR, chest radiograph; NPA, nasopharyngeal aspirate.

feeding is a commonly practiced method to ease nasal congestion, but this has not been subjected to a randomised trial.

Physiotherapy

A Cochrane review found no evidence to support the use of physiotherapy in the care of infants with bronchiolitis.[29]

Nasal continuous positive airway pressure

The role of nasal continuous positive airway pressure has increased in recent years. It has been shown to be efficacious in the setting of rising oxygen requirements in an infant who is tiring, where it is useful for reducing the need for endotracheal intubation.[28] The utility of continuous positive airway pressure is also seen in preterm infants or very young term infants with apnoea.

Pharmacological Treatment at Presentation

Oxygen

Supplemental oxygen delivered via headbox or nasal catheters is the mainstay of therapy for infants with hypoxaemia. However, despite the fact that the oxygen flow rate required to maintain satisfactory oxygenation is used as a proxy for severity, it has been recently demonstrated that it is not possible to reliably estimate the FiO_2 reliably from nasal oxygen flow rates in infants with bronchiolitis.[30] There are no universally accepted thresholds for introducing or weaning supplemental oxygen. In general terms, one would aim to maintain an $SpO_2 \geq 93\%$ in the acute phase and, during recovery, an $SpO_2 \geq 90\%$ in an infant who was feeding adequately and otherwise ready for discharge.[3]

Bronchodilators

There is no evidence that the bronchodilators salbutamol and ipratropium bromide are associated with a clinically significant benefit when administered to infants with bronchiolitis.[31,32] Limited by overlap between infants with bronchiolitis and patients with viral-induced recurrent wheeze, a Cochrane review found that bronchodilators did not improve oxygenation or duration of hospitalisation, but did modestly improve clinical scores.

Adrenaline

An Australian randomised controlled trial[33] and a Cochrane review[34] have failed to demonstrate any clinically significant benefit for the use of nebulised adrenaline for infants admitted to hospital with bronchiolitis.

Systemic corticosteroids

Another Cochrane review determined that systemic corticosteroids for bronchiolitis have no impact on clinical scores, admission rates, length of stay or readmission rates.[35]

Combined nebulised adrenaline and oral dexamethasone

A recent study suggested a modest benefit of this combined therapy in bronchiolitis, despite the lack of efficacy of the individual treatments.[36] One would need to treat 11 infants for 1 to benefit. The clinical significance of this treatment is unclear and not recommended for routine therapy.

Nebulised 3% hypertonic saline

One of the few therapies, albeit on the basis of only four small trials assessed in a Cochrane Review, shown to improve clinical scores and reduce the length of stay is nebulised 3% hypertonic saline.[37] Bronchodilators were given in three of the four studies to minimise the risk of induced bronchospasm from the hypertonic saline.

Antibiotics

There is no role for the routine use of antibiotics, including macrolides, in bronchiolitis, as the rate of bacteraemia and secondary bacterial infection is extremely low.[3,38,39]

Ribavirin

This expensive therapy has been used in the intensive care setting but has not been shown to be efficacious in the treatment of bronchiolitis in a Cochrane Review.[40] Ribavirin has not

Table 5 Summary of Cochrane Reviews of treatment options in bronchiolitis

Intervention	Year of Cochrane Review	Conclusion
Physiotherapy	2005[29]	No benefit
Systemic corticosteroids	2007[35]	No benefit
Inhaled corticosteroids	2007[41]	No benefit
Bronchodilators	2006[31]	Probably no significant benefit: not recommended. (case definition problems)
Nebulised adrenaline	2004[34]	No benefit
Nebulised 3% hypertonic saline	2008[37]	Useful: improved clinical scores
Antibiotics	2007[38]	No benefit
Ribavirin	2004[40]	No benefit

been shown to reduce hospitalisation or mortality, and no long-term benefits have been demonstrated with regard to the prevalence of recurrent wheeze or pulmonary function results. There exist concerns about cost, toxicity to staff and, in particular, potential teratogenicity.

Immunoglobulins

There is no evidence to support the use of intravenous immunoglobulins in the treatment of bronchiolitis.[27]

Clinical Course

The course for infants requiring hospitalisation varies considerably, from a brief period of observation and improvement over 1–3 days up to prolonged admissions, more commonly in those with predisposing respiratory, cardiac or neuromuscular conditions. During the admission, care is supportive with the provision of adequate hydration and satisfactory oxygenation. Due care is required to minimise the risk of cross infection, with standard hand-washing practices widely used to minimise the risk of fomite spread.[3] Pharmacological treatment options are limited (Table 5). The criteria for discharge vary, but most infants can be discharged when feeding adequately and when able to maintain adequate oxygenation ($SpO_2 > 90$–92%).[3] Discharge timing will be influenced by the ability of the parents to attend to the needs of the recovering infant. Ideally, infants admitted to hospital should be reviewed by their general practitioner in the week following discharge. Should the infant develop a persisting cough, tachypnoea or wheeze, review by a paediatrician or respiratory paediatrician should be considered.

Pharmacological Treatment of Post-Bronchiolitis Wheezing

Montelukast

Studies have examined the role of the non-steroidal leukotriene receptor antagonist, montelukast, commenced during an episode of bronchiolitis[42] and for post-bronchiolitic wheeze,[43] and found the treatment no better than placebo.

Inhaled corticosteroids

Neither nebulised budesonide (1 mg bd) delivered via a nebuliser during acute bronchiolitis[44] nor twice daily beclometasone (200 mcg bd) via a metered dose inhaler and spacer for 3 months following RSV-positive bronchiolitis[45] was of any clinically significant benefit.

Prophylaxis Against RSV Infection

There are no vaccines available to prevent RSV infection. The only commercially available pharmacological strategy to prevent RSV infection in Australasia presently is palivizumab, a mouse monoclonal antibody given in five monthly injections that can be used to provide passive immunity to infants at risk of RSV infection.[3] The therapy reduced the risk of hospitalisation for RSV infection by 50%, from approximately 10% to 5%, in randomised controlled trials in children born preterm[46] and in children with haemodynamically significant congenital heart disease.[47] The therapy is licensed in Australia, is expensive and is not currently reimbursed by the Pharmaceutical Benefits Scheme. Palivizumab has been criticised as not being cost-effective,[27,48] but, despite this, it is used widely overseas, with many countries having their own guidelines encompassing its use in preterm infants with and without chronic neonatal lung disease, congenital heart disease and immunodeficiencies.[3,49] The use of palivizumab is arguably best considered on a more limited scale for the most vulnerable infants.[50]

Declaration of Potential Conflict of Interest

Over the last 5 years, DF has received remuneration from Abbott Australasia, makers of Synagis (palivizumab), for advice on the role of this drug in Australia. In addition, DF has presented at, and/or attended, educational meetings in Australia either partly or wholly sponsored by Merck, Sharpe & Dohme Australasia, GlaxoSmithKline and AstraZeneca, makers of asthma medications.

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Appendix I

Multiple choice questions

1. Infants at greater risk for hospitalisation with RSV +ve bronchiolitis:

a. Secundum ASD   [F]
b. Tetralogy of Fallot   [T]
c. Preterm delivery at <28 weeks gestation   [T]
d. Transient tachypnoea of the newborn   [F]
e. Hereditary spherocytosis   [F]

Infants with extreme preterm delivery and those with haemodynamically significant cardiac disease are at greater risk of hospitalisation for RSV +ve bronchiolitis.

2. The following pharmacological treatments are of benefit in infants hospitalised with bronchiolitis:

a. Inhaled corticosteroids   [F]
b. Nebulised 3% hypertonic saline   [T]
c. Nebulised adrenaline   [F]
d. Ribavirin   [F]
e. Montelukast   [F]

Only nebulised 3% hypertonic saline has been shown to be of benefit in bronchiolitis.

3. An infant with mild bronchiolitis will display the following signs:

a. Mild tachypnoea   [T]
b. Significant hypoxaemia (SpO2 < 90%)   [F]
c. Dehydration   [F]
d. Carbon dioxide retention on a blood gas   [F]
e. Apnoea   [F]

Mild bronchiolitis will be associated with mild tachypnoea, although gas exchange, feeding and hydration will not be significantly compromised.