

Viral bronchiolitis is a common worldwide disease of infants and young children. It is a significant cause of hospitalisation in infancy. In the year 2002–3, 0.1% of all hospital bed days in England were for acute bronchiolitis with a mean length of stay of 2.7 days,<sup>1</sup> and in a study in one UK region the incidence of bronchiolitic related admission was 30.8 per 1000 infants.<sup>2</sup>

### **PATHOPHYSIOLOGY**

The underlying pathophysiology is inflammation of the small airways (bronchioles). Infection of the bronchiolar and ciliated epithelial cells produces increased mucous secretion, cell death and sloughing, followed by a peribronchiolar lymphocytic infiltrate and submucosal oedema.<sup>3</sup> This combination of debris and oedema results in distal airway obstruction. During expiration, the additional dynamic narrowing produces disproportionate airflow decrease and air trapping. The effort of breathing is increased due to increased end expiratory lung volume and decreased lung compliance.<sup>3</sup> Recovery of pulmonary epithelial cells occurs after 3–4 days, but cilia do not regenerate for approximately two weeks.<sup>3</sup> The debris is cleared by macrophages.

### **EPIDEMIOLOGY**

Fifty to ninety per cent of bronchiolitis is caused by respiratory syncytial virus (RSV) infection.<sup>4</sup> RSV is a negative-sense, enveloped RNA virus that is unstable in the environment, surviving only a few hours on environmental surfaces. RSV is spread from respiratory secretions through close contact with infected persons or contact with contaminated surfaces or objects. Infection can occur when infectious material contacts mucous membranes of the eyes, mouth, or nose, and possibly through the inhalation of droplets generated by a sneeze or cough.<sup>5</sup> RSV infects virtually all infants and young children in the first 3 years of life with a peak incidence of hospitalised patients between 2–6 months of life.<sup>6</sup> During their first RSV infection, between 25–40% of infants and young children have signs or symptoms of bronchiolitis or pneumonia, and 0.5–2.5% require hospitalisation.<sup>2, 5</sup> In the USA it is estimated that there are 90 000 hospitalisations and 4500 deaths annually with RSV bronchiolitis, and in the UK there are 20 000 admissions annually with this condition.<sup>3, 4</sup> Mortality runs as high as 0.5–1.5% in hospitalised patients, increasing to 3–4% for patients with underlying cardiac or pulmonary disease.<sup>3, 4</sup>

RSV is the only respiratory virus to produce predictably a sizeable outbreak of infection each year.<sup>6</sup> There are two main antigenic groups, A and B, and RSV A and RSV B may both be present in an epidemic, the proportion of the two groups varying each year and by location.<sup>4</sup> Epidemics occur in the winter months in temperate climates, and in tropical climates during the hottest months and the rainy season.<sup>4, 7</sup> In the UK, epidemics run from mid November to late March with annual variation in the severity of the epidemics.<sup>4</sup> Because RSV infection only confers partial protection from subsequent infection, re-infection with RSV is frequent and occurs throughout life, but after 3 years of age infections are generally milder and confined to the upper respiratory tract.<sup>4, 6, 8</sup>

Other organisms that cause bronchiolitis include parainfluenza, rhinovirus, adenovirus, influenza, *Mycoplasma pneumoniae*, and metapneumovirus.<sup>4, 9</sup>

### **RISK FACTORS**

There are host and environmental factors related to disease severity (table 1). Host factors that are associated with increased severity of disease include prematurity, infection before 6 months of age, congenital heart disease, bronchopulmonary dysplasia, cystic fibrosis, and immune deficiency.<sup>4, 7, 10, 11</sup> There are some indicators that there may be a genetic predisposition to severe infection.<sup>4, 6, 12, 13</sup>

Environmental factors that are associated with increased severity of disease include poverty, crowding, exposure to tobacco smoke, and malnutrition.<sup>7, 10, 14, 15</sup>

Factors that increase incidence of infection include young age, multiple gestation, family history of atopy, lack of parental education, household crowding, lack of breastfeeding, older

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**Table 1** Risk factors for severe bronchiolitis

Host factors	Environmental factors
Preterm	Poverty
Age less than 6 weeks	Over crowding
Congenital heart disease	Exposure to postnatal tobacco smoke
Chronic respiratory disease (BPD, CF)	Malnutrition
Immune deficiency	

BPD, bronchopulmonary dysplasia; CF, cystic fibrosis

school age siblings, daycare attendance, passive smoke exposure, and discharge from a neonatal intensive care unit between September and December (northern hemisphere).<sup>4 7 11 16</sup> Boys are 1.25 times more likely to be admitted than girls.<sup>3 4</sup>

### CLINICAL FEATURES

The clinical syndrome of bronchiolitis typically begins with an upper respiratory tract infection manifest by fever and coryza. After 2–3 days, the lower respiratory tract involvement becomes obvious with worsening cough and shortness of breath. Apnoea is a frequent complication and may occur in up to 20% of cases, particularly in premature infants.<sup>6</sup> Clinical examination findings include increased respiratory effort, wheezing and fine crackles on auscultation, and dehydration.

Most infants show signs of improvement within 3–4 days after the onset of lower respiratory tract disease.

Otitis media is frequently seen in association with RSV bronchiolitis.<sup>6 17</sup> However, serious bacterial infection rarely accompanies RSV bronchiolitis.<sup>6 18</sup> Routine antibiotic treatment does not improve the recovery of infants with RSV lower respiratory infection.<sup>6 18 19</sup>

The chest x ray, if performed, typically shows hyperinflation. Consolidation is found in up to 25% of cases but generally the severity of the infant's illness is not mirrored by radiological changes.<sup>6 20</sup>

### DIAGNOSIS

Diagnosis can be confirmed by finding evidence of RSV infection from nasopharyngeal aspirates. Rapid diagnosis is available using immunofluorescence, both direct and indirect, which has high sensitivity and specificity, and by enzyme linked immunosorbent assay (ELISA) which has slightly less sensitivity. Cell culture generally takes too long (4–5 days) to be of use clinically. Serological diagnosis is not appropriate in infants as there may be a poor serological response and seroconversion may take weeks.<sup>6</sup>

## MANAGEMENT OF ACUTE ILLNESS

### Investigations

The diagnosis is usually a clinical one and investigations are not generally needed to confirm diagnosis.

Confirmation of RSV infection can be made by isolation of the virus from nasopharyngeal aspirates by immunofluorescence or ELISA. This is particularly useful if infants are to be nursed in the same room or by the same nurse, as RSV is a major nosocomial pathogen in paediatric wards.<sup>6</sup>

It is not necessary to perform a chest x ray routinely on infants as it does not predict severity and does not alter management.<sup>6 20</sup> Infants requiring assisted ventilation by continuous positive airways pressure (CPAP) or full ventilation may benefit from a chest x ray.

Blood tests are not usually helpful in management and should not be routinely performed.

### Therapeutic interventions

Treatment is largely supportive, paying attention to hydration and maintaining satisfactory oxygenation (table 2).<sup>21–24</sup>

#### Oxygen

The oxygen saturation level should at least be kept above 92%. Some units elect to maintain the oxygen saturation above 95%. There are no systematic reviews or randomised controlled trials on the use of oxygen, but extrapolated evidence from case-control studies shows hypoxaemia as a risk factor for near-fatal asthma.<sup>25</sup>

#### Antibiotics

As mentioned above, there is no place for the routine use of antibiotics in infants with bronchiolitis. They do not alter the course of disease.<sup>19</sup> Although the risk of serious bacterial infection is low in infants with RSV bronchiolitis,<sup>18</sup> many clinicians would elect to add antibiotics to the regimen of infants requiring assisted ventilation.

#### Bronchodilators

Bronchodilators are used frequently in the management of bronchiolitis.<sup>26–28</sup> In the UK, ipratropium bromide is used frequently, while in the USA salbutamol (albuterol) is used more often. Systematic reviews have shown there is only modest benefit from bronchodilators in short term clinical scores.<sup>29–31</sup> The significance of this effect is not clear, particularly as the studies in the systematic reviews used different agents and different outcome measures. Many units elect to give a trial of a bronchodilator and, if there is no positive response, it is discontinued. As some of these first time wheezing infants may have asthma, this does not seem an unreasonable approach.

**Table 2** The evidence behind the treatments for acute bronchiolitis

Oxygen	Observational studies	Give if oxygen saturation < 92%
Antibiotics	Controlled trial/observational studies	Not indicated routinely
Bronchodilators	Systematic reviews	Only modest improvement in clinical score. Trial may be indicated
Adrenaline	Systematic review	Some benefit in outpatient setting. Trial may be indicated. Further research needed
Steroids	Systematic review	No evidence of benefit
Chest physiotherapy	Systematic review awaited	No evidence of benefit currently
Ribavirin	Systematic review	No evidence although a suggestion of benefit in high risk infants. Consider if very ill infant with risk factors
RSV Ig	Systematic review awaited	No evidence of benefit currently
Palivizumab	Randomised controlled trial	No evidence of benefit currently

## Adrenaline

Adrenaline (epinephrine) has both  $\alpha$  and  $\beta$  adrenergic properties and the  $\alpha$  adrenergic effect, via vasoconstriction of the pulmonary vessels and reduction in oedema, has been considered a possible useful action in the treatment of bronchiolitis.<sup>32</sup> One study found that adrenaline substantially improved respiratory system resistance but not oxygenation or ventilation indices.<sup>33</sup>

Most of the studies of adrenaline show it has a good safety profile,<sup>32 34-42</sup> although there is one report of non-fatal myocardial infarction in a child who presented with croup and was given repeated doses of nebulised adrenaline. In studies where a benefit has been seen in bronchiolitis (in the outpatient setting), only limited doses of adrenaline have been given.<sup>32 35</sup>

A systematic review on the use of nebulised adrenaline in bronchiolitis has shown some benefits in the outpatient setting (such as clinical score improvements and improved oxygenation) but little convincing evidence for its use in the inpatient setting.<sup>43 44</sup> The authors concluded that large multicentre randomised controlled trials are necessary to address fully the usefulness of adrenaline in the treatment of bronchiolitis. Like bronchodilators, a trial may be appropriate to assess the individual infant's response.

## Steroids

Steroids (inhaled and oral) have been used in the acute management of bronchiolitis in an attempt to reduce both acute symptoms and post-bronchiolitic wheeze (see below). Despite studies with varying results, a systematic review has failed to show any benefit from steroids in the acute management of bronchiolitis.<sup>45 46</sup> Studies where positive effects have been shown have often failed to exclude infants with recurrent wheeze who may have asthma and so respond to steroids.<sup>31</sup> There is no evidence to support the use of steroids in the acute management of bronchiolitis.

## Chest physiotherapy

There is no compelling evidence on the effectiveness of chest physiotherapy in bronchiolitis and a Cochrane review is

currently underway.<sup>47</sup> Minimal handling is thought by many to be important in the acute management of bronchiolitis<sup>21</sup> and without any evidence to support the use of chest physiotherapy, it should not be part of routine management.

## Ribavirin

Ribavirin is a purine nucleoside analogue. It is believed to interfere with the normal function of viral nucleic acid.<sup>48</sup> Ribavirin has activity towards RSV, influenza, and hepatitis C.<sup>48</sup> Systematic reviews have failed to show any effect from the use of ribavirin in the acute setting, although there is a suggestion of benefit (although not significant) in those with severe disease requiring intensive care.<sup>31 49</sup>

Although early guidelines suggested that it be administered as an aerosol for 12–18 hours daily, it has been used in shorter bursts (two hours three times per day) in the same dose of 6 g/day. It is given for 3–5 days. The short burst regimen cannot be used in ventilated patients as it causes increased deposition in ventilator circuits.

Ribavirin is expensive and difficult to administer and, as a result, its use is generally restricted to those patients who are at risk of severe infection.<sup>48</sup> Ribavirin is potentially toxic not only to the patient but also to those in close contact with the patient. It has been shown to be teratogenic in animal studies and pregnant women should avoid contact with patients receiving the drug.<sup>48</sup> The difficulty of administration along with the potential toxicity and the limited evidence supporting its use means ribavirin is not widely used as a treatment for acute bronchiolitis.

## RSV immunoglobulin

RSV immunoglobulin (RSV Ig) is derived from adult donors with high anti-RSV titres. It has a low risk of blood borne viral transmission because of the sterilisation process it goes through.<sup>48</sup> RSV Ig has been used for the acute treatment of bronchiolitis and for prevention (see below).

There is currently no evidence to support the use of RSV Ig in the acute management of bronchiolitis.<sup>31</sup> A systematic review is planned.<sup>50</sup>

ep83

**Table 3** Suggested guideline for management of outpatient management of bronchiolitis

### Management depends on severity

#### Mild (fulfils criteria below)

Minimal respiratory distress only	Oxygen saturation >95% in air
Feeding well	No risk factors
At least 3 months of age	Respiratory rate <50
No social concerns	Parents happy for discharge

No specific treatment or investigations necessary. Can be discharged. Advise parents to give small, frequent feeds. Advise them to return promptly if there is deterioration in symptoms, such as inability to feed or infant working harder

#### Moderate (fulfils criteria below)

Mild-moderate respiratory distress	Oxygen saturation 92–95% in air
Respiratory rate 50–70	No risk factors

Refer to paediatric team. Needs a period of assessment, including serial assessment of respiratory distress, oxygen saturations, and monitoring of feeds.

Consider trial of two doses of adrenaline 3 ml 1:1000 nebulised 30 minutes apart (observe for at least 2 hours following administration of adrenaline)

If feeding satisfactory and respiratory distress improved, discharge with advice to return promptly if there is deterioration in symptoms, such as inability to feed or infant working harder. Advise small, frequent feeds

#### Severe (fulfils any of the following criteria)

Moderate-severe respiratory distress	Oxygen saturation <92%
Risk factors (table 1)	Respiratory rate >70
Poor feeding	Looks ill/toxic
Apnoea	Social concerns

Admit

**Table 4** Suggested guideline for infants admitted with bronchiolitis

Investigations	<i>Not usually required</i> Nasopharyngeal aspirate: not required if diagnosis clear and no need for cohort nursing FBC, U&E, blood cultures: only consider if siting an intravenous (iv) line Chest x ray: only if deteriorating or requiring ventilatory support Arterial blood gas: only if tiring or if $\text{FI}_{\text{O}_2} > 40\%$
Prevention of cross infection	Strict handwashing for staff and family Isolate or cohort nurse If nursing in cohort, nurse RSV positive babies together
Oxygen	To maintain $\text{SaO}_2 > 92\%$ humidified Give via headbox in infants < 3 months of age to avoid blocking nostril
Fluids	Small, frequent feeds 2–3 hourly Orally if no increased oxygen requirements with feeds and RR < 50 Via orogastric or nasogastric if RR 50–60, and respiratory distress does not increase with feeds Give iv fluids at 2/3 maintenance if RR > 60 or respiratory distress increases with gastric feeds
Bronchodilators	Consider giving trial of ipratropium 125 µg. Reassess 10–20 mins after administration and only continue if clear benefit
Ventilatory support	Consider if increasing oxygen requirements, increasing respiratory distress, fatigue, recurrent apnoea, arterial blood gases deteriorating, agitation, peripheral shut down

FBC, full blood count;  $\text{FI}_{\text{O}_2}$ , fraction of inspired oxygen; RR, respiratory rate; RSV, respiratory syncytial virus;  $\text{SaO}_2$ , arterial oxygen saturation; U&E, urea and electrolytes.

### Palivizumab

Palivizumab is a humanised monoclonal antibody produced with recombinant DNA technology and has similar activity against both strains (A and B) of RSV.<sup>48</sup> There is no evidence that palivizumab is effective in the acute treatment of bronchiolitis.<sup>31</sup> It has been used to prevent RSV bronchiolitis (see below).

### Assisted ventilation

RSV bronchiolitis can cause severe respiratory compromise and occasionally ventilatory support is necessary. Many units have the facility for continuous positive airway pressure (CPAP) in a high dependency area and there is good supportive evidence for this practice.<sup>51–52</sup> Some infants require full ventilation in an intensive care setting.

### Other treatments

Other treatments including interferon, vitamin A, and recombinant human deoxyribonuclease I (rhDNaseI) have been tried but have shown no benefit. Chinese herbs,<sup>53</sup> surfactant,<sup>54–55</sup> and Heliox<sup>56–58</sup> possibly warrant further investigation. On current evidence, surfactant and Heliox (helium and oxygen) should be reserved for use in patients in paediatric intensive care units.

### PROGNOSIS

A significant number of patients who are hospitalised for bronchiolitis subsequently have recurrent episodes of wheeze and may develop asthma later in life.<sup>31</sup> There is some evidence that infants who develop RSV bronchiolitis have reduced lung function before becoming infected with RSV<sup>59</sup> and that there is a genetic predisposition to post-bronchiolitic wheeze.<sup>13</sup> Debate continues around the exact mechanism of the post-bronchiolitic wheeze and whether RSV is a cause or a consequence of airway pathology.<sup>60</sup>

It is apparent from cohort studies that if there is no family history of atopy, the wheezing tendency post-bronchiolitis will resolve by 10 years of age.<sup>45–61–62</sup>

### Prevention of post-bronchiolitic wheeze

Despite many studies looking to prevent the post-bronchiolitic wheeze seen after RSV bronchiolitis, no treatment has been shown to be effective. Steroids, used during the acute phase, have been studied most widely in this context without

revealing consistently successful results. A systematic review of the use of steroids to prevent post-bronchiolitic wheeze has shown no effect and currently there is no evidence to support the use of steroids in bronchiolitis to prevent post-bronchiolitic wheeze.<sup>45</sup> Ribavirin has also been studied without success.<sup>49–63</sup>

### PREVENTATIVE TREATMENTS

As mentioned above, a number of treatment regimens have been employed to reduce infection with RSV bronchiolitis.

#### RSV Ig and palivizumab

Both RSV Ig and palivizumab have been shown to reduce RSV bronchiolitis admissions.<sup>64–65</sup> Although both RSV Ig and palivizumab are licensed for use in prevention of RSV bronchiolitis, only palivizumab can be used in infants with haemodynamically significant congenital heart disease.<sup>66</sup> If RSV Ig is used, it must be remembered that it may inactivate live vaccines (such as measles-mumps-rubella) and these may need to be repeated nine months after the administration of RSV Ig.

Both RSV Ig and palivizumab are expensive to administer (RSV Ig is given monthly by intravenous injection for five months, and palivizumab is given monthly by intramuscular injection for five months—starting October to December), but palivizumab has been shown to be more cost effective and is generally favoured as the prophylactic agent of choice.<sup>66–67</sup>

Palivizumab was seen in a large multicentre randomised controlled trial to reduce hospital admissions by 55% when used prophylactically in high risk infants (preterm less than 32 weeks' gestation) although there was no difference in mortality.<sup>64</sup> The expense of introducing routine prophylaxis with palivizumab is considered prohibitive and several

**Table 5** Discharge advice for parents

- ▶ Inform parents that they should refrain from smoking
- ▶ Inform parents that re-infection may occur
- ▶ Inform the parents that there is an increased risk of wheezing after bronchiolitis, more so if there is a history of atopy. If there is no history of atopy, most infants "grow out" of their wheeze by age 10 years

studies have examined the feasibility of such an approach.<sup>33–68–71</sup> The consensus seems to be that palivizumab prophylaxis should not be routinely administered to all preterm infants but be reserved for those most at risk.<sup>33–68–71</sup> A cost effectiveness study showed that preterm infants with bronchopulmonary dysplasia who were discharged home from the neonatal intensive care unit between September and December and required home oxygen were those most likely to benefit.<sup>67</sup> The American Academy of Pediatrics has published revised guidance on the use of palivizumab for prevention of RSV infection to only cover preterm infants who have at least two other risk factors rather than routine administration to all preterm infants.<sup>66</sup>

### Handwashing and limiting contact

There are no systematic reviews or randomised controlled trials on these measures, but observational studies have shown that cohort nursing, handwashing, and eye-nose goggles all reduce nosocomial infection when used alone.<sup>31</sup> Guidance from the Centers for Disease Control and Prevention suggest frequent handwashing and not sharing items such as cups, glasses, and utensils with persons who have RSV illness should reduce the risk of spread.<sup>8</sup> It is not thought necessary to exclude children with colds or other respiratory illnesses (without fever), who are well enough to attend, from daycare or school settings.<sup>8</sup> In the hospital setting, general consensus is that there should be strict adherence to handwashing, and gowns and gloves should be worn.<sup>8</sup> There is also advice to limit the numbers of patient contacts and visitors during epidemics.<sup>6</sup>

### Smoking

There is strong evidence that smoking increases the risk of admission with bronchiolitis and this appears to be a post-natal exposure rather than antenatal.<sup>10–14</sup> It would follow that ensuring parents did not smoke in the same room as their infants would be wise advice to reduce RSV bronchiolitis.

### Vaccination

Development of a RSV vaccine is a high research priority. The problems are that the vaccine would have to induce an immunity that is more durable than that seen after natural infection, and it would have to be given at a very young age when maternal antibodies are present (neonates receive high titres of maternally acquired anti-RSV antibody which explains why infection is uncommon in the first 4 weeks of life<sup>4</sup>). The first vaccine produced was an inactivated vaccine which produced high levels of serum antibody but resulted in a more severe course of disease following infection by the wild virus.<sup>4–6</sup> Currently, trials are being carried out on various vaccines including vaccines that target the fusion (F) and attachment (G) transmembrane glycoproteins of the RSV virus.<sup>4–6</sup>

### USE OF A GUIDELINE FOR MANAGEMENT OF BRONCHIOLITIS

Even within countries, there is wide variation in the management of bronchiolitis<sup>27–28–69</sup> and it has been shown that introduction of an evidence based clinical practice guideline can significantly alter practice, such as reducing the routine use of bronchodilators and the requests for chest x rays.<sup>72–73</sup> Consideration should be given to developing local guidance that is evidence based to ensure appropriate management of this common condition. Suggested guide-

lines for the management of bronchiolitis in the inpatient and outpatient (usually a paediatric acute assessment unit or emergency department) settings are included in this paper (tables 3–5). They are based on the evidence as discussed in the paper and can be used in the published form or modified for local use.

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