Bronchiolitis: an update on management and prophylaxis

ABSTRACT

Bronchiolitis is an acute respiratory illness that is the leading cause of hospitalization in young children less than 2 years of age in the UK. Respiratory syncytial virus is the most common virus associated with bronchiolitis and has the highest disease severity, mortality and cost. Bronchiolitis is generally a self-limiting condition, but can have serious consequences in infants who are very young, premature, or have underlying comorbidities. Management of bronchiolitis in the UK is guided by the National Institute for Health and Care Excellence (2015) guidance. The mainstays of management are largely supportive, consisting of fluid management and respiratory support. Pharmacological interventions including nebulized bronchodilators, steroids and antibiotics generally have limited or no evidence of efficacy and are not advised by National Institute of Health and Care Excellence. Antiviral therapeutics remain in development.

As treatments are limited, there have been extensive efforts to develop vaccines, mainly targeting respiratory syncytial virus. At present, the only licensed product is a monoclonal antibody for passive immunisation. Its cost restricts its use to those at highest risk. Vaccines for active immunisation of pregnant women and young infants are also being developed.

Bronchiolitis, an acute respiratory illness, is the leading cause of hospitalization in children less than 2 years of age in developed countries (Hasegawa et al, 2013). In the UK, 2–3% of all infants less than 12 months of age will be hospitalized with bronchiolitis (Murray et al, 2014). Bronchiolitis is caused by respiratory viruses that invade the epithelial cells of the small airways leading to excessive mucus production, obstruction of the bronchioles, varying degrees of bronchospasm and air trapping. Respiratory syncytial virus is the most common virus associated with bronchiolitis, followed by rhinovirus, parainfluenza virus, human metapneumovirus, influenza virus, adenovirus, coronavirus and human bocavirus. In roughly one third of cases, more than one virus is detected (Mansbach et al, 2012).

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Bronchiolitis begins with upper respiratory tract symptoms of rhinorrhoea followed by persistent cough, tachypnoea, chest wall recessions and widespread crackles, wheeze or both, which peak on days three to five and then gradually resolve in most previously healthy infants (Florin et al, 2017). In a systematic review including 590 children with mild disease that did not require admission to hospital, cough resolved in half of the cases within 2 weeks and in 90% within 3 weeks (Thompson et al, 2013). However, infants less than 3 months of age, or born prematurely (less than 32 weeks' gestation) or with underlying cardiopulmonary disease (chronic lung disease, haemodynamically significant congenital heart disease), or immunodeficiency, or neuromuscular disorders are at high risk of severe disease. The most common complications are dehydration, apnoea and secondary bacterial infection.

A small proportion of infants with bronchiolitis may develop respiratory failure and require mechanical ventilation. An association between hospitalization with respiratory syncytial virus bronchiolitis and asthma later in life is increasingly recognized (Régnier and Huels, 2013). Likewise, higher use of asthma medication has been observed during the first year after hospitalization in infants with rhinovirus-positive bronchiolitis (Bergroth et al, 2016).

In the UK, hospital admission rates for bronchiolitis rose sevenfold between 1979 and 2011 (Green et al, 2016). In this period intensive care admission rates did not increase, suggesting that rising hospital admissions for bronchiolitis are not related to changes in disease severity but to clinical practice. Much of this increase relates to how readily relative hypoxaemia is identified using pulse oximetry.

The high incidence of disease, the lack of a highly effective treatment or preventive intervention and the need for cost-effective use of health-care resources led to a large body of research integrated into national guidelines that tried to tackle the inconsistency in clinical practice. Multiple studies use a range of differing outcome measures, ranging from changes in physiological parameters, the need for escalation of therapy through to length of stay. For the majority of admitted infants who will not need intensive care, duration of admission matters most. This is usually driven by duration of supplementary oxygen. In most cases, ability to tolerate feeds recovers

before dependency on oxygen. Overall, proxy outcomes such as heart rate, respiratory rate, oxygen saturation or work of breathing are considered less important than length of admission.

In England and Wales, the National Institute for Health and Care Excellence (2015) published a guideline for the hospital management of bronchiolitis (*Tables 1* and *2*). Before this, hospital trusts in the UK based their local guidelines on the Scottish Intercollegiate Guideline Network guideline published in 2006 and withdrawn in 2015. This article summarizes current recommendations by National Institute for Health and Care Excellence on the management and prevention of bronchiolitis, and focuses on some important more recent publications.

Fluid management

The combination of increased work of breathing, persistent cough and copious nasal secretions can affect oral intake. Oxygen supplementation can improve respiratory distress to allow adequate fluid intake. Small and frequent feeds are usually tolerated better. For those who cannot maintain hydration orally, orogastric or nasogastric feeding may be needed. A randomized trial in Australia and New Zealand including 759 infants less than 1 year of age admitted to hospital with bronchiolitis showed no benefit of giving fluids intravenously *vs* via nasogastric tube on length of hospital stay (absolute difference 4.5 h, 95% confidence interval -3.9–12.9; P=0.30). Nasogastric insertion was easier than intravenous cannulation (first attempt success rate 85% *vs* 56%; P<0.0001) (Oakley et al, 2013). Intravenous fluids should be reserved for infants with impeding respiratory failure unable to tolerate enteral feeding. In this case, fluid replacement is better restricted to two thirds of maintenance requirement to prevent electrolyte imbalance caused by inappropriate secretion of antidiuretic hormone (Hanna et al, 2003).

Respiratory support

Respiratory support is generally provided in a stepwise approach. Most children receive nasal suctioning. Supplemental oxygen is administered to those with oxygen saturations below 92%. Those with more severe disease often receive a trial of heated humidified high-flow nasal cannula therapy and/or continuous positive airway pressure before endotracheal intubation, although in the most severe cases intubation should not be delayed by a trial of non-invasive ventilation.

Nasal suctioning

Routine suctioning of the nasopharynx is not supported by the existing evidence (Mussman et al, 2013). However, it is recommended by the National Institute for Health and Care Excellence for symptomatic relief of nasal congestion in infants with apnoeas, respiratory distress or feeding difficulties, and in children with apnoea even in the absence of obvious secretions.

Table 1. Indications for hospital admission

Apnoea (observed or reported)	
Persistent oxygen saturation less than 92%	
Inadequate oral fluid intake (50–75% of usual volume)	
Signs of severe respiratory distress	■ Respiratory rate >70/min
	■ Nasal flaring
	■ Grunting
	■ Severe chest wall recessions

From National Institute for Health and Care Excellence (2015)

Table 2. Key recommendations for hospital management

Do not routinely perform chest X-rays or blood gases
Do not routinely prescribe bronchodilators, nebulized adrenaline, steroids, nebulized hypertonic saline, antibiotics, leukotriene receptor antagonists or ribavirin
Do not routinely perform physiotherapy
Give supplemental oxygen if saturations <92% in air
Give fluids by nasogastric or orogastric tube in children with bronchiolitis if they cannot take in enough fluid by mouth
Perform upper airway suctioning in babies with apnoea
Provide written information for parents

From National Institute for Health and Care Excellence (2015)

Supplemental oxygen

Oxygen is the mainstay of treatment for respiratory distress, and is usually administered via nasal cannula, face mask, head box, or wafted near the face to minimize handling. Even though pulse oxygen saturation is widely used to guide decisions to initiate oxygen administration, there is no agreed definition of hypoxaemia in bronchiolitis. In the UK, the National Institute for Health and Care Excellence recommends supplemental oxygen when oxygen saturation readings drop below 92%, while the American Academy of Pediatrics suggests a threshold of 90% (Ralston et al, 2014). A double-blind, randomized, equivalence trial of 615 infants admitted with bronchiolitis in the UK compared pulse oxygen saturation of 94% with a lower threshold of 90% (Cunningham et al, 2015). No difference was found in duration of cough, need for invasive respiratory support or rates of readmission, whereas the length of hospital stay was shorter in the 90% threshold arm. This suggests that stopping supplementary oxygen therapy in the recovery phase sooner than recommended in current guidelines is likely to be safe.

High-flow nasal cannula therapy

High-flow nasal cannula oxygen is a non-invasive method of ventilation. Its main advantage is that it allows

Table 3. Impending respiratory failure

If any signs of exhaustion are present:	Listlessness
	Decreased respiratory effort
	Recurrent apnoea
	Failure to maintain adequate oxygen saturation despite oxygen supplementation

From National Institute for Health and Care Excellence (2015)

high-flow oxygen to be safely delivered without damaging the respiratory mucosa because the air is heated and humidified. Its beneficial effect is exerted by reducing the respiratory resistance of the nasal passages and delivering low levels of positive airway pressure.

In recent years high-flow nasal cannula therapy has been increasingly used for the management of bronchiolitis. Despite this, its use is not recommended in current National Institute for Health and Care Excellence guidelines. A Cochrane review in 2014 concluded that evidence was insufficient to determine the effectiveness of high-flow nasal cannula therapy (Mayfield et al, 2014). However, two randomized trials have shown benefit in preventing paediatric intensive care unit admissions and escalation of care. In a randomized controlled trial in a non-intensive care setting of 202 children younger than 2 years of age fewer children experienced treatment failure on high-flow nasal cannula therapy at 1 litre/kg/min compared with standard therapy (14% *vs* 33%, risk difference -19%; 95% confidence interval -30% to -8%; P=0.0016) (Kepreotes et al, 2017). Of those who failed on standard treatment 60% were subsequently rescued by high-flow nasal cannula therapy and avoided intensive care. Following 'rescue', intensive care unit admission rates were similar for both groups, implying that high-flow nasal cannula therapy will not prevent mechanical ventilation in the most severe cases.

In an unmasked randomized controlled trial in 17 emergency departments and general paediatric wards in Australia and New Zealand that included 1472 infants younger than 12 months of age, the use of high-flow nasal cannula therapy at 2 litres/kg/min decreased the rate of escalation in care as a result of treatment failure by 11% compared to standard oxygen therapy (12% *vs* 23%, risk difference -11%; 95% confidence interval -15% to -7%; P<0.001) (Franklin et al, 2018). Interestingly, there was no difference between groups in length of hospital stay (approximately 3 days), duration of oxygen therapy (approximately 2 days) and rate of adverse events (<1%). Further trials are needed to determine the optimal flow rate and weaning schedules.

Continuous positive airway pressure

Continuous positive airway pressure is widely used in infants with severe bronchiolitis to avoid intubation and paediatric intensive care unit admission. Its role in improving ventilation and oxygenation has been suggested by several observational and randomized studies. A Cochrane review of two randomized controlled trials with a total of 50 infants under 12 months of age that compared continuous positive airway pressure with standard oxygen therapy showed a reduction of the need for mechanical ventilation, but there was considerable imprecision of the estimated effect because of the small size of the cohorts (risk ratio 0.19, 95% confidence interval 0.01–3.63; P=0.27) (Jat and Mathew, 2015). A second systematic review of six observational and two randomized studies also concluded that the evidence to support the use of continuous positive airway pressure is inconclusive because of poor methodological quality (Donlan et al, 2011). The National Institute for Health and Care Excellence's recommendation is to consider continuous positive airway pressure in children with bronchiolitis who have impending respiratory failure (*Table 3*).

Endotracheal intubation

Infants with worsening severe distress who fail to improve on standard treatment may require endotracheal intubation and mechanical ventilation. Recognition of impending respiratory failure is essential to trigger an escalation of care response.

Chest physiotherapy

Routine chest physiotherapy is not supported by the existing evidence. National Institute for Health and Care Excellence identified seven randomized controlled trials of chest physiotherapy in patients with bronchiolitis. They reported no difference in time to recover or need for ventilation between the intervention and the control groups. The quality of the evidence available ranged from moderate to very low. However, chest physiotherapy may be beneficial in infants with neuromuscular disorders or severe tracheomalacia who face additional difficulties to clear secretions, or those admitted to the paediatric intensive care unit.

Pharmacological interventions

Bronchodilators (salbutamol, ipratropium, adrenaline)

Bronchodilators are a well-established treatment for asthma and viral-induced wheeze. They reverse bronchoconstriction by causing relaxation of the airway smooth muscle. Even though the pathogenesis of bronchiolitis is somewhat different from asthma, it is proposed that bronchodilators might relieve respiratory distress in patients with bronchiolitis. On the other hand, bronchodilators may cause adverse effects (tachycardia and tremor) and increase the cost of care.

A range of nebulized or inhaled bronchodilators including β2 agonists, anticholinergic agents and adrenaline has been trialled. A Cochrane review identified 30 trials involving 1992 infants that compared bronchodilators (other than adrenaline) with placebo (Gadomski and Scribani, 2014). There was no difference

in the need for hospitalization (11.9% in bronchodilator group *vs* 15.9% in placebo group, odds ratio 0.75, 95% confidence interval 0.46–1.21), or length of stay (mean difference 0.06, 95% confidence interval -0.27–0.39). There was considerable heterogeneity in the studies included in the meta-analysis with variable study designs, small sample sizes and the lack of standardized validated outcomes.

Although routine administration of inhaled bronchodilators is not recommended, a small group of children with bronchiolitis, especially those with wheeze without crackles and/or a personal or family history of atopy, may have bronchodilator-responsive airway obstruction. The pragmatic approach of a one-time trial of inhaled salbutamol to distinguish non-responders from responders is often hampered by baseline variability in observations within an individual. Apparent improvement may often be transient.

Nebulized adrenaline targets both β and α receptors, so has bronchodilator effects and reduces mucosal oedema. The Canadian Bronchiolitis Epinephrine Steroid Trial, a double-blind, placebo-controlled trial involving 800 infants under 1 year of age, showed a decrease in hospitalizations 7 days after treatment with combined adrenaline and oral dexamethasone compared to placebo (risk ratio 0.65; 95% confidence interval 0.45–0.95, *P*=0.02) (Plint et al, 2009). However, the result was insignificant after adjusting for multiple comparisons (*P*=0.07). A Cochrane review that included 19 studies with a total of 2256 participants concluded that adrenaline reduced rates of admission compared with placebo on the day of the emergency department visit (risk ratio 0.67; 95% confidence interval 0.50–0.89) but found no difference at 1 week (Hartling et al, 2011). Taking into consideration the short-term effect of nebulized adrenaline and its limited use outside the hospital setting, discharging an infant home from the emergency department after nebulized adrenaline administration raises safety concerns. Adrenaline is not recommended in children with bronchiolitis except as a rescue agent in hospital.

Hypertonic saline

The use of hypertonic saline in management of bronchiolitis has been extensively trialled. It is believed to improve airway obstruction by increasing mucociliary clearance. A Cochrane review from 2013 analysed 11 randomized controlled studies and concluded that it reduced the length of stay among hospitalized infants (Zhang et al, 2013). However, more recent studies reported no benefit. The UK SABRE study, an open label non-blinded trial that randomized 317 infants to receive hypertonic saline or no nebulized treatment, showed no difference in time to discharge (Everard et al, 2014). The most recent Cochrane review from 2017 of 17 trials involving 1867 infants found low-quality evidence that, compared to normal saline, nebulized hypertonic saline reduces length of stay by approximately half a day (mean difference -0.41 days, 95% confidence interval -0.75 to -0.07; *P*=0.02, I^2 = 79%) (Zhang et al, 2017). Another meta-analysis found no difference when the data were reanalysed to control for heterogeneity (Brooks et al, 2016). The National Institute for Health and Care Excellence (2015) concluded that the use of hypertonic saline did not reduce the length of hospital stay compared to standard treatment and recommended against its use.

Glucocorticoids

Glucocorticoids are part of the standard treatment of children with asthma largely because of their anti-inflammatory effects. Their use in bronchiolitis is not supported by the existing evidence. A 2013 Cochrane review of 17 trials involving 2596 children under 2 years of age with acute bronchiolitis showed that the use of systemic or inhaled glucocorticoids did not improve duration of hospital stay or severity of symptoms (Fernandes et al, 2013).

Heliox

The use of heliox is not recommended in the National Institute for Health and Care Excellence guidelines for the treatment of bronchiolitis. A 2015 Cochrane review of seven heterogeneous randomized trials concluded that heliox did not reduce the rate of intubation, rate of discharge from the emergency department, or the length of treatment for respiratory distress (Liet et al, 2015).

Leukotriene inhibitors

A 2015 Cochrane review of five randomized trials, with a total of 1296 infants less than 24 months of age hospitalized with bronchiolitis, found that the use of leukotriene inhibitors had no effect on duration of hospitalization or clinical scores (Liu et al, 2015).

Antibiotics

Antibiotics are not recommended in the treatment of bronchiolitis. A 2014 Cochrane review of seven randomized controlled trials involving 824 infants under 2 years of age concluded that there was no evidence to support the use of antibiotics (amoxicillin, ampicillin, clarithromycin, azithromycin, erythromycin) in bronchiolitis (Farley et al, 2014). However, antibiotics should be used in cases of concomitant or secondary pneumonia. It must be remembered that chest radiographs in bronchiolitis may show areas of patchy atelectasis attributable to the underlying pathology. These can be misinterpreted to indicate bacterial lower respiratory tract infection leading to the unnecessary use of antibiotics. Routine radiographs in bronchiolitis should therefore be avoided.

Ribavirin

Antiviral drugs such as ribavirin are not recommended in bronchiolitis. A 2007 Cochrane review concluded that

Table 4. Cost-effective use of palivizumab

	Gestational age at birth (weeks+days)						
Chronological age (months)	**24^{+0}**	**24^{+1} to 26^{+0}**	**26^{+1} to 28^{+0}**	**28^{+1} to 30^{+0}**	**30^{+1} to 32^{+0}**	**32^{+1} to 34^{+0}**	**$34^{\pm1}$**
<1.5	*	*	*	*	*	†	
1.5 to <3	*	*	*	*	†		
3 to <6	*	*	*	†			
6 to <9	*	†					
⩾9							

Chronological age is calculated at the start of the respiratory syncytial virus season. Adapted from Public Health England (2015)

trials of ribavirin lack sufficient power to reliably estimate the effects (Ventre and Randolph, 2007). In addition, ribavirin is associated with possible carcinogenicity and teratogenicity, and there are concerns regarding occupational exposure (Mooney et al, 2014).

Anti-respiratory syncytial virus preparations

Palivizumab, an anti-respiratory syncytial virus monoclonal antibody, did not improve duration of hospitalization or severity of illness when used for treatment of respiratory syncytial virus bronchiolitis (Sáez-Llorens et al, 2004). Similar results were reported in a trial of motavizumab (Ramilo et al, 2014). A number of molecules are currently in pre-clinical or clinical development, the most advanced of which is ALS-8176, a RNA polymerase inhibitor which has been found to be efficacious in a proof-of-concept human challenge study (DeVincenzo et al, 2015).

Prevention of respiratory syncytial virus

Respiratory syncytial virus bronchiolitis has the highest mortality, morbidity and cost of all respiratory viral pathogens associated with lower respiratory tract disease, particularly in children younger than 6 months of age (Shi et al, 2017). As a result, preventative treatment is mainly focused around respiratory syncytial virus. Despite ongoing research efforts over the last 50 years, there is no validated vaccine, and the only treatment licensed for respiratory syncytial virus prevention worldwide is palivizumab.

Palivizumab

Palivizumab is a humanized monoclonal antibody that provides passive immunoprophylaxis against respiratory syncytial virus (Wegzyn et al, 2014). It is delivered as a monthly intramuscular injection during the respiratory syncytial virus season.

There is extensive evidence that it reduces hospital admission rates and disease severity as well as length of hospital stay in preterm infants (<35 weeks) with and without chronic lung disease (The IMpact-RSV Study Group, 1998), and haemodynamically significant congenital heart disease (Li et al, 2017). There is also some evidence for use in children with Down's syndrome (Yi et al, 2014), while the evidence is still inconclusive in other conditions such as cystic fibrosis and neuromuscular disorders (Simões et al, 2018). It is a generally safe medication which is well tolerated (Chen et al, 2015; Simões et al, 2018). However, at present guidelines in many countries restrict the use of palivizumab to high-risk children as a result of cost–benefit considerations (American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee, 2014).

Palivizumab is recommended in the UK for three groups (Public Health England, 2015):

Lung disease

1. Premature babies requiring oxygen or respiratory support at 36 weeks post-menstrual age as per *Table 4* (* and †)
2. Infants less than 12 months of age at the start of the respiratory syncytial virus season on long-term ventilation (who have failed to be weaned 3 months after mechanical ventilation began)
3. Infants less than 24 months of age at the start of the respiratory syncytial virus season on long-term ventilation, and with significant comorbidities (e.g. cardiac or lung pathology).

Congenital heart disease

1. Premature babies with haemodynamically significant, acyanotic congenital heart disease of appropriate chronological age as per *Table 4* (* only)
2. Children with cyanotic or acyanotic congenital heart disease with significant comorbidities, particularly if multiple organ systems are involved.

Severe combined immunodeficiency

1. Children under 24 months of age with severe combined immunodeficiency, until immune reconstituted.

A maximum of five doses 1 month apart from October to the end of February is advised.

Vaccine candidates

Despite the efficacy of palivizumab, its restriction to specific high-risk groups on cost grounds means there is still a significant unmet need for preventative treatment against respiratory syncytial virus (Jaberolansar et al, 2016; Neuzil, 2016), as more than 70% of hospital admissions as a result of respiratory syncytial virus bronchiolitis are for children with no underlying medical condition (Bont et al, 2016). Unfortunately, early attempts to develop a respiratory syncytial virus vaccine during the 1960s were

unsuccessful, with vaccinated children having more severe disease (Simões et al, 2018). There are currently about 40 vaccines in various stages of pre-clinical and clinical development (PATH, 2018).

There are broadly two approaches for development of a respiratory syncytial virus vaccine: vaccinating young children or infants, and vaccinating mothers in late pregnancy. While active immunisation of infants would be the ideal solution for respiratory syncytial virus prevention (Neuzil, 2016), obtaining a good antibody response in the first 6 months of life when infants are most at risk (Higgins et al, 2016) is less reliable (Simões et al, 2018). As a result, most vaccines targeting the paediatric population have been studied in children over 6 months, with the most promising candidate thought to be a live-attenuated vaccine currently in phase I trials (Karron et al, 2015).

A potential solution to provide protection in this age group is maternal immunisation to prevent infant disease, similar to pertussis and tetanus immunisation in pregnancy. This approach is the closest to being fully developed, with a phase III trial of a recombinant respiratory syncytial virus vaccine expected to be completed in July 2019 (https://clinicaltrials.gov/ct2/show/NCT02624947). This is a promising area of development over the next few years and it may well be that a combined approach could help to reduce the disease burden of respiratory syncytial virus bronchiolitis.

Conclusions

Bronchiolitis continues to be a major cause of morbidity and health-care cost despite over 60 years of research. There is still very little evidence for any therapeutic pharmacological treatment, and while vaccination may be a potential way to reduce the burden of the disease, there is still much work to be done in terms of vaccine development as well as developing a coherent and cost-effective vaccination strategy. BJHM

Conflict of interest: none.

American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014 Aug. 134(2): 415–420. https://doi.org/10.1542/peds.2014-1665

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KEY POINTS

- In the UK, hospital admission rates for bronchiolitis rose sevenfold between 1979 and 2011.
- The National Institute for Health and Care Excellence published a guideline for the hospital management of bronchiolitis in June 2015 that advised avoidance of nebulised therapies, and recommended the use of continuous positive airway pressure in patients with impending respiratory failure.
- New evidence for the use of high-flow nasal cannula oxygen has emerged since the publication of the guideline.
- Maternal immunization may be a potential way to reduce the burden of the disease over the vulnerable first months of infancy, but there is still much work to be done in terms of vaccine development as well as developing a coherent and cost-effective vaccination strategy.

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