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Bronchiolitis: An update on management and prophylaxis

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Abstract

Bronchiolitis is an acute respiratory illness that is the leading cause of hospitalisation in young children less than 2 years of age in the UK. Respiratory Syncytial Virus (RSV) 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 co-morbidities. Management of bronchiolitis in the UK is guided by the National Institute of Clinical Excellence (NICE) guidance published in 2015. Currently, the mainstays of management are largely supportive, consisting of fluid management and respiratory support. Pharmacological interventions including nebulised bronchodilators, steroids and antibiotics generally have limited or no evidence of efficacy and are not advised by NICE. Anti-viral therapeutics remain in development.

As treatments are limited, there have been extensive efforts to develop vaccines. As the major cause of bronchiolitis, RSV has been the main target for vaccines. 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.

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Introduction

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 hospitalised 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 (RSV) 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 the cases, more than one virus is detected (Mansbach et al. 2012).

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. 2016). In a systematic review including 590 children with mild disease that did not require admission to the 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 of 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. 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. In addition, an association between hospitalisation with RSV bronchiolitis and asthma later in life is increasingly recognised (Régnier and Huels 2013). **Likewise, higher use of asthma medication has been observed during 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 hypoxemia 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 healthcare 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, it is duration of admission that matters most. This is usually driven by duration of supplementary oxygen. In most cases, ability to tolerate feeds recovers prior to 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 (NICE) published a guideline for the hospital management of bronchiolitis in 2015 (Table 1,2) (NICE 2015). Prior to this, hospital Trusts in the UK based their local guidelines on the Scottish Intercollegiate Guideline Network (SIGN) guideline published in 2006 and withdrawn in 2015 (SIGN 2006). In this review, we summarise current recommendations by NICE on the management and prevention of bronchiolitis, and bring focus onto 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 randomised trial in Australia and New Zealand including 759 infants less than 1 year of age admitted to hospital with bronchiolitis showed no benefit of intravenous fluids compared to nasogastric tube in length of hospital stay (absolute difference 4.5 h 95% CI -3.9 to 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 impending 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 (HFNC) therapy and/or continuous positive airway pressure (CPAP) 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 NICE for symptomatic relief of nasal congestion in infants with apnoeas, respiratory distress or feeding difficulties. NICE recommends suctioning in children with apnoea even in the absence of obvious secretions.

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 face to minimise 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, NICE recommends supplemental oxygen when oxygen saturation readings drop below 92%, while the American Academy of Pediatrics (AAP) suggests a threshold of 90% (Ralston et al. 2014). A double-blind, randomised, equivalence trial of 615 infants admitted with bronchiolitis in 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.

HFNC therapy

High-flow nasal cannula oxygen (HFNC) is a non-invasive method of ventilation. Its main advantage is that allows high flow oxygen to be safely delivered without causing damage to 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 HFNC has been increasingly used for the management of bronchiolitis. Despite this, its use is not recommended in the current NICE guidelines. A Cochrane review in 2014 concluded that evidence was insufficient to determine the effectiveness of HFNC therapy (Mayfield et al. 2014). However, two recent randomised trials have shown benefit in preventing PICU admissions and escalation of care. In a randomized controlled trial in a non-ICU setting of 202 children less than 2 years of age fewer children experienced treatment failure on HFNC at 1 L/kg per minute compared with standard therapy (14% versus 33%, risk difference, -19%; 95% CI, -30% to -8%; $p=0.0016$) (Kepreotes et al. 2017). 60% of those who failed on standard treatment were subsequently rescued by HFNC and avoided intensive care. Following 'rescue', intensive care unit admission rates were similar for both groups, implying that HFNC will not prevent mechanical ventilation in the most severe cases. In an unmasked randomised controlled trial on 17 emergency departments and general paediatric wards in Australia and New Zealand that included 1472 infants less than 12 months of age, the use of HFNC at 2 L/kg per minute decreased the rate of escalation in care due to treatment failure by 11% compared to standard oxygen therapy (12% versus 23%, risk difference, -11%; 95% CI, -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.

CPAP

CPAP is widely used in infants with severe bronchiolitis to avoid intubation and PICU admission. Its role in improving ventilation and oxygenation has been suggested by several observational and randomized studies. A Cochrane review of two randomised controlled trials with a total of 50 infants under 12 months of age that compared CPAP with standard oxygen therapy showed a reduction on the need for mechanical ventilation, but there was a considerable imprecision on estimated effect because of the small size of the cohorts (risk ratio (RR) 0.19, 95% CI 0.01 to 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 CPAP is inconclusive because of poor methodological quality (Donlan et al. 2011). NICE's recommendation is to consider CPAP in children with bronchiolitis who have impending respiratory failure (Table 3).

Endotracheal intubation

Infants with worsening severe distress who fail to improve to 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. NICE identified seven randomised controlled trials of chest physiotherapy in 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 that face additional difficulties to clear secretions or those admitted in PICU.

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 nebulised or inhaled bronchodilators including β 2 agonists, anticholinergic agents and adrenaline have 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 versus 15.9% in placebo group, odds ratio (OR) 0.75, 95% CI 0.46 to 1.21), or length of stay (mean difference (MD) 0.06, 95% CI -0.27 to 0.39). Because of variable study designs, small sample sizes and the lack of standardized validated outcomes, there was considerable heterogeneity in the studies included in the meta-analysis. 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, therefore has bronchodilator effects and reduces mucosal oedema. The Canadian Bronchiolitis Epinephrine Steroid Trial, a double-blind, placebo-controlled trial involving 800 infants under one year of age showed a decrease in hospitalizations 7 days after treatment with combined adrenaline and oral dexamethasone compared to placebo (RR 0.65; 95% CL 0.45 to 0.95, P=0.02) (Plint et al. 2009). However, the result was insignificant after adjusting for multiple comparisons (P = .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 ED visit (RR 0.67; 95% CI 0.50 to 0.89) but found no difference at one week (Hartling et al. 2011). Taking into consideration the short-term effect of nebulised adrenaline and its limited use outside hospital setting, discharging an infant home from the ED after nebulised adrenaline administration raises safety concerns. Adrenaline is not recommended in children with bronchiolitis except as a rescue agent in hospital.

Hypertonic saline (HS)

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 randomised controlled studies and concluded that it reduced the length of stay among hospitalised infants (Zhang et al. 2013). However, further studies in recent years reported no benefit. The UK SABRE study, an open label non-blinded trial, that randomised 317 infants to receive HS or no nebulised 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 nebulized hypertonic saline compared to normal saline reduces length of stay by approximately half day (MD -0.41 days, 95% CI -0.75 to -0.07; P = 0.02, I²= 79%) (Zhang et al. 2017). Another meta-analysis found no difference when the data were reanalyzed to control for heterogeneity (Brooks et al. 2016). NICE in its recent recommendation

concluded that the use of HS 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 due to 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 NICE 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 hospitalised with bronchiolitis found 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 randomised 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 trials of ribavirin lack sufficient power to provide reliable estimates of 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-RSV preparations

Palivizumab, an anti-respiratory syncytial virus (RSV) monoclonal antibody did not improve duration of hospitalization or severity of illness when used for treatment of RSV bronchiolitis (Sáez-Llorens et al. 2004). Similar results 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 RSV

RSV bronchiolitis has been shown to have the highest mortality, morbidity and cost, particularly in children younger than 6 months of age (Shi et al. 2017). As a result, preventative treatment is mainly focused around RSV. Despite ongoing research efforts over the last 50 years, there is no validated vaccine to date, and the only treatment licensed for RSV prevention worldwide is Palivizumab.

Palivizumab

Palivizumab is a humanized monoclonal antibody that provides passive immunoprophylaxis against RSV (Wegzyn et al. 2014). It is delivered as a monthly intramuscular injection that is administered over the RSV 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. 2016). There is also some evidence for use in 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 has been shown to be 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 only as a result of cost-benefit considerations (AAP 2014).

Palivizumab is recommended in the UK for 3 groups (PHE 2015):

1. Lung Disease
 - a. Premature babies requiring oxygen or respiratory support at 36 weeks post-menstrual age as per Figure 1 (Green and light green boxes)
 - b. Infants less than 12 months of age at the start of the RSV season on Long Term Ventilation (who have failed to be weaned three months after mechanical ventilation began)
 - c. Infants less than 24 months of age at the start of the RSV season on Long Term Ventilation, and significant co-morbidities (eg. Cardiac/Lung pathology)
2. Congenital Heart Disease
 - a. Premature babies with haemodynamically significant, acyanotic congenital heart disease of appropriate chronological age as per Figure 1 (Light green boxes only)
 - b. Cyanotic/Acyanotic congenital heart disease with significant co-morbidities particularly if multiple organ systems are involved
3. Severe Combined Immunodeficiency (SCID)
 - a. Children under 24 months of age with SCID, until immune reconstituted

A maximum of 5 doses one month apart from October to the end of February is advised.

Vaccine Candidates

Despite the efficacy of Palivizumab, its restriction on cost grounds to specific high-risk groups means there is still a significant unmet need for preventative treatment against RSV (Jaberolansar et al. 2016; Neuzil 2016), as greater than 70% of hospital admissions due to RSV Bronchiolitis are for children with no underlying medical condition (Bont et al. 2016). Unfortunately, early attempts at an RSV 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, as seen in Figure 2 (PATH 2018).

There are broadly two approaches for development of an RSV Vaccine – by vaccinating young children/infants, and by vaccinating mothers in late pregnancy. While active

immunisation of infants would be the ideal solution for RSV 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 1 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 recombinant RSV vaccine currently in Phase 3 trials that would be completed in 2020 (Clinicaltrials.gov 2017). 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 RSV Bronchiolitis.

Conclusions

Bronchiolitis continues to be a major cause of morbidity and healthcare cost despite over 60 years of research. There is still very little evidence for any therapeutic pharmacological treatment, and whilst 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.

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Figure 1 – Cost effective use of Palivizumab [Shaded Area] (adapted from PHE 2015)

Note: Chronological Age is calculated at the start of the RSV Season

Chronological age (months)	Gestational age at birth (weeks+days)						
	$\leq 24^{+0}$	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}	$\geq 34^{+1}$
<1.5	Shaded	Shaded	Shaded	Shaded	Shaded	Shaded	
1.5 to <3	Shaded	Shaded	Shaded	Shaded	Shaded		
3 to <6	Shaded	Shaded	Shaded				
6 to <9	Shaded						
≥ 9							

RSV Vaccine and mAb Snapshot

TARGET INDICATION: P = PEDIATRIC M = MATERNAL E = ELDERLY

	PRECLINICAL				PHASE 1			PHASE 2	PHASE 3	MARKET APPROVED
LIVE-ATTENUATED/CHIMERIC	Codagenix, LID/NIAID/NIH RSV	LID/NIAID/NIH RSV			Intravacc ^P Delta-G RSV	Sanofi, LID/NIAID/NIH RSV ΔNS2/Δ1313/11314L ^P	Sanofi, LID/NIAID/NIH RSV 6120/ΔNS2/1030s ^P			
	LID/NIAID/NIH PIV1-3/RSV	Meissa Vaccines RSV			Pontificia Universidad Catolica de Chile BCG/RSV ^P	Sanofi, LID/NIAID/NIH RSV D46/NS2/N/ΔM2-2-HindIII ^P	SIPL, St. Jude Hospital SeV/RSV ^P			
WHOLE-INACTIVATED	Blue Willow Biologics RSV									
PARTICLE-BASED	AgilVax VLP	Fraunhofer VLP	TechnoVax VLP	VBI Vaccines VLP	Novavax ^P RSV F Nanoparticle			Novavax ^E RSV F Nanoparticle	Novavax ^M RSV F Nanoparticle	
	Artificial Cell Technologies Peptide microparticle	Georgia State University VLP	University of Massachusetts VLP	Virometix VLP						
SUBUNIT	Instituto de Salud Carlos III RSV F Protein	University of Georgia RSV G Protein			Beijing Advaccine Biotechnology RSV G Protein ^{P E}	Immunovaccine, VIB DPX-RSV-SH Protein ^E	NIH/NIAID/VRC RSV F Protein ^{E M}	Pfizer ^{E M} RSV F Protein		
	Sciogen RSV G Protein	University of Saskatchewan RSV F Protein			GlaxoSmithKline ^{E M} RSV F Protein	Janssen Pharmaceutical ^E RSV F Protein				
NUCLEIC ACID	CureVac RNA	Inovio Pharmaceuticals DNA								
RECOMBINANT VECTORS	BravoVax Adenovirus			Vaxart ^E Adenovirus			Bavarian Nordic ^E MVA	Janssen Pharmaceutical ^{P E} Adenovirus		
							GlaxoSmithKline ^P Adenovirus			
IMMUNO-PROPHYLAXIS/COMBINATION	Arsanis Anti-F mAb	Biomedical Research Models DNA prime, Particle boost	Pontificia Universidad Catolica de Chile Anti-N mAb	UCAB, mAbXience Anti-F mAb	Merck ^P Anti-F mAb			MedImmune, Sanofi ^P Anti-F mAb	MedImmune ^P Synagis	

UPDATED: December 10, 2018

Indicates Change

<http://vaccineresources.org/details.php?i=1562>



Table 1. Indications for hospital admission (NICE 2015)
-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)

Table 2. Key Recommendations for hospital management (NICE 2015)
Do not routinely perform chest x-rays or blood gases
Do not routinely prescribe bronchodilators, nebulised adrenaline, steroids, nebulised 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

Table 3. Impending respiratory failure (NICE 2015)
If any signs of exhaustion are present:
listlessness
decreased respiratory effort
recurrent apnoea
failure to maintain adequate oxygen saturation despite oxygen supplementation