Appendix A: Summary of evidence from surveillance

2019 surveillance of Bronchiolitis in Children: diagnosis and management (2015) NICE guideline 9

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence and stakeholder feedback to reach a view on the need to update each section of the guideline.

1.1 Assessment and diagnosis

1.1.1 When diagnosing bronchiolitis, take into account that it occurs in children under 2 years of age and most commonly in the first year of life, peaking between 3 and 6 months.

1.1.2 When diagnosing bronchiolitis, take into account that symptoms usually peak between 3 and 5 days, and that cough resolves in 90% of infants within 3 weeks.

1.1.3 Diagnose bronchiolitis if the child has a coryzal prodrome lasting 1 to 3 days, followed by:

- persistent cough **and**
- either tachypnoea or chest recession (or both) **and**
- either wheeze or crackles on chest auscultation (or both).

1.1.4 When diagnosing bronchiolitis, take into account that the following symptoms are common in children with this disease:

- fever (in around 30% of cases, usually of less than 39°C)
- poor feeding (typically after 3 to 5 days of illness).

1.1.5 When diagnosing bronchiolitis, take into account that young infants with this disease (in particular those under 6 weeks of age) may present with apnoea without other clinical signs.

1.1.6 Consider a diagnosis of pneumonia if the child has:

- high fever (over 39°C) **and/or**
- persistently focal crackles.

1.1.7 Think about a diagnosis of viral-induced wheeze or early-onset asthma rather than bronchiolitis in older infants and young children if they have:

- persistent wheeze without crackles **or**
- recurrent episodic wheeze **or**
- a personal or family history of atopy.

  Take into account that these conditions are unusual in children under 1 year of age.

1.1.8 Measure oxygen saturation in every child presenting with suspected bronchiolitis, including those presenting to primary care if pulse oximetry is available.

1.1.9 Ensure healthcare professionals performing pulse oximetry are appropriately trained in its use specifically in infants and young children.

1.1.10 Suspect impending respiratory failure, and take appropriate action as these children may need intensive care (see recommendations 1.2.1 and 1.4.5), if any of the following are present:

- signs of exhaustion, for example listlessness or decreased respiratory effort
- recurrent apnoea
- failure to maintain adequate oxygen saturation despite oxygen supplementation.

Surveillance proposal

This section of the guideline should not be updated.

Editorial amendments

- Recommendation 1.1.6: It is suggested that a line is added at the end of this recommendation to ensure that clinicians consider sepsis as an alternative diagnosis. The proposed amendment would be as follows:

Consider a diagnosis of pneumonia if the child has:

- high fever (over 39°C) **and/or**
- persistently focal crackles.

See also the NICE guideline on Sepsis and risk stratification tools for sepsis in under 5s

2019 surveillance summary

No relevant evidence was identified.

Intelligence gathering

Measuring oxygen saturation

One topic expert suggested that pulse oximetry is not widely available in general practice and is not perceived to be affordable. It was suggested that the wording "if available" be removed from the guideline as this was insinuating that pulse oximetry measurement was potentially unnecessary and that there may be alternative, cheaper clinical assessment methods available. Attention was also brought to the American Paediatric Guidelines (2019) which states that pulse oximetry in children with bronchiolitis is prone to errors of measurement.

Diagnosing bronchiolitis

One topic expert noted that ways of diagnosing bronchiolitis should be revisited and more should be done to identify the different viruses that are associated with the condition. A report suggests that there are 3 main clusters of patient groups who suffer from bronchiolitis. These are: respiratory syncytial virus (RSV) induced bronchiolitis usually associated with the younger patients and increased risk of recurrent wheezing; rhinovirus-induced wheezing which carries a high risk of asthma development and evidence shows that in severe cases this can be reversed with systemic corticosteroids; and wheeze due to other viruses which can be less frequent and less severe. If these can be distinguished at diagnosis then patients can be offered different and more effective treatments.

Considering sepsis at diagnosis

NG51 Sepsis: recognition, diagnosis and early management suggests that bronchiolitis could be an alternative diagnosis to sepsis and should be considered at presentation. This is if patients present with 1 or more high risk criteria which are noted as: altered mental state; raised respiratory rate; 25 breaths per minute or more; oxygen levels under 92%; blood pressure 90 mmHg or less; raised heart rate; not passed urine in previous 18 hours; mottled or ashen appearance. In NG9 bronchiolitis can be diagnosed in children who present with: raised respiratory rate; oxygen levels under 92%; clinical dehydration; child looks seriously unwell – many of which are similar to risk factors for sepsis.

Impact statement

Measuring oxygen saturation

When NG9 was developed in 2015 the committee noted that pulse oximetry could also be helpful in a primary care setting but recognised that the equipment and staff training might not always be available in primary care. Moreover, the severity of symptoms would, on average, be less severe in the children seen in primary care than those seen in an emergency department. They therefore recommended that the oxygen saturation be measured in children presenting with bronchiolitis in primary care if the technique was available. Given the resource implications and the lack of research evidence, the committee

developed a recommendation that research be carried out on the value of universal saturation monitoring for children presenting to primary care with bronchiolitis.

The committee also stated that the cost of a simple device for pulse oximetry is low and therefore the cost per use in primary care will be minimal. If using pulse oximetry in primary care avoids unnecessary referrals to hospital then it is likely to be cost saving overall. Costs were identified for pulse oximetry monitors to consider the impact of introducing this monitoring to primary care: full details can be found in Appendix A of the guideline.

NG9 currently recommends measuring oxygen saturation in every child presenting with suspected bronchiolitis, including those presenting to primary care if pulse oximetry is available.

No new evidence was found that suggests that pulse oximetry should not be recommended for use in primary care. There was also no evidence found that suggests pulse oximetry is ineffective at measuring oxygen levels. Therefore, no impact on the guideline is expected.

Considering sepsis at diagnosis

New intelligence was identified that suggests that clinicians should consider the possibility of sepsis when carrying out their assessments. Sepsis and bronchiolitis can have similar symptoms and the NICE guideline on sepsis suggests that bronchiolitis could be an alternative diagnosis to sepsis and should be considered at presentation.

NG9 currently only recommends considering a diagnosis of pneumonia if the child has a high fever or persistently focal crackles.

It is proposed that NG9 cross-refers to NICE Guideline NG51 Sepsis: recognition, diagnosis and early management to ensure that clinicians consider the possibility of sepsis as well as pneumonia when carrying out their assessments.

Diagnosing bronchiolitis

New intelligence was identified that suggests there are 3 types of bronchiolitis that can be diagnosed at presentation and more effort should be made to appropriately diagnose the causing virus in order to treat this appropriately.

Current recommendations in NG9 do not discuss different strains of the bronchiolitis virus. The current scope states that screening for RSV in primary care and viral testing in hospital to prevent transmission will not be covered within the guideline.

There was no further evidence found regarding the diagnosis of bronchiolitis that would suggest the need to add any further recommendations or amend the scope, and therefore no impact on the guideline is expected.

New evidence is unlikely to change guideline recommendations.

1.2 When to refer

1.2.1 Immediately refer children with bronchiolitis for emergency hospital care (usually by 999 ambulance) if they have any of the following:

- apnoea (observed or reported)
- child looks seriously unwell to a healthcare professional
- severe respiratory distress, for example grunting, marked chest recession, or a respiratory rate of over 70 breaths/minute
- central cyanosis
- persistent oxygen saturation of less than 92% when breathing air.

1.2.2 Consider referring children with bronchiolitis to hospital if they have any of the following:

- a respiratory rate of over 60 breaths/minute
- difficulty with breastfeeding or inadequate oral fluid intake (50–75% of usual volume, taking account of risk factors [see recommendation 1.3.3] and using clinical judgement)
- clinical dehydration.

1.2.3 When deciding whether to refer a child with bronchiolitis to secondary care, take account of the following risk factors for more severe bronchiolitis:

- chronic lung disease (including bronchopulmonary dysplasia)
- haemodynamically significant congenital heart disease
- age in young infants (under 3 months)
- premature birth, particularly under 32 weeks
- neuromuscular disorders
- immunodeficiency.

1.2.4 When deciding whether to refer a child to secondary care, take into account factors that might affect a carer's ability to look after a child with bronchiolitis, for example:

- social circumstances
- the skill and confidence of the carer in looking after a child with bronchiolitis at home
- confidence in being able to spot red flag symptoms (see recommendation 1.6.1)

- distance to healthcare in case of deterioration.

Surveillance proposal

This section of the guideline should not be updated.

Editorial amendments

- Recommendation 1.2.3: It is suggested that this wording is amended to ensure that the list of risk factors is not considered exhaustive:

When deciding whether to refer a child with bronchiolitis to secondary care, take account of ~~the following~~ any known risk factors for more severe bronchiolitis such as:

- chronic lung disease (including bronchopulmonary dysplasia)
- haemodynamically significant congenital heart disease
- age in young infants (under 3 months)
- premature birth, particularly under 32 weeks
- neuromuscular disorders
- immunodeficiency.

2019 surveillance summary

Risk factors for more severe bronchiolitis

A focused search on failure to thrive as a risk factor for severe bronchiolitis was conducted for the surveillance review following a request from a topic expert.

Three studies were identified that looked at risk factors for bronchiolitis.

An analysis (Green et al., 2016) of English hospital records suggested maternal and perinatal risk factors associated with child bronchiolitis related hospital admissions were young maternal age; low social class; low birth weight and maternal smoking.

In 1 prospective cohort study (Hasegawa et al., 2015) of 2104 children under 2 years old who were hospitalised with bronchiolitis and subsequently transferred to intensive care units, the predictive factors for this were low birth weight and respiratory rate high of 70 breath/minute.

In 1 prospective multicentre study (Bakalovic, Dzinovic, Baljic, Dizdar, & Selimovic, 2015) 155 infant children were analysed and the risk factors for severe forms of bronchiolitis were noted as artificial diet; low birth weight; prematurity; congenital heart anomalies and bronchopulmonary dysplasia.

Intelligence gathering

Risk factors for bronchiolitis

A topic expert informed us that the list of risk factors that are given for more severe bronchiolitis is not fully exhaustive of all risk factors associated with bronchiolitis, however it can be taken as such due to the way that the recommendation is worded. The topic expert suggested that this recommendation is incorrect and unsafe.

Oxygen saturation levels

One topic expert suggested that the recommendation to admit a child by ambulance if their oxygen saturation is less than 92% should be revisited according to the American Paediatric Guidelines as the current recommendation may lead to over emergency referrals.

Paediatric Early Warning Score (PEWS)

One topic expert noted that PEWS is being used as an assessment tool that can lead to unnecessary emergency referrals. PEWS is not mentioned in the NICE guideline, however it is a research recommendation. It was suggested by the topic expert that if no positive evidence exists for its use then this should be stated within the guideline to prevent unnecessary emergency referrals.

Impact statement

Risk factors for bronchiolitis

New evidence was identified that suggests low birth weight can be a risk factor for bronchiolitis. Three studies suggested low birth weight as a risk factor, however it was unclear as to whether this was a risk factor for more severe or less severe bronchiolitis. Failure to thrive was not noted as a risk factor in the studies.

NG9 currently states that the decision on whether to refer a child with bronchiolitis to secondary care should take account of the following risk factors including: chronic lung disease; hemodynamically significant congenital heart disease; age in young infants; premature birth; neuromuscular disorders; immunodeficiency.

It is proposed that the wording of the recommendation be amended to ensure it is not considered exhaustive. It is suggested that recommendation 1.2.3 should be amended to state “take into account any risk factors for more severe bronchiolitis, such as”. This should help remove any confusion around the set list of risk factors and may improve the safety of patients and their care.

Paediatric Early Warning Score

One topic expert suggested PEWS are leading to unnecessary emergency referrals.

NG9 does not mention PEWS within its recommendations, however a research recommendation states “In children with bronchiolitis can paediatric early warning score (PEWS) predict deterioration?”

No new evidence was identified regarding the use of PEWS in referring children with bronchiolitis to emergency care and therefore the research recommendation can remain within the guideline and no impact to the guideline is expected.

Oxygen saturation levels

One topic expert suggested that minimum oxygen saturation levels could be lowered from 92% to 90% before referral to emergency care is required.

NG9 currently recommends immediately referring children with bronchiolitis for

emergency hospital care (usually by 999 ambulance) if they have persistent oxygen saturation of less than 92% when breathing air.

During the development of NG9 the committee advised that infants with an oxygen saturation of 92% or lower should be referred immediately because this allows a margin of safety given the rapid reduction in blood oxygen carriage when the oxygen saturation of 92% were more likely to fall to 90% as the illness progressed.

It is proposed that no new evidence was identified to suggest that a child can safely be referred for emergency care if their oxygen levels are 90% or lower, therefore no impact to the recommendation is expected.

New evidence is unlikely to change guideline recommendations.

1.3 When to admit

1.3.1 Measure oxygen saturation using pulse oximetry in every child presenting to secondary care with clinical evidence of bronchiolitis.

1.3.2 When assessing a child in a secondary care setting, admit them to hospital if they have any of the following:

- apnoea (observed or reported)
- persistent oxygen saturation of less than 92% when breathing air
- inadequate oral fluid intake (50–75% of usual volume, taking account of risk factors [see recommendation 1.3.3] and using clinical judgement)
- persisting severe respiratory distress, for example grunting, marked chest recession, or a respiratory rate of over 70 breaths/minute.

1.3.3 When deciding whether to admit a child with bronchiolitis, take account of the following risk factors for more severe bronchiolitis:

- chronic lung disease (including bronchopulmonary dysplasia)
- haemodynamically significant congenital heart disease
- age in young infants (under 3 months)
- premature birth, particularly under 32 weeks
- neuromuscular disorders

- immunodeficiency.

1.3.4 When deciding whether to admit a child, take into account factors that might affect a carer's ability to look after a child with bronchiolitis, for example:

- social circumstances
- the skill and confidence of the carer in looking after a child with bronchiolitis at home
- confidence in being able to spot red flag symptoms (see recommendation 1.6.1)
- distance to healthcare in case of deterioration.

1.3.5 Clinically assess the hydration status of children with bronchiolitis.

1.3.6 Do not routinely perform blood tests in the assessment of a child with bronchiolitis.

1.3.7 Do not routinely perform a chest X-ray in children with bronchiolitis, because changes on X-ray may mimic pneumonia and should not be used to determine the need for antibiotics.

1.3.8 Consider performing a chest X-ray if intensive care is being proposed for a child.

1.3.9 Provide parents or carers with key safety information (see recommendation 1.6.1) if the child is not admitted.

Surveillance proposal

This section of the guideline should not be updated.

Editorial amendments

- Recommendation 1.3.3: It is suggested that this wording is amended to ensure that the list of risk factors is not considered exhaustive:

When deciding whether to admit a child with bronchiolitis, take account of ~~the following~~ any known risk factors for more severe bronchiolitis such as:

- chronic lung disease (including bronchopulmonary dysplasia)
- haemodynamically significant congenital heart disease
- age in young infants (under 3 months)
- premature birth, particularly under 32 weeks
- neuromuscular disorders

- immunodeficiency.

2019 surveillance summary

Measure oxygen saturation

A parallel-group superiority RCT (McCulloh et al., 2015) (n=161 infants under 2 years of age hospitalised for bronchiolitis) compared intermittent pulse oximetry monitoring with continuous pulse oximetry monitoring. There was no significant difference in the mean length of stay in hospital, rates of escalation of care or duration of supplemental oxygen.

Intelligence gathering

Risk factors for bronchiolitis

A topic expert informed us that the list of risk factors that are given for more severe bronchiolitis is not fully exhaustive of all risk factors associated with bronchiolitis, however it can be taken as such due to the way that the recommendation is worded. The topic expert suggested that this recommendation is incorrect and unsafe.

Chest X-rays

It was identified that NICE Guideline CG160 Fever in under 5s: assessment and initial management recommends that chest X-rays should be performed in infants younger than 3 months who have a fever and show signs of respiratory difficulties. NG9 recommends not routinely performing chest X-rays in children with bronchiolitis and does not make separate recommendations for children presenting with any other symptoms.

Impact statement

Risk factors for bronchiolitis

NG9 currently states that the decision on whether to admit a child with bronchiolitis to secondary care should take account of the following risk factors including: chronic lung disease; hemodynamically significant congenital heart disease; age in young infants; premature birth; neuromuscular disorders; immunodeficiency.

A topic expert raised an issue of safety regarding the wording around risk factors in bronchiolitis which they believed needed clarification in order to ensure this recommendation was not considered an exhaustive list of what could be acceptable practice. The topic expert also wished NICE to consider failure to thrive as a risk factor for severe bronchiolitis. NICE conducted a focused search looking at evidence for failure to thrive as a risk factor however no evidence was found. The recommendation will be refreshed however to help avoid confusion around the list of risk factors.

The same argument applies to this recommendation as to the recommendation in section 1.2. It is proposed that recommendation 1.3.3 should be amended to state “take into account any risk factors for more severe bronchiolitis, such as”. This should remove any confusion around the set list of risk factors and may improve the safety of patients and their care.

Chest X-ray

Information from NICE Guideline CG160 Fever in under 5s: assessment and initial management was identified that suggests that infants younger than 3 months who

have a fever and show signs of respiratory difficulties should be offered a chest X-ray.

NG9 currently recommends not routinely performing a chest X-ray in children with bronchiolitis, because changes on X-ray may mimic pneumonia and should not be used to determine the need for antibiotics.

It is proposed that the NG9 recommendation is still valid as the wording states that chest X rays should not be routinely performed in children with bronchiolitis and children who are younger than 3 months and present with fever and respiratory problems would not be considered routine cases. Therefore, it is felt that the populations discussed above are separate and an amendment to the recommendation is not needed at this time.

New evidence is unlikely to change guideline recommendations.

1.4 Management of bronchiolitis

1.4.1 Do not perform chest physiotherapy on children with bronchiolitis who do not have relevant comorbidities (for example spinal muscular atrophy, severe tracheomalacia).

1.4.2 Consider requesting a chest physiotherapy assessment in children who have relevant comorbidities (for example spinal muscular atrophy, severe tracheomalacia) when there may be additional difficulty clearing secretions.

1.4.3 Do not use any of the following to treat bronchiolitis in children:

- antibiotics
- hypertonic saline
- adrenaline (nebulised)
- salbutamol
- montelukast
- ipratropium bromide
- systemic or inhaled corticosteroids
- a combination of systemic corticosteroids and nebulised adrenaline.

1.4.4 Give oxygen supplementation to children with bronchiolitis if their oxygen saturation is persistently less than 92%.

1.4.5 Consider continuous positive airway pressure (CPAP) in children with bronchiolitis who have impending respiratory failure (see recommendation 1.1.10).

1.4.6 Do not routinely perform upper airway suctioning in children with bronchiolitis.

1.4.7 Consider upper airway suctioning in children who have respiratory distress or feeding difficulties because of upper airway secretions.

1.4.8 Perform upper airway suctioning in children with bronchiolitis presenting with apnoea even if there are no obvious upper airway secretions.

1.4.9 Do not routinely carry out blood gas testing in children with bronchiolitis.

1.4.10 Consider carrying out capillary blood gas testing in children with severe worsening respiratory distress (when supplemental oxygen concentration is greater than 50%) or suspected impending respiratory failure (see recommendation 1.1.10)

1.4.11 Give fluids by nasogastric or orogastric tube in children with bronchiolitis if they cannot take enough fluid by mouth.

1.4.12 Give intravenous isotonic fluids (see the NICE guideline on intravenous fluids therapy in children) to children who:

- do not tolerate nasogastric or orogastric fluids **or**
- have impending respiratory failure.

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

Levels of oxygen saturation

No relevant evidence was identified.

Hypertonic saline

Seven studies were identified: 1 Cochrane review, 1 systematic review, 1 systematic review and meta-analysis, 3 meta-analyses and 1 RCT, which all suggested that hypertonic saline was safe and effective to use in children with bronchiolitis when compared with 0.9% nebulised saline or standard treatment. Using hypertonic saline significantly improved clinical severity scores, reduced length of stay in hospital and reduced the risk of hospitalisation. Hypertonic saline was also effective when used with epinephrine, adrenaline and salbutamol.

A Cochrane review (Zhang, Mendoza-Sassi, Wainwright, & Klassen, 2017) of 28 RCTs involving 4195 children under 24 months with acute bronchiolitis compared nebulised hypertonic saline alone or in conjunction with bronchodilators with

nebulised 0.9% saline or standard treatment. Those treated with nebulised hypertonic saline had a significantly shorter mean length of hospital stay compared to those on nebulised saline. They also had significantly lower post-inhalation clinical scores. The risk of hospitalisation was also lowered in the group who received nebulised hypertonic saline.

A systematic review (Zhang, Mendoza-Sassi, Klassen, & Wainwright, 2015) of 24 trials involving 3209 patients examined studies comparing nebulised hypertonic saline with 0.9% saline or standard treatment in infants with acute bronchiolitis. Patients who received nebulised hypertonic saline had shorter length of stay in hospital than those in the control groups. The hypertonic saline group also had lower posttreatment clinical scores and had reduced risk of hospitalisation. There were no significant adverse effects reported.

A systematic review and meta-analysis (Maguire, Cantrill, Hind, Bradburn, & Everard, 2015) of 15 trials involving 1922 infants less than 2 years old hospitalised with acute bronchiolitis compared hypertonic saline with standard care. It was noted that there was a significant difference in the hypertonic saline group in terms of reduction in the mean length of stay in hospital.

A meta-analysis (Heikkila, Renko, & Korppi, 2018) of 18 studies involving 2102 children under 24 months with bronchiolitis compared hypertonic saline with normal saline and considered the cumulative mean difference in length of stay in hospital between the 2 groups. Regardless of the age limit placed, there was always a minimal difference between the groups however hypertonic saline showed slight statistically significant clinical benefits and reduction in length of stay in hospital.

A meta-analysis (Chen, Lee, Wang, & Chou, 2014) of 11 studies examined nebulised hypertonic saline treatment in 1070 infants with acute bronchiolitis. It found that nebulised hypertonic saline treatment significantly reduced the length of hospitalisation and the rate of hospitalisation compared to normal saline. The clinical severity score was also significantly reduced in the hypertonic saline group.

A meta-analysis (Zhang, Gunther, Franco, & Klassen, 2018) of 8 RCTs involving 1708 infants up to 24 months of age with acute bronchiolitis compared hypertonic saline with normal saline and showed there was a significant reduction in hospitalisation in the subgroup analysis where hypertonic saline was mixed with bronchodilators.

A RCT(Bashir, No Author Provided, 2018) (n=189 infants under 18 months with acute bronchiolitis) compared 3% nebulised hypertonic saline (n=96) with 0.9% normal saline (n=93). There was a significantly greater reduction in clinical severity score in the hypertonic saline group and length of stay in hospital was significantly shorter in the hypertonic saline group.

Two RCTs were identified that suggested that hypertonic saline was not safe and effective to use in children with bronchiolitis.

A double blind RCT (Flores, Mendes, & Neto, 2016) (n=68) involving hospitalised infants with bronchiolitis aged younger

than 12 months, received either nebulised 3% hypertonic saline (n=33) or 0.9% normal saline (n=35) during their hospital stay. No significant differences were found in terms of length of hospital stay or severity scores during their stay or need for supplemental oxygen. The patients who received hypertonic saline did have significant differences in adverse events regarding worsening cough and rhinorrhoea.

A multicentre, double blind RCT (Angoulvant et al., 2017) (n=777 children 6 weeks to 12 months of age with acute bronchiolitis) compared 2 20-minute nebulisation treatments of 4 ml of hypertonic saline 3% (n=385) with 4 ml of normal saline 0.9% (n=387). There was a significant difference in terms of the mean respiratory distress assessment instrument score where improvement was greater in the hypertonic saline group. However, there were significant differences in adverse events such as worsening of cough in the hypertonic saline group compared to the control group. Nebulised hypertonic saline treatment did not significantly reduce the rate of hospital admissions, which was the primary endpoint

Six RCTs were identified that suggested using hypertonic saline compared with normal saline did not make any significant difference to the outcome of the patient.

A parallel-group, pragmatic RCT (Everard et al., 2015) (n=290 infants with acute bronchiolitis) compared hypertonic saline (n=141) to standard care (n=149) in infants in hospital with bronchiolitis. There was no difference in discharge time or adverse events.

A multicentre, double blind RCT (Teunissen et al., 2014) (n=247 children hospitalised with bronchiolitis with a mean age of 3.4 months) assigned patients to nebulised 3% and 6% hypertonic saline compared with 0.9% normal saline. Salbutamol was added to each. There was no difference in hospital length of stay or need for supplemental oxygen between the 2 groups.

A double blind RCT (Silver et al., 2015) (n=190 infants younger than 12 months old with bronchiolitis) compared 3% hypertonic saline (n=93) with normal saline (n=97). There was no significant difference between the groups in length of hospital stay or readmission rate.

An open label, multicentre RCT (Morikawa et al., 2018) (n=128 infants with RSV bronchiolitis) compared nebulised hypertonic saline treatment with a normal saline group which were both administered by bronchodilator. There was no significant difference between the 2 groups in terms of length of stay in hospital.

A prospective, double blinded RCT (Kose et al., 2016) (n=104 infants with acute bronchiolitis) compared the effect of nebulised hypertonic saline 7% plus salbutamol and 3% hypertonic saline plus salbutamol with 0.9% saline plus salbutamol. There were no significant differences on the length of stay in hospital between the hypertonic saline groups and the normal saline groups.

A double blind RCT (Ratajczyk-Pekrul, Gonerko, & Peregud-Pogorzelski, 2016) (n=78 infants younger than 18 months with mild to moderate bronchiolitis) compared nebulised 3% hypertonic saline (n=41) plus salbutamol against 0.9% saline

(n=37) solution plus salbutamol. There were no significant differences in duration of hospital stay and clinical improvement between the 2 groups.

Adrenaline

Two RCTs compared nebulised hypertonic saline and nebulised adrenaline in infants with bronchiolitis and showed significantly favourable outcomes for the intervention group.

A double blind, placebo-controlled RCT (Flores-Gonzalez et al., 2015) (n=185 infants hospitalised with acute moderate bronchiolitis) compared epinephrine 3% nebulised hypertonic saline (n=94) with 3% hypertonic saline (n=91) on its own. Length of hospital stay was significantly reduced in the epinephrine group compared to the control. The severity of bronchiolitis significantly decreased in the intervention group also.

A double blind prospective RCT (Uysalol, Haslak, Ozunal, Vehid, & Uzel, 2017) (n=378 infants with acute bronchiolitis and a mean age of 7 months) compared 3% nebulised hypertonic saline, nebulised adrenaline, nebulised adrenaline mixed with 3% hypertonic saline, nebulised salbutamol and standard care of 0.9% normal saline. The group who received nebulised adrenaline mixed with 3% hypertonic saline had a significantly higher discharge rate and shorter length of hospital stay.

Montelukast

Montelukast is not licensed for use in bronchiolitis within the UK.

Two studies compared montelukast with a placebo or no treatment in infants with bronchiolitis. One Cochrane review and 1 RCT showed no significant differences between the intervention and control groups.

A Cochrane review (Liu et al., 2015) of 5 RCTs involving 1296 infants under 2 years of age with bronchiolitis examined the use of montelukast. Two studies compared 4 mg montelukast with a placebo during a hospital stay and 3 compared montelukast with a placebo for 3 weeks after the hospital stay. There were no significant differences between any of the groups on length of stay in hospital and all-cause mortality.

A RCT (Tahan, Celik, & Eke, 2015) (n= 50 infants with acute bronchiolitis) compared montelukast 4 mg over 5 days compared to no treatment. There were no significant differences found in clinical severity score.

Inhaled corticosteroids

Inhaled corticosteroids are not licensed for use in bronchiolitis within the UK.

Three studies were identified that examined corticosteroids compared to control treatments. Two meta-analyses did not find any significant differences between the intervention and the control. One systematic review showed significant improvements in oxygen saturation levels when corticosteroids were combined with adrenaline.

A meta-analysis (Alarcon-Andrade & Cifuentes, 2018b) of 20 RCTs considered the efficacy of systemic corticosteroids for infants under 2 years of age with bronchiolitis. The results showed that the intervention had no significant benefits on the treatment of bronchiolitis compared to the control treatments.

A meta-analysis (Alarcon-Andrade & Cifuentes, 2018a) of 11 RCTs involving children under 2 years old with bronchiolitis examined inhaled corticosteroids. The results showed that the intervention did not reduce recurrent wheeze or asthma when compared to control treatments.

A systematic review and meta-analysis (Kua & Lee, 2017) of 5 RCTs involving 1157 infants with acute bronchiolitis examined the effectiveness of combined epinephrine and corticosteroid therapy for acute bronchiolitis compared to placebos or epinephrine monotherapy in infants. Combination therapy significantly improved oxygen saturation levels. There were no other significant differences in hospital admission or length of hospital stay between the groups.

Oxygen supplementation

Four studies looked at different methods of oxygen supplementation. Three RCTs looked at high flow oxygen therapy with 2 comparing to standard care. One systematic review compared CPAP with standard care.

A multicentre RCT (Franklin et al., 2018) (n=1472 infants younger than 12 months with bronchiolitis) compared high flow oxygen therapy (HFOT) (n=739) with standard oxygen therapy (n=733). Escalation of care was significantly lower in the HFOT group compared to the standard therapy group. Over half of those in the standard therapy group who had treatment failure responded well to HFOT.

An open, phase 4 RCT (Kepreotes et al., 2017) (n=202 infants under 24 months with moderate bronchiolitis) compared high flow warm humidified oxygen (HFWHO) (n=101) with standard therapy (cold wall oxygen) (n=101). Significantly fewer children experienced treatment failure in the intervention group, however the amount of time the children were on oxygen was higher in the intervention group. Over half of those who had been on standard therapy and experienced treatment failure were rescued by HFWHO.

A RCT (Bueno et al., 2014) (n=75 infants with moderate bronchiolitis mean age of 2.4 months) compared heated humidified high flow nasal cannula oxygen therapy (n=32) with inhaled hypertonic saline solution (n=43). All patients received epinephrine as a bronchodilator. There were no significant differences between the 2 groups in regard to mean respiratory assessment change score, length of hospital stay or admission to paediatric intensive care unit.

A systematic review (Jat & Mathew, 2019) of 3 RCTs involving 122 children under 3 years of age with acute bronchiolitis compared nasal continuous positive airways pressure (CPAP) with standard care. CPAP significantly improved respiratory rate. There was no significant difference in length of hospital stay.

The following interventions were not considered by NG9 and are outside of the original scope. Magnesium sulfate and furosemide are also not licensed for use in bronchiolitis within the UK.

Magnesium sulfate

Three studies considered magnesium sulfate alongside other interventions compared with other treatments or placebos in infants with bronchiolitis.

An RCT (Kan, Zhang, Zhen, & Chen, 2016) (n=96 infants under 2 years old with bronchiolitis) compared magnesium sulfate micro air pump suction (n=49) with an intravenous drip of magnesium sulfate (n=47). There was a significantly greater decrease in carbon dioxide levels in the intervention group. The intervention group also had favourable significant differences with effect rate, adverse reaction rate, resolution time and time in hospital where all results were improved compared to the control group.

A 3-centre double masked RCT (Modaresi et al., 2015) (n=120 infants with moderate to severe bronchiolitis) compared nebulised magnesium sulfate and nebulised epinephrine with nebulised epinephrine. There were no significant differences in hospital stay between the groups. Respiratory distress assessment score was significantly better in those that had been treated with magnesium sulfate.

An RCT (Alansari, Sayyed, Davidson, Al, & Ghadier, 2017) (n=162 infants under 18 months with acute bronchiolitis) compared 100 mg/kg of IV magnesium sulfate (n=78) with a placebo (n=82). Patients also received bronchodilator therapy and nebulised hypertonic saline. The clinical severity scores were similar for both groups. There was a significantly greater rate of readmission for those in the intervention group.

Furosemide

A double blind RCT (Williamson, Bredin, Avarello, & Gangadharan, 2018) (n=46 infants with moderate to severe bronchiolitis) compared furosemide with a placebo. There were no significant differences in respiratory rates, oxygen saturation, intensive care unit admission rates or length of stay in hospital.

Retrograde Rhinopharangeal Clearance

An RCT (Gomes, Calvete, Rosito, & Donadio, 2016) (n= 100 infants up to 12 months old with acute bronchiolitis) compared retrograde rhinopharyngeal clearance with nasopharyngeal aspiration. There was a significant reduction in nasal bleeding in the clearance group. There were no other significant differences between the groups.

Non-invasive ventilation

A systematic review (Combret, Prieur, Le, & Medrinal, 2017) of 14 studies involving 379 children under 2 years old with bronchiolitis examined non-invasive ventilation as a treatment. It is not noted what this was compared against. In 2 RCTs there was a significant reduction in carbon dioxide measurements.

Intelligence gathering

Oxygen supplementation

One topic expert suggested that the recommendation around giving oxygen supplementation to children with bronchiolitis if their oxygen saturation is persistently less than 92% should be revised as a study had been identified that showed 90% oxygen saturation was safe and clinically effective in acute bronchiolitis for commencing and stopping supplemental oxygen. It was also noted that the American Paediatric Guidelines for bronchiolitis also recommend levels of 90% oxygen saturation during the treatment of bronchiolitis.

Two topic experts mentioned strengthening recommendations around

supportive measures to maintain oxygen saturation or ventilation including HFOT and nasal CPAP. Both topic experts said that these procedures are being used more increasingly across the UK and therefore should be covered by the guideline.

An ongoing study is looking at giving oxygen through a nasal cannula at either high pressure or at high flow rates in children up to 2 years old with bronchiolitis. This study is expected to complete in September 2019.

Hypertonic saline

One topic expert noted that the American Paediatric Guidelines (2019) for bronchiolitis currently recommend that clinicians may administer nebulised hypertonic saline to infants and children hospitalised for bronchiolitis.

An ongoing study is looking at the effectiveness of nebulised mucolytic therapy with acetylcysteine in the treatment of children with viral bronchiolitis. The study is due to complete in May 2020.

Magnesium sulfate

An ongoing Cochrane review is looking at RCTs comparing magnesium sulfate for acute bronchiolitis in children under 2 years of age with either placebo, hypertonic saline, epinephrine or bronchodilators.

Nasal suctioning

An ongoing study is looking at nasal suctioning via a standardised nasal aspiration ZoLi device compared to standard care. This trial is still recruiting.

Azithromycin

An ongoing study is looking at azithromycin compared to routine bronchiolitis care in infants who have been hospitalised with RSV bronchiolitis to see if it reduced the occurrence of recurrent wheeze in future years. The study is due to complete in December 2021.

Impact statement

NG9 currently recommends that clinicians should not use the following to treat bronchiolitis: antibiotics, hypertonic saline; adrenaline; salbutamol; montelukast; ipratropium bromide; systemic or inhaled corticosteroids; a combination of systemic corticosteroids and nebulised adrenaline.

The scope recommends that the guideline consider evidence around the following treatments for bronchiolitis: chest physiotherapy; antibiotic treatment; inhaled therapies (including epinephrine. Salbutamol, corticosteroids, ipratropium bromide); systemic corticosteroids; nebulised hypertonic saline; heliox; combined bronchodilator and corticosteroid therapy; montelukast.

According to the scope the guideline should also consider evidence around supportive measures to maintain SpO2 or ventilation including: oxygen supplementation (including humidified oxygen); humidified high flow oxygen and CPAP. The guideline should consider indication for fluids and nutrition support, as well as use of nasal suction and the criteria for discharge from hospital.

The scope recommends that any supportive treatments other than those specified above will not be covered by the guideline, however we considered treatments outside of the scope where evidence was available.

Hypertonic saline

New evidence was identified around the use of hypertonic saline. Seven studies were identified that stated that hypertonic saline was safe and effective to use in regard to improving clinical severity scores, reducing length of stay in hospital and reducing the risk of hospitalisation. The American Paediatric Guidelines (2019) also recommends that hypertonic saline is safe and effective to use, however 2 studies were found which suggested that hypertonic saline worsened episodes of cough. There were 6 studies that indicated hypertonic saline did not make a difference to primary outcomes when the heterogeneity of the evidence was fully considered. Homogeneity is difficult to achieve between these studies as the population can differ in terms of age, setting and severity of symptoms. The method of administering treatment can alter and other drugs can be given alongside the hypertonic saline such as salbutamol, nebulised adrenaline which can skew the results. It is proposed that there is not enough consistent high quality evidence to suggest that nebulised hypertonic saline should be used in the management of bronchiolitis in infants and therefore no impact on the recommendation is expected. This area will be considered again at the next surveillance review.

Adrenaline

New evidence was identified that suggested that adrenaline administered alongside nebulised hypertonic saline reduced length of hospital stay in infants with acute bronchiolitis. It its proposed that there is not enough evidence to suggest that adrenaline should be used in the management of bronchiolitis in infants and therefore no impact on the guideline is expected.

Montelukast

New evidence was identified that suggested the use of montelukast was ineffective in the management of bronchiolitis. This treatment is also not licensed for use in bronchiolitis within the UK. Therefore, no impact on the guideline is expected.

Inhaled corticosteroids

New evidence was identified that suggested there were no significant benefits to using corticosteroids in the management of bronchiolitis. In 1 systematic review there were improvements in oxygen saturation levels when corticosteroid therapy was combined with adrenaline. However, it is proposed that there is not enough evidence to suggest that corticosteroids should be used in the management of bronchiolitis in infants and therefore no impact on the guideline is expected.

Furosemide

New evidence was identified which suggests there were no significant benefits to using furosemide in the management of bronchiolitis. It is noted that furosemide is currently not licensed for use in infants with bronchiolitis within the UK. Therefore, no impact on the guideline is expected.

Retrograde rhinopharangeal clearance

New evidence was identified which suggests there were no significant benefits to using retrograde rhinopharangeal clearance in the management of

bronchiolitis. Therefore no impact on the guideline is expected.

Non-invasive ventilation

One systematic review was identified that suggested limited significant benefits in using non-invasive ventilation in the management of bronchiolitis. Therefore, no impact on the guideline is expected.

Nasal suctioning

No published evidence was identified to suggest that there were any significant benefits to using nasal suctioning in the management of bronchiolitis. It is recommended that this area is reviewed after the publication of the ongoing study. No impact on the guideline is expected.

Azithromycin

No published evidence was identified to suggest that there were any significant benefits to using azithromycin in the management of bronchiolitis. It is recommended that this area is reviewed after the publication of the ongoing study. No impact on the guideline is expected.

Magnesium sulfate

New evidence was identified that suggests magnesium sulfate is considered safe and effective with 1 study showing significant reduction in length of hospital stay and 1 study showing improved respiratory distress assessment score. One study however suggested that the use of magnesium sulfate alongside nebulised hypertonic saline significantly increased readmission rates. A Cochrane review is ongoing looking at the effectiveness of magnesium sulfate compared to other treatments for bronchiolitis. It is noted that magnesium sulfate is currently not licensed for use in infants with bronchiolitis within the UK.

It is proposed that this area is reconsidered after the publication of the Cochrane review and that there is currently not enough evidence to warrant an update to the guideline at this time. Therefore, no impact on the guideline is expected.

Oxygen supplementation

Two topic experts suggested that HFOT and nasal CPAP are being used more frequently in the UK. New evidence was identified that showed few significant differences between these methods of oxygen supplementation compared to standard care, however 1 study did show that escalation of care was significantly lower in the HFOT group compared to standard care and that over half of those in the standard therapy group who had treatment failure responded well to HFOT.

NG9 does not mention these procedures in its guideline. Recommendations 1.1.10 and 1.4.4 recommend the use of oxygen supplementation but do not give suggestions on which method to use.

One topic expert also suggested that oxygen levels should be reduced to less than 90% when considering the use of oxygen supplementation. The guideline currently recommends giving oxygen supplementation to children with bronchiolitis if their oxygen saturation is persistently less than 92%.

It is proposed that there is currently not enough evidence to recommend the use of HFOT or nasal CPAP, and similarly there is not enough evidence to safely suggest oxygen saturation levels should be lessened to 90% when considering oxygen

supplementation. Therefore no impact on the recommendations is expected.

New evidence is unlikely to change guideline recommendations.

1.5 When to discharge

1.5.1 When deciding on the timing of discharge for children admitted to hospital, make sure that the child:

- is clinically stable
- is taking adequate oral fluids
- has maintained oxygen saturation over 92% in air for 4 hours, including a period of sleep.

1.5.2 When deciding whether to discharge a child, take into account factors that might affect a carer's ability to look after a child with bronchiolitis, for example:

- social circumstances
- the skill and confidence of the carer in looking after a child with bronchiolitis at home
- confidence in being able to spot red flag symptoms (see recommendation 1.6.1)
- distance to healthcare in case of deterioration.

1.5.3 Provide parents or carers with key safety information (see recommendation 1.6.1) when the child is discharged.

Surveillance proposal

This section of the guideline should be updated.

2019 surveillance summary

Levels of oxygen saturation

A multicentre, parallel-group, double blind RCT (Cunningham et al., 2015) (n=615 infants aged 6 weeks to 12 months who were in hospital with bronchiolitis) compared 2 groups requiring either a target oxygen saturation of ≥=94% (n=308) or >90% (n=307). All infants received routine care. There was no difference regarding time to cough resolution between the 2 groups. There were significant differences in terms of time for discharge with the patients in the lower oxygen saturation group being discharged sooner than the higher oxygen

saturation group. Reattendance numbers were not significantly different between the 2 groups. An economic analysis was performed which suggested that overall patient costs were reduced for the modified group, however the reduction in costs to the NHS were not statistically significant. Adverse effects were lower in the 90% group, however it was unclear if this was statistically significant.

Intelligence gathering

Levels of oxygen saturation

One topic experts noted that there is evidence to suggest that oxygen saturation levels could be safely lowered to 90% at discharge, as is stated by the American Paediatric Guidelines (2019).

Early supported discharge

The Quality Standard QS122 on Bronchiolitis in Children has a placeholder statement regarding admission avoidance and early supported discharge. It is noted in the placeholder statement that further guidance is needed on admission avoidance and early supported discharge of children with bronchiolitis.

However, NG9 already gives recommendations on when to discharge a child and to consider the home environment of where they will be discharged to. It also discusses the key safety information to give to parents when a child is discharged. It suggests that bronchiolitis is self-limiting and that children should not be admitted unless they show some signs of issues such as apnoea, oxygen saturation of less than 92%, inadequate oral fluid intake or persisting severe respiratory distress.

Impact statement

Levels of oxygen saturation

New evidence was identified from 1 study that suggested oxygen saturation levels can be safely lowered from 94% in children with bronchiolitis to 90% prior to discharge and not cause any adverse effects. Three topic experts also suggested lowering required oxygen saturation levels. The American Paediatric Guidelines (2019) on Bronchiolitis have already amended their recommendation to state that oxygen levels can be lowered to 90% during treatment of bronchiolitis in infants.

NG9 currently recommends when deciding on the timing of discharge for children admitted to hospital, make sure that the child has maintained oxygen saturation over 92% in air for 4 hours, including a period of sleep.

It was originally proposed at consultation for the surveillance proposal that there was not enough evidence to safely amend the required level of oxygen saturation needed for discharge, however post consultation this was reconsidered. The original recommendation was based on committee consensus supported by little relevant evidence. Stakeholder comments requested NICE revisit the evidence. On reconsideration of the evidence identified through surveillance it was felt that lowering the threshold to 90% during discharge could have resource implications and there is now evidence directly related to the safety and efficacy of oxygen saturation levels in children with bronchiolitis prior to discharge to propose that the recommendation regarding discharge is updated at this time. It is noted that the current evidence only

addresses children aged between 6 weeks and 12 months and therefore further evidence may be needed to address the population outside of these age groups.

Early support discharge

A placeholder in the NICE quality standard on Bronchiolitis in Children was identified.

NG9 gives numerous criteria around when to refer children to emergency hospital care, when to admit children to hospital and when to discharge children who have been admitted to hospital.

Despite this placeholder suggestion it is proposed that NG9 currently gives adequate information regarding early support discharge of children with bronchiolitis and therefore no impact on the recommendation is expected.

New evidence identified that may change current recommendations.

1.6 Key safety information for looking after a child at home

1.6.1 Provide key safety information for parents and carers to take away for reference for children who will be looked after at home. This should cover:

- how to recognise developing 'red flag' symptoms:
    - worsening work of breathing (for example grunting, nasal flaring, marked chest recession)
    - fluid intake is 50–75% of normal or no wet nappy for 12 hours
    - apnoea or cyanosis
    - exhaustion (for example, not responding normally to social cues, wakes only with prolonged stimulation).
- that people should not smoke in the child's home because it increases the risk of more severe symptoms in bronchiolitis
- how to get immediate help from an appropriate professional if any red flag symptoms develop
- arrangements for follow-up if necessary.

Surveillance proposal

No new information was identified at any surveillance review.

Editorial amendments

During surveillance of the guideline we identified the following points in the guideline that should be amended.

- Recommendation 1.1.6: It is suggested that a line is added at the end of this recommendation to ensure that clinicians consider Sepsis as an alternative diagnosis. The proposed amendment would be as follows:

Consider a diagnosis of pneumonia if the child has:

- high fever (over 39°C) **and/or**
- persistently focal crackles.

See also the NICE guideline on Sepsis and risk stratification tools for sepsis in under 5s

- Recommendation 1.2.3: It is suggested that this wording in this recommendation regarding referring children to hospital is amended to ensure that the list of risk factors is not considered exhaustive:

When deciding whether to refer a child with bronchiolitis to secondary care, take account of ~~the following~~ any known risk factors for more severe bronchiolitis such as:

- chronic lung disease (including bronchopulmonary dysplasia)
- haemodynamically significant congenital heart disease
- age in young infants (under 3 months)
- premature birth, particularly under 32 weeks
- neuromuscular disorders
- immunodeficiency.

- Recommendation 1.3.3: It is suggested that this wording in this recommendation regarding admitting children to hospital is amended to ensure that the list of risk factors is not considered exhaustive:

When deciding whether to admit a child with bronchiolitis, take account of ~~the following~~ any known risk factors for more severe bronchiolitis such as:

- chronic lung disease (including bronchopulmonary dysplasia)
- haemodynamically significant congenital heart disease
- age in young infants (under 3 months)
- premature birth, particularly under 32 weeks
- neuromuscular disorders
- immunodeficiency.

Research recommendations

What is the clinical and cost effectiveness of oxygen saturation (SpO2) measurement in primary care in children with bronchiolitis?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

In children with bronchiolitis can paediatric early warning score (PEWS) predict deterioration?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

What is the efficacy of combined bronchodilator and corticosteroid therapy?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

What is the clinical and cost effectiveness of high-flow humidified oxygen versus standard supplemental oxygen?

Summary of findings

The new evidence shows that HFOT can be effective at lowering escalation of care, improving failure of treatment scores and rescuing those who have been on standard treatment and failed to respond well.

What is the clinical and cost effectiveness of suction to remove secretions from the upper respiratory tract compared with minimal handling?

Summary of findings

No new evidence relevant to the research recommendation was found. An ongoing study looking at nasal suctioning via a standardised nasal aspiration ZoLi device compared to standard care is currently still recruiting.

In children with bronchiolitis what features predict progressive recovery?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

What is the effectiveness of chest physiotherapy in children with bronchiolitis and impending respiratory failure?

Summary of findings

One NIHR signal confirmed that chest physiotherapy for acute bronchiolitis in children under 2 has no benefits and may be harmful.

What is the efficacy of montelukast in the treatment of acute bronchiolitis in infants and children?

Summary of findings

Two studies compared montelukast with a placebo or no treatment in infants with bronchiolitis. One Cochrane review and 1 RCT showed no significant differences between the intervention and control groups. Montelukast is not licensed for use in bronchiolitis within the UK.

What is the efficacy of heliox?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

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